Reducing the Burden of Pneumococcal Disease in UK Adults

James Alexander Campling BSc. (Hons), MSc

PhD by Publication

University of East Anglia

Faculty of Medicine and Health Sciences

April 2024

Abstract

Background: *Streptococcus pneumoniae* is an encapsulated bacterium responsible for pneumococcal disease, with over 100 serotypes identified. Pneumococcal disease is a leading cause of morbidity and mortality in the UK and is categorised as non-invasive (sinusitis, otitis media and non-bacteraemic pneumonia) and invasive (bacteraemia and meningitis). Adults aged ≥65 years, or with certain underlying comorbidities, are at increased risk of pneumococcal disease. Pneumococcal conjugate vaccines (PCV13 and PCV20) have been successively licensed to help protect adults against pneumococcal disease caused by serotypes in each respective vaccine. The Joint Committee on Vaccination and Immunisation (JCVI) are responsible for advising the UK Government on immunisation programmes, reviewed PCV13 in 2015 but did not recommend its use in adults, based on cost-effectiveness.

Aim: A large epidemiological plan was devised to address data gaps and to establish a scientific consensus for parameters used in future health economic modelling.

Method: Work was initiated to critically assess modelling and identify shortcomings in the evidence. Key parameters identified with incomplete evidence were: 1) incidence of hospitalised community-acquired pneumonia (hCAP), 2) hCAP costs and 3) risk quantification for comorbid adults. Studies were designed and executed generating evidence for these key parameters.

Outcome: Peer-reviewed manuscripts were published describing evidence gaps, and evidence generated. This included estimates (pre- and intra-COVID-19 pandemic) of all-cause hCAP incidence of >450/100,000 in UK adults compared with a previous estimate of 80/100,000. Contemporary hCAP costs were estimated to be £3,904 vs. a prior estimate of £715. Finally, data were published reporting hCAP odds ratios for comorbid adults 1.18 (CI: 1.13, 1.23) for diabetes mellitus to 5.48 (CI: 5.28, 5.70) for chronic respiratory disease. In June 2023 the JCVI provided new advice for the adult pneumococcal programme, with a preference for PCV20, to help protect adults aged ≥65 years and all adults with certain underlying comorbidities.

List of contents

Critical Analysis Wordcount = 19,770

Abbreviations

aLRTD	Acute Lower Respiratory Tract Disease
BIA	Budget Impact Analysis
CAPiTA	Community-Acquired Pneumonia immunisation Trial in Adults
CAP	Community-Acquired Pneumonia
CCG	Clinical Commissioning Group
CEA	Cost-Effectiveness Analysis
CHD	Chronic Heart Disease
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
CRD	Chronic Respiratory Disease
COVID-19	Coronavirus Disease - 2019
DM	Diabetes Mellitus
GSK	Glaxosmithkline
ELISA	Enzyme-linked Immunosorbent Assay
GP	General Practice
HAP	Hospital Acquired Pneumonia
HES	Hospital Episodes Statistics
hCAP	Hospitalised Community-Acquired Pneumonia
IPD	Invasive Pneumococcal Disease
JCVI	Joint Committee on Vaccination and Immunisation
LRTI	Lower Respiratory Tract Infection
LSOA	Lower Layer Super Output Area
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OHID	Office for Health Improvement and Disparities
PCV7	7-Valent Pneumococcal Conjugate Vaccine
PCV10	10-Valent Pneumococcal Conjugate Vaccine
PCV13	13-Valent Pneumococcal Conjugate Vaccine
PCV15	15-Valent Pneumococcal Conjugate Vaccine
PCV20	20-Valent Pneumococcal Conjugate Vaccine
PCV21	21-Valent Pneumococcal Conjugate Vaccine
PPV23	23-Valent Pneumococcal Polysaccharide Vaccine
SARS-CoV-2	Severe Acute Respiratory Syndrome Related Coronavirus 2
OM	Otitis Media
QALY	Quality Adjusted Life Year

UKHSA	United Kingdom Health Security Agency
VT	Vaccine Type

List of Tables

List of Figures

Figure 13 Cost-effectiveness plane for alternative vaccination strategies among moderate- and high-risk adults aged 18–64 years and all adults aged 65–99 years in England (N = 15,635,909).

Acknowledgements

I am particularly grateful to Dr. Andrew Vyse who initially suggested I consider a PhD by publication. Dr. Vyse has helped guide me over the last 7 years, both technically and practically, including providing tips on how to navigate some of the challenges of the peer-review process.

I would like to thank Dr. Harish Madhava who first gave me the opportunity to lead on Pfizer's adult pneumococcal programme and supervised my early research. I would like to say a special thank you to my current manager, Dr. Gillian Ellsbury who has supported me professionally for more than 6 years now. Dr. Ellsbury ensured I was able to continue working on the adult pneumococcal programme throughout this time, has been involved with and supervised most of my research and endorsed my PhD application.

I would like to thank Prof. Mary Slack, from whom I have learnt a great deal. Prof. Slack was involved in much of my early work and supported and encouraged me over the last 8 years. I would also like to thank Prof. James Chalmers and Dr. Catherine Hyams for their respective collaborations, without which this PhD would not have been possible.

I would like to sincerely thank my supervisors, firstly Prof. David Livermore who not only agreed to supervise me but introduced me to my main supervisor, Prof. Paul Hunter. I am enormously appreciative of the time both have afforded me and for the guidance, and valuable expertise and experience they have provided throughout the process. I enjoyed our scientific discussions and hopefully we will be able to collaborate in the future.

Finally, I would like to thank my family who have given me the time and space to complete this PhD by looking after my son and daughter. I am particularly grateful to my wife, Ollya, my Mum and my father-in-law, Mykhailo for all their help. I would also like to mention my son and daughter, Theodore and Eloise, who in their own ways, have also helped me!

1 Introduction

1.1 *Streptococcus pneumoniae* (pneumococcus)

Streptococcus pneumoniae (the pneumococcus) is a Gram-positive, encapsulated pathogen causing many disease manifestations. It is a leading cause of morbidity and mortality in the UK.[1, 2] Its capsule is an important virulence factor impeding phagocytosis but also a vaccine target. More than 100 polysaccharide capsules (serotypes) have been identified.[1] Traditionally serotypes were identified by the Quellung reaction using specific antisera,[3] but molecular methods are increasingly preferred.[4]

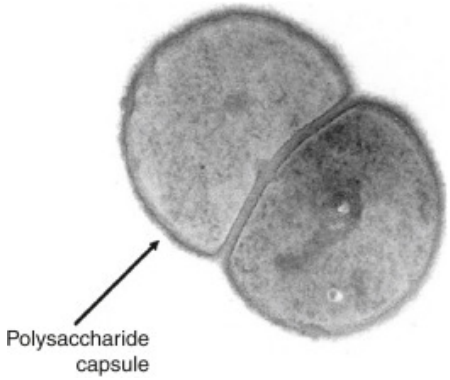


Figure 1: Electron micrograph of *Streptococcus pneumoniae* with its surrounding polysaccharide capsule. Taken from The Vaccine Book (Second Edition).[5]

Pneumococcal disease is categorised as non-invasive and invasive.[1] Non-invasive disease manifests as non-bacteraemic pneumonia, otitis media and sinusitis. Invasive disease, includes bacteraemic pneumonia, bacteraemia and meningitis and can occur as progression of non-invasive disease.[2] Pneumococcal disease predominantly affects the most vulnerable i.e., infants, older adults and those with immunodeficiencies.

The pneumococcus is part of the commensal flora of the upper respiratory tract, colonising the nasopharynx from the first few days of life in developing countries and approximately six months in developed countries.[5] Pneumococcal carriage is a pre-requisite for disease, however, the precise mechanism of action has not been fully characterised. The presence and role of colonisation in children differs from adults.[6] With a peak prevalence in 3-year-olds, young children are the most frequently-colonised group.[6] Carriage rates between 27.8%-

37.9% were reported from a longitudinal study of 1-4 year olds in Southampton between 2006-2018.[7] Colonisation is often harmless; however, it can lead to disease if the 'right' conditions are present, particularly in developing or dysfunctional immune systems. A mature immune system responds differently to the immune system of a young child when challenged by the pneumococcus. It is generally accepted that colonisation rates in adults are <10%.[8] It has been shown that low-level carriage in healthy adults serves as a natural booster, providing a protective effect against both the colonising serotype and more broadly.[9, 10] This is different in adults categorised as being at high-risk of developing pneumococcal disease, whose immune function is in some way altered, resulting in carriage that more frequently translates into disease. It is thought that in this circumstance, disease is preceded by only a short period of carriage.[10] Pneumonia is the most common manifestation of pneumococcal disease in adults.[2]

1.2 Pneumococcal Infection

1.2.1 Pneumonia

The pneumococcus is the leading causative agent of bacterial pneumonia.[11-13] The risk of pneumonia increases with age and in individuals with additional risk factors including lifestyle choices, chronic comorbidities, and immune compromise. [13, 14] Pneumonia occurring in hospital patients, >48 hours after admission is termed 'hospital-acquired' pneumonia (HAP); otherwise, it is termed community-acquired pneumonia (CAP). General Practitioners can treat cases of pneumonia with antibiotics (typically amoxicillin for low severity cases, or a macrolide for patients with known penicillin allergy.[15] More complicated or severe cases need hospitalisation and their illness is termed 'hospitalised CAP' (hCAP).

Pneumococcal pneumonia is officially categorised as non-invasive pneumococcal disease, however, if the pneumococcus enters the bloodstream, it becomes bacteraemic pneumococcal pneumonia (between 5-15% of cases), which is categorised as invasive pneumococcal disease (IPD).[1, 5] A prospective pneumococcal pneumonia study in England reported an overall 30-day case fatality rate of 7.5% for adults aged ≥ 16 years,[12] however, it is widely accepted this is higher in the elderly. Arnold and colleagues in the US found a 30-day case fatality rate of 17% for adults aged ≥ 65 years hospitalised with CAP in Louisville, US.[16]

A blood culture can diagnose a bacteraemic pneumococcal pneumonia, however, diagnosing non-invasive pneumococcal pneumonia is more difficult. Evidence of the causative pathogen

is required to confirm pneumococcal pneumonia which can be achieved through culturing the organism from an otherwise sterile site, by urinary antigen detection tests or by sputum culture.[17]

Although not ideal from an antibiotic stewardship perspective, in clinical practice, treatment for bacterial pneumonia does not rely on identifying the pathogen. Furthermore, antibiotic use can affect the sensitivity of diagnostic assays, which is problematic since up to 40% of adult patients receive antibiotics prior to collecting diagnostic samples.[17, 18] This is further compounded by additional costs incurred for conducting diagnostics. Due to the low and inconsistent use of diagnostics for routine clinical care, only formal research can provide reliable estimates of disease prevalence and incidence.

Cases of hospitalised pneumonia are recorded in England's national hospital database known as Hospital Episodes Statistics (HES), primarily for the purpose of reimbursement of treatment costs. It is not possible to reliably ascertain from HES data whether a hospitalised pneumonia case had hCAP or HAP. Furthermore, most cases (99%) of pneumonia in HES are recorded as 'unspecified' as opposed to assigning a (pneumococcal or other) aetiology.[19, 20]

1.2.2 Otitis Media

Acute Otitis Media (AOM) is a common infection in young children, affecting the middle ear, and is treated with antibiotics.[21] It is the most common manifestation of pneumococcal disease, with *Streptococcus pneumoniae* isolated from 28-55% of middle ear aspirates.[5] AOM is largely managed through primary care, though severe cases can lead to invasive disease and require hospitalisation. After the introduction of pneumococcal vaccines into the childhood immunisation schedule in the UK, cases of AOM declined which, in turn, led to a sharp reduction in antibiotic prescribing.[21] *Haemophilus influenzae* and *Moraxella catarrhalis* have now overtaken the pneumococcus as causes of AOM.[22]

1.2.3 Invasive pneumococcal disease

Invasive pneumococcal disease (IPD) is the most serious form of pneumococcal disease and includes pneumococcal meningitis, pneumococcal bacteraemia and pneumococcal bacteraemic pneumonia.[14] The case fatality rate for both pneumococcal meningitis and bacteraemia in

adults, not associated with pneumonia, is 20% and, for cases of bacteraemia, this increases up to 60% in the elderly.[5]

1.3 Prevention of Pneumococcal Disease

1.3.1 Pneumococcal Vaccines and Manufacturers

There are several strategies that can help to prevent pneumococcal disease in adults. Maintaining a healthy lifestyle by not smoking, maintaining a healthy weight, good diet and exercise helps to prevent risk factors for pneumococcal disease from developing.[23] Targeted prophylactic antibiotics for people at-risk of pneumococcal infection could be used but would have negative consequences, including driving antimicrobial resistance. Recently, the COVID-19 pandemic showed that non-pharmaceutical interventions i.e., social distancing had a dramatic effect in preventing pneumococcal disease; however, cases quickly rebounded once restrictions were lifted.[24]

The most practical strategy to prevent pneumococcal disease is through vaccination and two types of pneumococcal vaccines exist: polysaccharide vaccines and conjugate vaccines. The use of pneumococcal vaccines has profoundly impacted the epidemiology of the pneumococcus,[12, 25] which therefore must be viewed in the context of these vaccines.

Vaccine Name	Manufacturer
7-valent pneumococcal conjugate vaccine (PCV7)	Pfizer Inc. (formally Wyeth)
10-valent pneumococcal conjugate vaccine (PCV10)	GlaxoSmithKline Plc
13-valent pneumococcal conjugate vaccine (PCV13)	Pfizer Inc. (formally Wyeth)
15-valent pneumococcal conjugate vaccine (PCV15)	Merck & Co., Inc.
20-valent pneumococcal conjugate vaccine (PCV20)	Pfizer Inc.
23-valent pneumococcal polysaccharide vaccine (PPV23)	Merck & Co., Inc.

Table 1: Table of licensed pneumococcal vaccines with their respective manufacturers

1.3.2 PPV23

PPV23 was first approved for use in 1983[26] and, in the UK, is licensed to prevent both pneumonia and IPD[27]. In 1992 it was first recommended for adults in risk groups and subsequently in 2003, for all adults aged ≥65 years. PPV23 is a pneumococcal polysaccharide vaccine comprising of capsular polysaccharides from 23 pneumococcal serotypes (1, 2, 3, 4, 5, 6b, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F). PPV23 elicits a B cell-dependant immune response resulting in the production of IgM.[28] Children under 2 years old are not recommended to be vaccinated with PPV23 due to their immature immune system being unable to produce an acceptable immune response.[28]

There is a general consensus that PPV23 is somewhat effective against IPD, although the extent and duration of protection is not clear.[29-31] However, controversy exists regarding vaccine effectiveness of PPV23 against pneumonia, where data remain inconsistent.[29, 31-33]

1.3.3 Pneumococcal conjugate vaccines

Pneumococcal conjugate vaccines contain pneumococcal capsular polysaccharides conjugated to a highly immunogenic non-toxic diphtheria toxoid protein called Cross-Reactive Material 197 (CRM_{197}). This elicits a complex T cell-dependant immune response, stimulating T helper

cells, and in an enhanced primary response and generation of memory B cells, which can facilitate a booster response.[28, 31]

In 2000 PCV7 (against serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) was licensed for use in the USA to prevent pneumococcal disease and was shown to be effective in substantially reducing the burden of IPD. Three priming doses were administered at 2, 4 and 6 months followed by a booster dose at 12-14 months.[34]

The reduction in vaccine type (VT) disease led to the phenomenon of serotype replacement. This occurs where VT serotypes in the nasopharynx are replaced by previously rare serotypes, which then go onto cause pneumococcal disease. PPV23 does not induce mucosal immunity and therefore did not affect nasopharyngeal carriage. However, PCVs do induce mucosal immunity, and it is this immune pressure that causes serotype replacement.[35, 36] After the introduction of PCV 7 serotype replacement was particularly evident with the rises of serotypes 7F, 19A and 22F).[36-39] Considerable research has been conducted to determine how the pneumococcus is able to do this. The genes responsible for polysaccharide capsule synthesis and regulation and their location on the chromosome have been identified.[36, 39] This facilitated further research which has been able to describe the mechanism of action of capsule switching, which occurs through genetic recombination.[36, 39] Evidence from whole genome sequencing shows that although some replacement after the introduction of PCV7 was due to capsule switching, the majority was due to non-VTs filling ecological niches. However, the evolution of the pneumococcus in response to PCVs likely continues.[40]

In response to evolving serotype epidemiology, higher valency PCVs were developed by GSK and Pfizer and, in 2009 and 2010, marketing authorisations were granted for PCV10 (PCV7 + 1, 5, 7F) and PCV13 (PCV10 + 3, 6A, 19A) respectively.[38]

PCV10 was only approved for use in children but PCV13 also gained a license for use in adults for protection against IPD; however, the FDA omitted pneumonia from the adult license due to a lack of evidence. Subsequently, a large prospective efficacy study, Community-Acquired Pneumonia immunisation Trial in Adults (CAPiTA), was conducted in Dutch adults, which demonstrated PCV13 efficacy against IPD and pneumonia.[41] Shortly afterwards, a recommendation for PCV13 was made in the USA for adults aged ≥65 years.[42]

Further serotype replacement was evidenced (see Figures 2 and 3) and new, higher valency PCVs were developed: specifically, PCV15 (PCV13 + 22F, 33F) and PCV20 (PCV15 + 8,

10A, 11A, 12F, 15B) were licensed for use in adults only in 2021, with paediatric licenses granted in 2022 and 2023 respectively. [43]

PCV15 and PCV20 were licensed for UK adults in 2021 and 2022 respectively.[1]

1.4 Pneumococcal Epidemiology in the UK

1.4.1 IPD Epidemiology in the UK

IPD surveillance, led by UK Health Security Agency (UKHSA) (formerly known as Public Health England and the Health Protection Agency but referred to only as UKHSA in this critical analysis), provides excellent insight into the local epidemiology in England.[44] Until 2016/17 this programme covered both England and Wales but from 2017 onwards, only includes England.[24, 25] UKHSA mandates reporting all cases of IPD diagnosed in England to the Respiratory and Vaccine Preventable Bacteria Reference Unit, UKHSA, Colindale, London specifying "Cases of IPD are defined as *Streptococcus pneumoniae* cultured from a normally sterile site."[45] The UKHSA also seeks the pneumococcus culture for serotyping together with demographic data.[45] Since the introduction of PCV13 less than 10% of isolates sent to Colindale could not be serotyped and less than 1% of cases reported were missing age data.[45] This programme provides a dynamic comprehensive surveillance system that accurately reports IPD incidence stratified by serotype.[24, 45] In 2022/23 a total of 4,598 cases were submitted and IPD incidence, stratified by age and vaccine type (PCV13), since 2000 is shown in Figures 2 and 3.[24] Case numbers in 2022/3 reflect a near-full rebound in disease after the sharp decline seen during the COVID-19 pandemic, specifically related to social distancing measures.[24]

Figure 2 shows the dramatic impact that PCV7 and then PCV13 had on IPD in children, who received direct PCV vaccination, but also the indirect effect they elicited for unvaccinated adults. Figure 3 provides a more granular insight into the evolution of IPD serotype epidemiology, across age groups between 2017 and 2023. Although the majority of IPD is now caused by non-PCV13 serotypes there is a persistent burden of disease especially in adults. It is evident that individual serotypes affect the age groups differently. The most troublesome serotypes across all ages are ST3, 19A & 19F but with a greater representation of other PCV13 STs in older age groups; ST3 also remains a particular problem in this population. These data

demonstrate the role that serotype replacement has had on dampening the overall impact of these vaccines on IPD and why higher valency PCVs are needed.

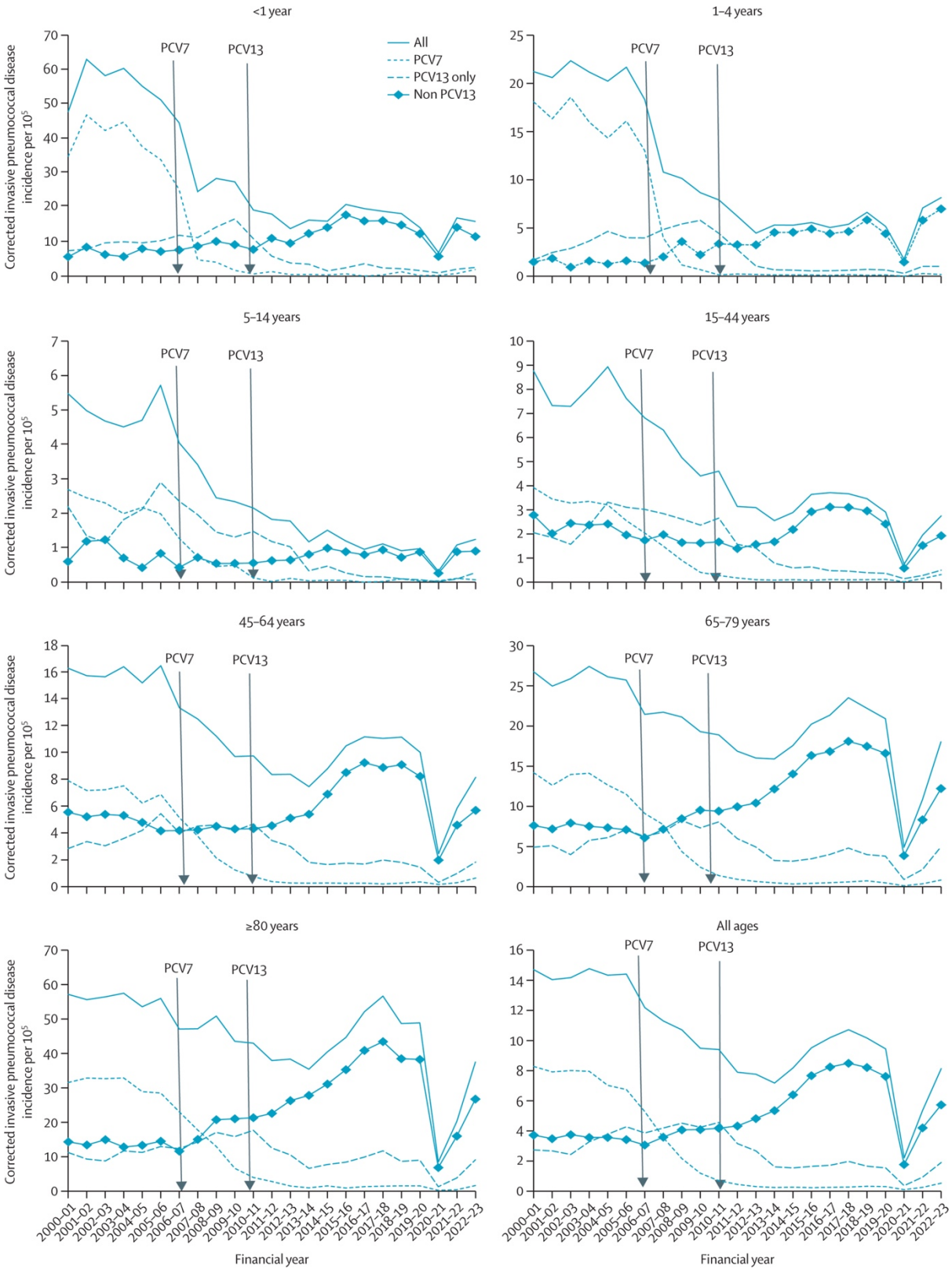


Figure 2: "Corrected disease incidence by age group, serotype group, and financial year, 2000–01 to 2022–23. The scales of the y-axes vary." Taken from Betran et. al Lancet Infect Dis. 2024 Feb 1:S1473-3099(23)00706-5.[24]

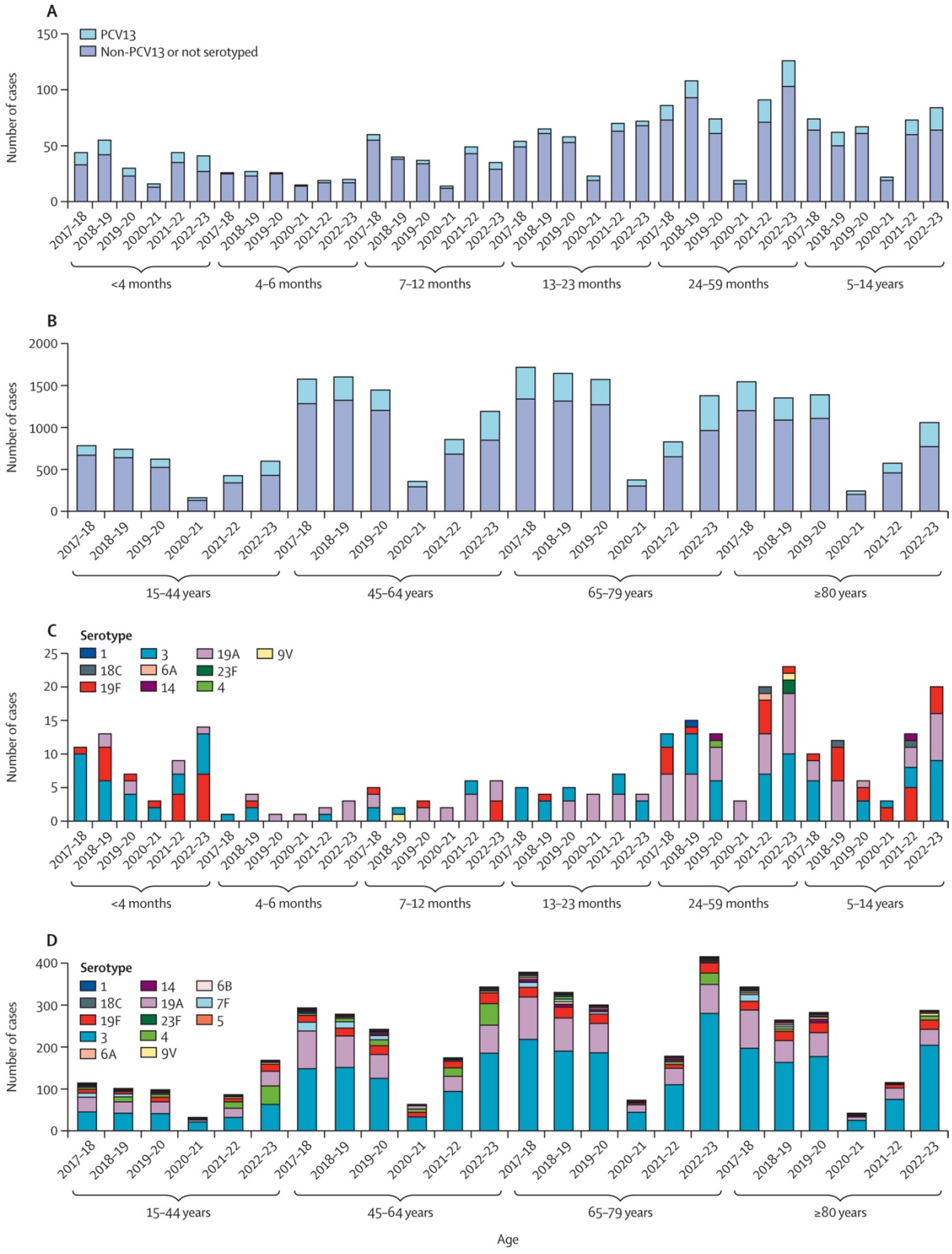
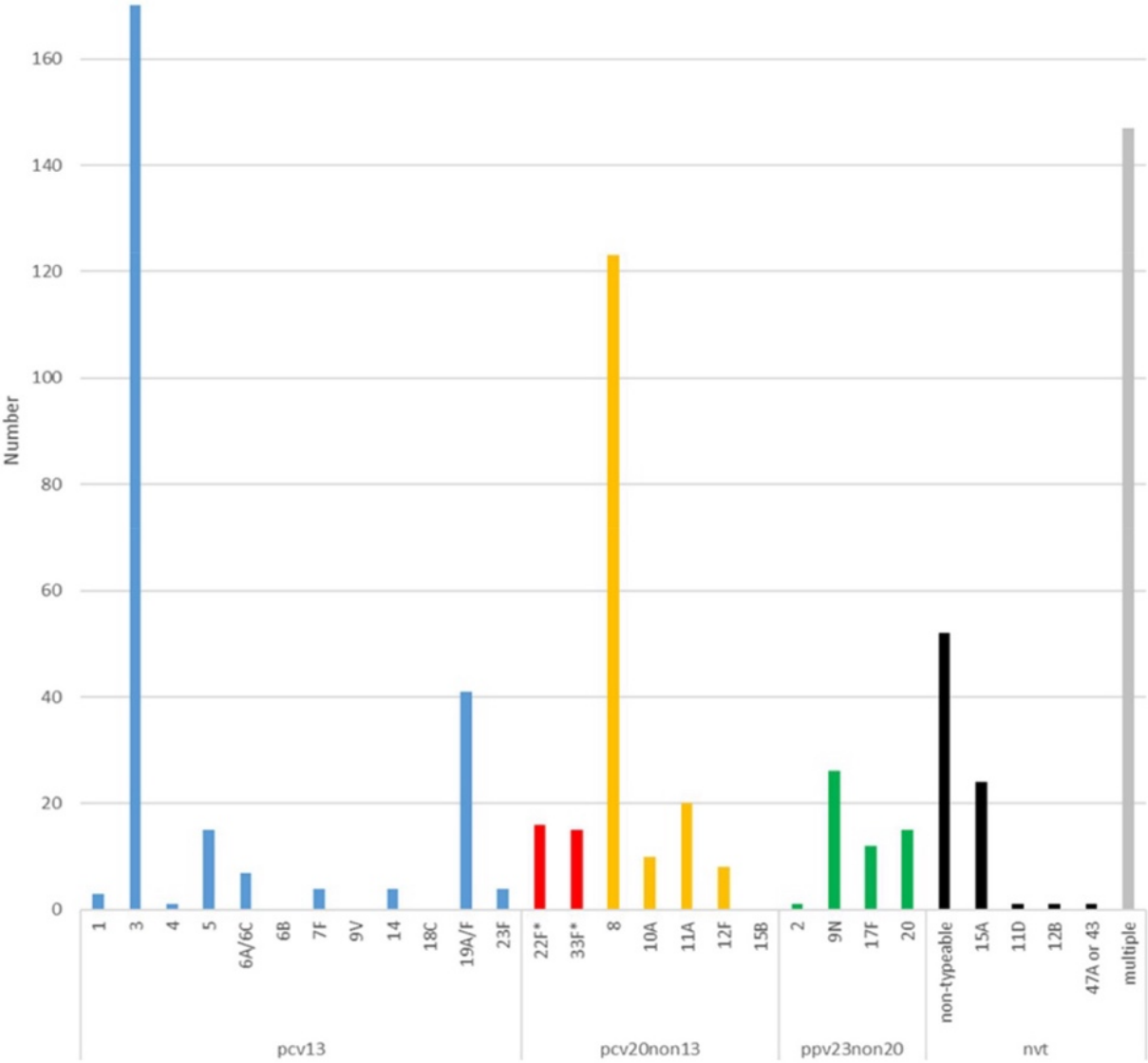


Figure 3: “Invasive pneumococcal disease cases by financial year, serotype, and age group.” Taken from Betran et. al Lancet Infect Dis. 2024 Feb 1:S1473-3099(23)00706-5.[24]

1.4.2 Pneumococcal hCAP Epidemiology in the UK

A recent, (though pre-COVID-19 pandemic) prospective, multi-centre study of pneumonia conducted in Nottingham, Liverpool and Edinburgh has reported that approximately 40% of all hCAP is caused by the pneumococcus.[46] Although the distribution of serotypes causing pneumococcal hCAP is similar to the epidemiology for IPD there are differences. This study used a 24-valent UAD assay developed by the UKHSA which covers all serotypes in PPV23 + 6A and therefore provides more detailed, contemporary information for hCAP than has currently been published for IPD.[12]



Serotypes 22F and 33F marked with * are PCV15 serotypes which are not covered in PCV13 but are also included in PCV20

- PCV13 serotypes
- PCV15 serotypes not covered by PCV13
- PCV20 serotypes not covered by PCV13 or PCV15
- PCV23 serotypes not covered by PCV13/15/20
- Non-vaccine serotypes
- Multiples serotypes detected

Figure 4: **"**Pneumococcal serotypes detected in patients by Bioplex-24 assay, grouped according to pneumococcal vaccine class in adults with pneumococcal CAP (N = 721)." Lansbury et. al Lancet Reg Health Eur. 2023 Dec 11:37[46]

1.5 UK pneumococcal vaccine policy

The Joint Committee on Vaccination and Immunisation (JCVI) is a statutory advisory committee that advises the Secretary of State for Health on vaccination and immunisation services.[47] The JCVI has a responsibility to assess vaccination programmes for cost-effectiveness, which is defined as being justified when the cost is less than £20,000-£30,000 / Quality-Adjusted Life Year (QALY) gained.[47]

PPV23 is currently recommended for use in the UK for all adults aged ≥65 years and anyone aged ≥2 years who is at-risk of pneumococcal disease, as defined in the Green Book.[1] The Green Book is owned and authored by the UK Department of Health & Social Care to provide an authoritative reference for all UK vaccine programmes by reflecting advice provided by the JCVI.[48]

PCV7 was first licensed for use in infants <2 years old in the UK in 2001[38] but was not introduced into the schedule until 2006, when the UKHSA mandatory pneumococcal surveillance system was established.[1] Unlike in the USA, PCV7 was introduced in the UK with only 2 priming doses, followed by a booster dose (2, 4 and 12 months), also known as 2+1.[1] At the time, the UK was the first and only country using a 2+1 schedule, which was outside of the approved license. PCV7 quickly demonstrated impact in this 2+1 schedule. VT pneumococcal disease in infants who had received the vaccine was reduced; in addition, VT disease in children and adults who were not vaccinated also reduced due to the indirect/herd effect.[37] PCV13 replaced PCV7 in the infant programme in 2010, causing a further reduction in VT disease in both those directly vaccinated but also those who were not via the indirect effect.

In 2015 the JCVI were asked to consider whether PCV13 should be introduced to directly protect adults aged 65 but recommended against it based on a cost-effectiveness analysis (CEA).[49] This analysis concluded that PCV13 needed a negative price to be cost-effective.[29]

In 2018 the JCVI provided new advice for how PCV13 should be used in the childhood programme advocating a single priming dose followed by a single booster dose, referred to as a 1+1 schedule, which constitutes an “off-license” use.[50] A number of specific criteria had been laid out that had to be met in order to go ahead with this programme which included: evidence of “a mature vaccination programme, where vaccine-type carriage is largely

eliminated in the community, high vaccine coverage of both doses can be assured, and careful monitoring is feasible."[51] Immunogenicity data from a study funded by the National Institute for Health and Care Research and the Bill & Melinda Gates Foundation evaluating a PCV13 1+1 schedule were published, providing evidence that a booster dose induced an immune response that was non-inferior to a 2+1 schedule.[52] The UK became the first country in the world to introduce a 1+1 schedule.

1.6 My Role / Research

I joined the Pfizer Vaccines Medical Affairs team in May 2015 as the UK lead for PCV13. Shortly afterwards, van Hoek & Miller published their model, which had been used to guide decision-making for PCV13 in UK adults.[29] Through critiquing this publication I was able to identify uncertainties and data gaps that existed. To address the data gaps identified, I put together a large epidemiological plan to ensure a robust evidence base existed for the next review of the adult programme.

PCV20 was already in development when I started my research and, with this in mind, my early work was based broadly on pneumococcal disease. This meant it could support either PCV13 or PCV20, but more recent publications have a stronger focus on PCV20.

Pfizer had also created a cost-effectiveness model for PCV13 in UK adults aged 65 years which concluded it would be a cost-effective intervention. Structurally this model was similar to the one published by van Hoek & Miller, but the input parameters used were markedly different.

The parameters found to be contributing most substantially to this dichotomy were: firstly, estimates for the incidence of pneumococcal hCAP and secondly, the prediction for future levels of VT disease. For the van Hoek & Miller model, disease incidence estimates came from a prospective pneumonia study in Nottingham along with a prediction that PCV13 would elicit an almost perfect indirect effect, resulting in the near elimination of VT disease. See Figure 5 below for graphs describing this for IPD and CAP.

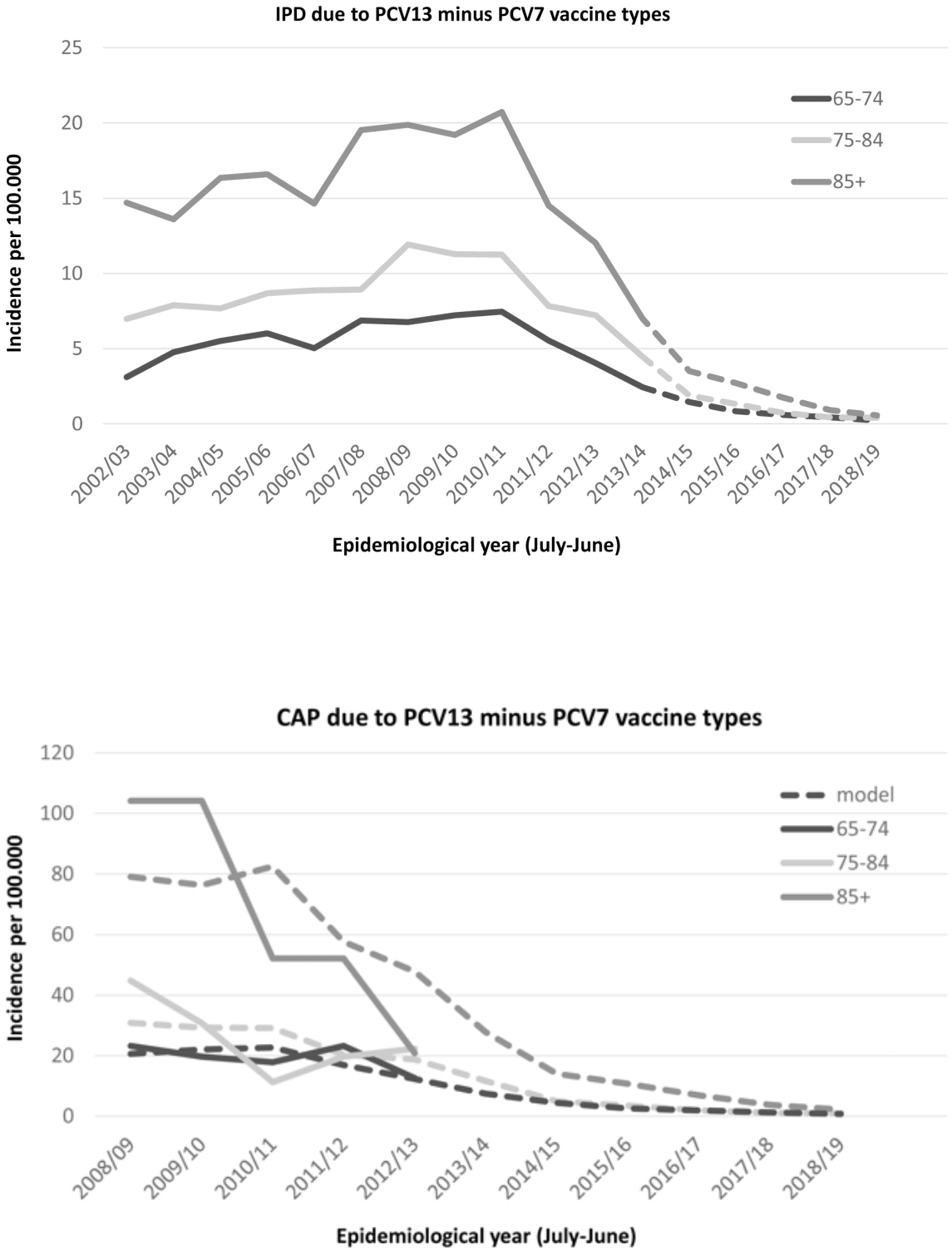


Figure 5: Prediction of future IPD and VT hCAP incidence from the van Hoek & Miller model. Taken from van Hoek AJ, Miller E. PLoS One. 2016 Feb 25;11(2)[29]

By contrast for the Pfizer model, disease incidence estimates came from an electronic healthcare records database for England and a predication for a smaller decline in VT disease in adults, followed by a steady state persistence, was made.

2 Aims & Objectives

The aim of my research was to generate evidence for some of the key parameters needed to answer the public health policy question: "Would the introduction of a pneumococcal conjugate vaccine for at-risk adults in the UK be a cost-effective public health intervention?"

The key parameters my research supported were:

1) Defining the UK burden of pneumococcal hCAP.

2) Evidence for risk of pneumococcal disease among adults with underlying comorbidities.

3) Hospital costs for hCAP.

The objective of my research was to close these key data gaps and to establish a scientific consensus for parameters to be used in health economic modelling.

3 The Burden of Disease

3.1 Publication 1: A systematic review of the burden of vaccine preventable pneumococcal disease in UK adults[2]

Research in Context

The JCVI's 2015 decision not to recommend PCV13 for older adults was partially driven by modelling that used incidence estimates for PCV13 preventable disease, derived from a single study conducted in Nottingham. It was therefore important to evaluate all UK data describing the burden of pneumococcal vaccine-preventable disease. To address this knowledge gap, I led a collaboration between Pfizer and the University of Dundee to conduct a systematic review.

Aims

To establish the burden of both, non-invasive and invasive, vaccine type and non-vaccine type pneumococcal disease in UK adults.[2]

Methods

A systematic review of observational studies in the UK conducted in line with MOOSE (meta-analysis and systematic review of observational studies epidemiology) guidelines.[53] A comprehensive literature search was conducted using PubMed and EMBASE for the period between 1990 to September 2015.[2]

Results

Of 2,483 papers identified, 38 cohorts were selected for data extraction. Robust data sources were limited to the UKHSA national surveillance programme (covering England + Wales) for IPD and a prospective observational study in Nottingham (Nottingham study) for hCAP. Evidence of the herd-effect against VT IPD and hCAP in adults due to the infant PCV7 and subsequent PCV13 programmes, was observed. However, the burden of VT IPD remained high at ~20% of all IPD for adults aged ≥65 years in 2013, and IPD ensues from only around 10% of the number of cases of pneumococcal CAP. Only limited data existed on the serotype distribution in risk groups and no data were available for pneumococcal CAP managed in the community.[2]

Strengths and Limitations

The paper comprised a formal systematic review that used pre-specified inclusion / exclusion criteria and reported on high-quality data. The main limitation was the paucity of serotype-

specific prospective data for hCAP. Although there was only one source of data for IPD - the UK pneumococcal surveillance programme – it is a well-established, high-quality programme measuring incidence and serotype trends for most of the UK population.[24] However, the hCAP Nottingham study, which was funded by Pfizer as an investigator-initiated research study, was primarily designed to evaluate pneumococcal serotype trends,[19] for which it is robust over time; however, hCAP incidence estimates reported from this study should be interpreted with caution due to its study design.[54]

Contribution to the literature

The data presented by this study suggest that VT pneumococcal disease continues to cause a high burden in UK adults despite the impact of childhood PCV13 vaccination. Furthermore, IPD estimates represent only a fraction of the total burden of pneumococcal disease. This review provides a thorough analysis of evidence in the UK, describing the burden of pneumococcal disease. It highlighted areas of high-quality, robust data but also highlighted considerable data gaps, specifically related to incidence data for hCAP. Although the data for this study were limited to the UK, the disease-specific aspect of the findings are applicable for other similar countries.

According to PubMed in November 2024, this publication has been referenced 33 times, including as part of a Cochrane Review of pneumococcal vaccines to prevent pneumonia in chronic obstructive pulmonary disease.[55]

3.2 Publication 2: Community-acquired pneumonia in the United Kingdom: a call to action[19]

Research in Context

The systematic review on pneumococcal disease (Publication 1) confirmed that prospective pneumonia data relevant to PCV performance in the UK were limited to the Nottingham study.[2] When reviewing the van Hoek & Miller publication,[29] I identified analyses that questioned the accuracy of pneumonia incidence estimates reported by the Nottingham study.

Specifically, I had noted that a sensitivity analysis had been conducted by van Hoek & Miller using double the incidence of pneumonia reported in Nottingham. Within appendix 1 of the supporting information, two tables help describe multiple assumptions, that attempted to compare hCAP incidence estimates. These estimates were derived from the Nottingham study in 2008/9, the CAPiTA study (which was not designed to report incidence and was conducted in The Netherlands) and English national HES data. Incidence estimates from Nottingham were approximately half those identified in the CAPiTA study and HES.[29] This explains why a sensitivity analysis using double incidence for CAP was conducted by van Hoek & Miller, but also questions the accuracy of the data. Moreover, the HES incidence estimates in the second comparison table in appendix 1,[29] came from the year 2004/5 from a study in England, which found hCAP incidence increased by 34% over 8 years.[56]

The Nottingham study had been funded by Pfizer as an investigator-initiated research study, and I was the study manager. Primarily, it had been designed to evaluate pneumococcal serotype trends, not to estimate disease incidence, but incidence had been reported.[54]

Furthermore, the van Hoek & Miller model only considered hCAP and not pneumonia managed in the community. The most recent UK prospective study of CAP in the community was conducted by Woodhead and colleagues in 1987.[57] They found that 80% of all-cause pneumonia presented in primary care.[57]

Aim

This paper attempted to identify and highlight shortcomings and data gaps regarding pneumonia in the UK, in the format of a short commentary.

Methods

I convened a face-to-face meeting in London with relevant experts to review a small comparative analysis I had conducted. This compared incidence data reported by the

Nottingham study with HES data for hCAP for the same two hospitals used for the Nottingham study. The subsequent discussion was written up as a commentary/discussion piece.

Results

This analysis reported a 5-fold greater number of cases of all-cause hCAP in HES compared with hCAP cases reported by the Nottingham study at the same hospitals. As an author group we published a short commentary based on our discussion, which concluded in an urgent call for action for research in the field of pneumonia.[19] A chronic lack of investment in pneumonia existed compared with other diseases. This needed attention due to the large burden that pneumonia places on the NHS.

Strengths and Limitations

This paper was written by a diverse mix of recognised UK experts in their field. It was supported by data and raised questions related to an important public health decision in the UK. This paper raised the profile of pneumonia research and highlighted the potentially damaging consequences of continuing to overlook pneumonia research.

A limitation of this publication is that incidence data from Nottingham were derived from a prospective observational study whereas the HES analysis was retrospective; moreover, HES data have previously been criticised for inaccuracies.[58] HES is however, used for financial reimbursement for all NHS hospitals in England.[59] Furthermore, the size of the discrepancy found here was unexpectedly large.

In respect of pneumococcal disease incidence, Figure 6, attempts to compare incidence estimates across several countries, but these came from different study designs, which confound comparison. In particular, the different studies used different age groups and age is a significant risk factor for hCAP. For example, the “UK bar” which reflects the Nottingham data, was only for the age group 65-74 because that is how the study team stratified their data. Upon reflection this was not scientific or appropriate and the age cohort for this figure should have been standardised across each study.

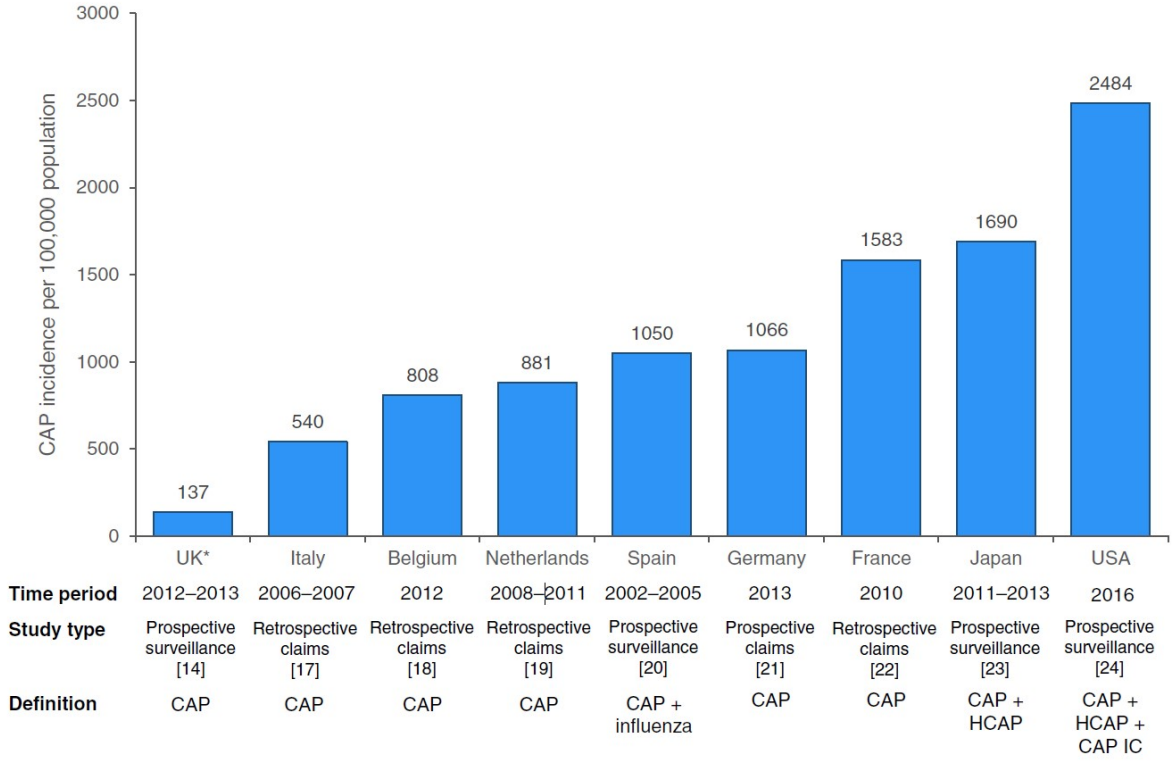


Figure 6: Incidence rates of CAP around the world. *Age group 65–74 years only. CAP, community-acquired pneumonia; CAP IC, community-acquired pneumonia in children; HCAP, healthcare-acquired pneumonia. Taken from Chalmers et. al Pneumonia (Nathan). 2017 Oct 5;9:15.[19]

All authors took part in the discussion, and independently highlighted issues and data they felt were important. The final conclusions of the paper were not controversial: that additional attention and research in the field could only be a benefit from a scientific perspective.

Contribution to the literature

This paper gave prominence to potential inaccuracies regarding the UK's only prospective, longitudinal study of pneumococcal hCAP. The Nottingham study had been designed to evaluate pneumococcal serotype trends, but study data were also used to estimate hCAP incidence, which was highlighted in this publication.

In October 2014, the JCVI agreed that assessments of future vaccines should attempt to quantify the suppression of antimicrobial resistance (which is strongly associated with several vaccine-targeted serotypes)[60] as a potential benefit of vaccine programmes. This paper stated that this potential benefit of vaccines had still not been incorporated into the assessment process. The potential reduction of antibiotic prescriptions due to preventing cases of pneumonia, and the implication of this were therefore not considered when PCV13 was

assessed. [19, 29] This is a complex issue, and it appears that work is now underway to establish how antimicrobial resistance should be considered as part of the vaccine assessment process..[61]

Although the primary focus of this paper was the UK many of the issues raised are not unique, as shown by the paucity of data available for figure 6; and it has since been referred to by researchers in other countries.

This publication provided the foundation for the rest of my research. I presented the HES analysis described in this paper at the 2017 British Thoracic Society Winter Meeting.[59] According to PubMed in November 2024, this commentary had been cited 22 times, including by the NHS Long Term Plan.[62]

3.3 Publication 3: The proportion of contemporary invasive pneumococcal disease and pneumococcal pneumonia in UK adults reflected by serotypes included in the 13-valent pneumococcal conjugate vaccine and next generation higher valency pneumococcal conjugate vaccines in development[63]

Research in Context

At the time this paper was published, PCV13 and PPV23 were the only vaccines licensed in the UK to prevent pneumococcal disease in adults; however, there was an expectation that PCV15 and PCV20 would soon be licensed. The impact a vaccine can have depends on the burden of disease, but the epidemiology of the pneumococcus varies enormously between countries and over time.[64] This is in part due to the way vaccines are used in a country's schedule. It is crucial therefore, to have local epidemiology data to determine how much disease could be prevented. In 2018 and 2020, papers were published describing contemporary data for both IPD and pneumococcal hCAP.[12, 25, 30] This provided an opportunity to analyse these new data and to put the potential benefits of PCV15 and PCV20 into context, assuming they were licensed.

Aims

We sought to amalgamate data describing the serotype coverage of both existing and new adult pneumococcal vaccines in relation to UK pneumococcal epidemiology, based on contemporary, publicly available data.

Methods

In 2020, an analysis was conducted on the data from the routine UKHSA IPD surveillance programme and the Nottingham study.[12, 25] Data were presented stratified by PCV i.e., PCV13, PCV15 and PCV20.

Results

The proportion of disease that could potentially be prevented by each PCV in adults based on the then contemporary data is presented in Figure 7. For IPD, in 2016/17 PCV13 and PCV15 covered 22% and 33% of disease respectively whereas PCV20 covered 65%. The data were similar for hCAP where, in 2017/18, PCV13 and PCV15 covered 36% and 39% of disease respectively, whereas PCV20 covered 64%.

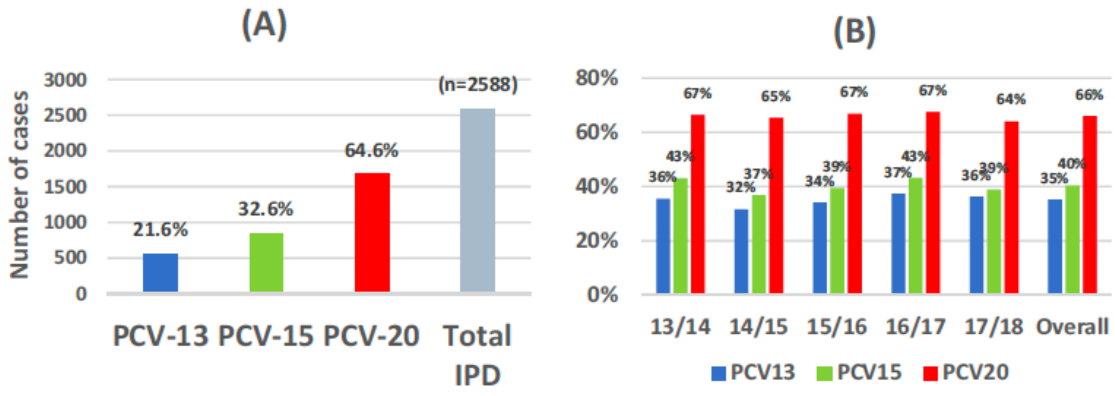


Figure 7: The numbers and proportions of cases due to serotypes included in PCV13, PCV15 and PCV20 in (A) IPD in adults 65+ years in England and Wales in 2016/17 (B) hospitalised pneumococcal CAP in adults 16+ years in Greater Nottingham. Figure taken from Vyse A, et al. Vaccine. 2020 Dec 3;38(51):8068-8070.[63]

Strengths and limitations

A key strength of this analysis is that it is based on prospectively collected peer-reviewed data.

Two main limitations related to the data are – first – that they were already ~3-4 years old at the time of publication. Secondly, the difference in reporting of age groups between IPD and pneumococcal hCAP meant it was not possible to compare coverage data between the two manifestations of disease. Furthermore, while IPD data were national, pneumonia data were limited to a single geography.

A criticism could be lodged that PPV23 coverage was not presented for comparison with the PCVs, but the objective was to highlight the potential benefits of PCV15 / PCV20; PPV23 was already part of the national immunisation programme.

Contribution to the literature

This publication brought together published UK evidence to emphasise the coverage of existing and soon-to-be-licensed PCVs. In 2015, van Hoek & Miller had predicted there would be near elimination of PCV13 VT disease, due to the paediatric herd effect.[29] This paper drew attention to the fact that this prediction had not come true. Therefore, this commentary marked a public challenge to evidence used for the decision not to introduce PCV13 for at-risk adults in the UK. In doing so it also underscores a critical shortcoming of the arguable, over-reliance on mathematical modelling, to make decisions.

Although this publication has limitations, owing to the age of the data described and the vaccines it focused on, it provides a template that can be updated. When more contemporary

data and information about novel vaccines become available, analysis and presentation of these in a consistent format, based on this publication, would help facilitate a clear comparison of vaccine type serotype coverage, relative to the burden of disease.

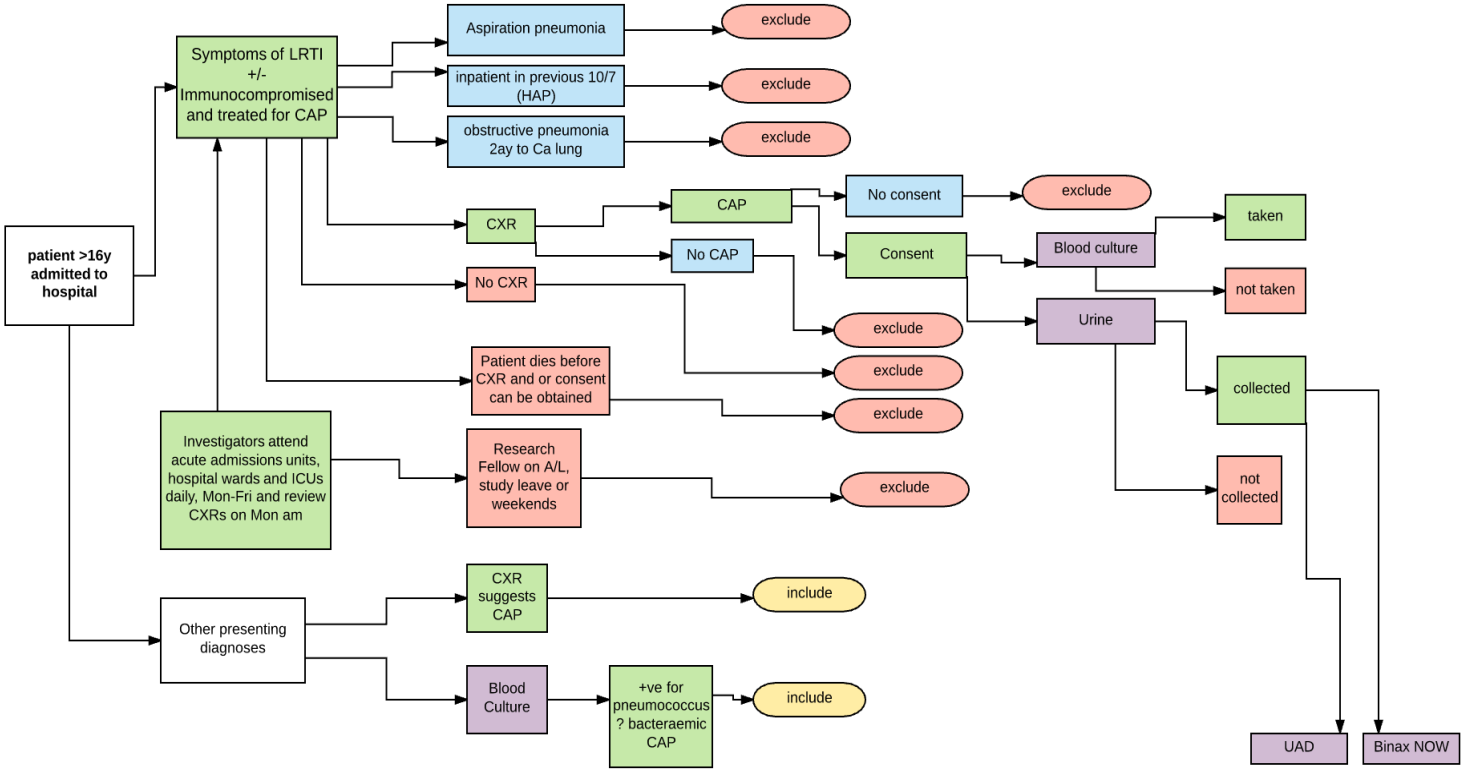
4 Estimating Pneumonia Incidence

4.1 Introduction

The incidence of pneumococcal pneumonia is a critical parameter for any attempt to model the benefit of a pneumococcal vaccine. The pneumococcal incidence estimates from the Nottingham study appeared to be under-estimates, as described in section 3. The discrepancy identified through the HES comparative analysis, along with the discrepancy between hCAP estimates from Nottingham with other countries, warranted further scrutiny.

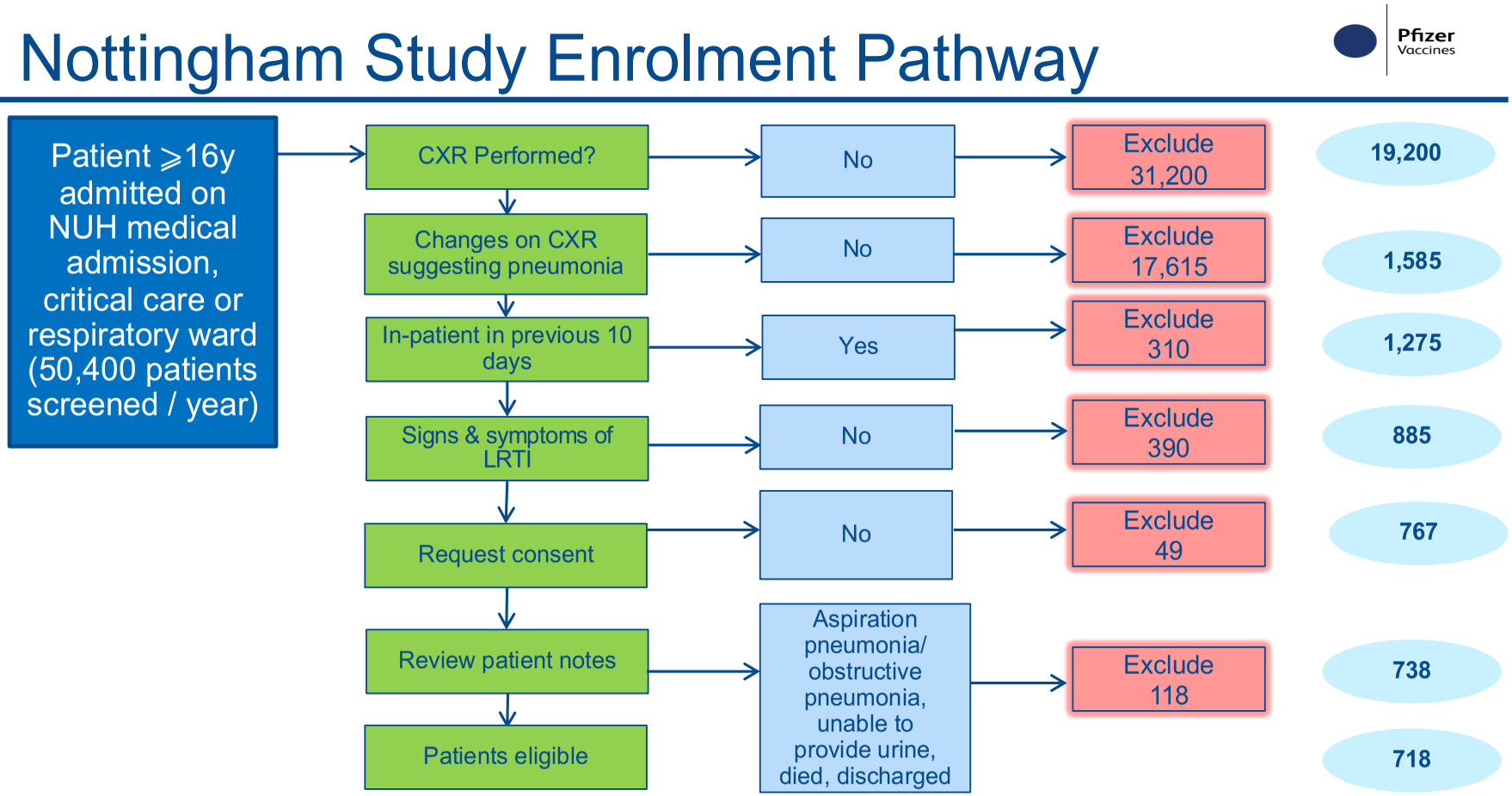
It was necessary to work closely with the Nottingham study team to understand how patients were enrolled into the study to understand how patients might be missed. Findings from this work were presented, with the permission of the study team, as an oral presentation at the BTS Winter Meeting in 2017.[65] Figure 8 is an extract from this presentation showing the patient journey and inclusion / exclusion criteria for the study. (see appendix 2–A2.1 for complete presentation)

Nottingham Study – patient journey



Data from Rodrigo et al ERJ, 2015; 45: 1524

Figure 8: Patient Pathway in the Nottingham Study



In summary, patients in Nottingham were first identified by the study team reviewing the X-Ray list for both study hospitals twice a week. The rationale for this was that a positive chest X-Ray was required for study enrolment, in addition to clinical features of pneumonia as defined by the BTS.[66]

I was able to describe many causes of the discrepancy between the Nottingham study and the HES analysis. These causes included exclusion based on X-Ray status / interpretation, patients who did not provide consent, patients who were unable to / did not provide a urine or patients who presented to the hospital over the weekend. However, the problem remained that the only published prospective data came from the Nottingham study, which was not designed specifically to measure incidence.

The only way to resolve the issue was to set up a new prospective study in the UK, specifically designed to estimate hCAP incidence. A collaboration between Pfizer and the University of Bristol was initiated.[67]

This study was to be known as the AvonCAP study and was established at two large secondary care hospitals in Bristol - North Bristol NHS Trust (NBT), and University Hospitals Bristol NHS Foundation Trust & Weston NHS Foundation Trust (UHBW).[68] At the protocol design stage I shared my learnings with the study team and became an active member of the study team. The next three publications are related to AvonCAP.

4.1.1 Publication 4: A novel approach to estimate the local population denominator to calculate disease incidence for hospital-based health events in England[69]

Research in Context

AvonCAP was designed to measure the incidence of acute lower respiratory tract disease (aLRTD). aLRTD comprises pneumonia, non-pneumonic lower respiratory tract infection, acute bronchitis, exacerbation of underlying respiratory diseases (including asthma and chronic obstructive pulmonary disease) and acute heart failure.[70] For AvonCAP to estimate the incidence of aLRTD and therefore pneumonia, two data points were needed. Firstly, the total number of cases of aLRTD treated in the study hospitals, to provide the numerator. Secondly, the denominator, the total catchment population for the study hospitals, was equally critical but no standard methodology existed to estimate a hospital's denominator for the purpose of incidence studies. The Nottingham study team had estimated their denominator using a population estimate from the Nottingham City Council based on census estimates for the Greater Nottingham area.[54] A problem I identified with this approach was that, due to its geographical location and proximity to other major towns and cities, there were a number of other hospitals within and around the Greater Nottingham area, which could admit Nottingham pneumonia patients.

Map-based methodologies such as the approach used in Nottingham rely on census data within a boundary line drawn on a map. The scope for error is large due to the many non-specific assumptions made. A particular problem with this approach is related to an important principle of the NHS: that patients in England are free to choose where they receive medical care, free of charge at the point of use.[71] Since there is no mandated requirement for selecting a hospital, many factors determine the hospital at which a patient presents with aLRTD. Distance and travel time from home are, of course, major considerations but additional influences exist, such as "availability of public transport, parking availability / costs, traffic *en route* to the hospital, recommendations from General Practitioner, friends, family or personal experience / preference, hospital capacity, reputation, or provision of specialist services."[69] Therefore, simple map-based approaches for estimating hospital local population size cannot be relied upon.

Aim

The aim of this publication was to describe an innovative data-driven methodology I devised to estimate hospital catchment populations to support incidence estimates for AvonCAP.[69]

Methods

Novel methodology:

Data captured in HES were linked with aggregated General Practice (GP) data to determine historical hospital utilisation behaviour of the population registered with each GP practice located within the geographical boundary of the Bristol, North Somerset and South Gloucestershire (BNSSG) Clinical Commissioning Group (CCG). The proportion of patients expected to use study hospitals for treatment of aLRTD was multiplied by the practice population for each GP surgery, stratified by age and combined with each GP in the CCG to provide a local population estimate for the study hospitals.[69] For clarity if:

- E = Calculated catchment population
- SHP = Number of patients at a GP practice hospitalised at a study hospital with aLRTD during 2017–2019
- OL = Overall number of patients at a GP practice hospitalised in England with aLRTD during 2017–2019
- POP = Local GP population
- i = Each individual practice

Then:

$$E = \sum \left(\left(\frac{\mathrm{SHP}_i}{\mathrm{OL}_i} \right) \mathrm{POP}_i \right)$$

Drive-time methodology:

The BNSSG CCG responsible for the Bristol area had suggested using a 20-minute drive-time method to determine the denominator for the AvonCAP study. To evaluate the impact of altering this travel time, a comparison of drive-time estimates was undertaken. Drive-time data according to the Automobile Association were obtained from the CCG for small geographical areas used by the UK census known as Lower Layer Super Output Areas (LSOA) for each study hospital was obtained. UK population data stratified by LSOA were combined with the LSOA drive-time data to estimate the population by drive-time. (see Table 2) A map was also plotted to visually represent these data. (see Figure 9)[69]

Results

96% of patients treated at the study hospitals were registered with any of 82 GP practices within the BNSSG CCG. The expected proportion of patients from GP practices in the CCG varied from 12% to 100%.

Age group	Estimated catchment (Study method)	Total CCG catchment	Estimated based on ⩽20 min drive-time	Estimated based on ⩽25 min drive-time	Estimated based on ⩽30 min drive-time	Estimated based on <40 min drive-time	Estimated based on <60 min drive-time
Five adult age groupings							
18–34	231 342	268 093 (↑16%)	208 924 (↓10%)	238 301 (↑3%)	295 130 (↑28%)	442 590 (↑91%)	870 841 (↑276%)
35–49	184 269	211 568 (↑15%)	130 881 (↓29%)	162 469 (↓12%)	211 452 (↑15%)	337 781 (↑83%)	714 415 (↑288%)
50–64	152 380	178 970 (↑17%)	108 404 (↓29%)	143 508 (↓6%)	196 307 (↑29%)	331 795 (↑118%)	732 702 (↑381%)
65–74	74 245	89 015 (↑20%)	52 954 (↓29%)	73 368 (↓1%)	102 148 (↑38%)	175 757 (↑137%)	391 718 (↑428%)
75–84	45 989	55 720 (↑21%)	33 712 (↓27%)	46 919 (↑2%)	65 244 (↑42%)	111 109 (↑142%)	239 310 (↑420%)
85+	19 229	23 938 (↑24%)	15 280 (↓21%)	20 400 (↑6%)	28 261 (↑47%)	47 108 (↑145%)	99 865 (↑419%)
Two adult age groupings							
18–64	567 991	658 631 (↑16%)	448 209 (↓21%)	544 278 (↓4%)	702 889 (↑24%)	1 112 166 (↑96%)	2 317 958 (↑308%)
⩾65	139 463	168 673 (↑21%)	101 946 (↓27%)	140 687 (↑1%)	195 653 (↑40%)	333 974 (↑139%)	730 893 (↑424%)
Total	707 454	827 304 (↑17%)	550 155 (↓22%)	684 965 (↓3%)	898 542 (↑27%)	1 446 140 (↑104%)	3 048 851 (↑331%)

Table 2: Comparison of study hospital catchment population estimates based on different approaches. Taken from Campling et. al Epidemiol Infect. 2022 Jul 11;150:e150.[69]

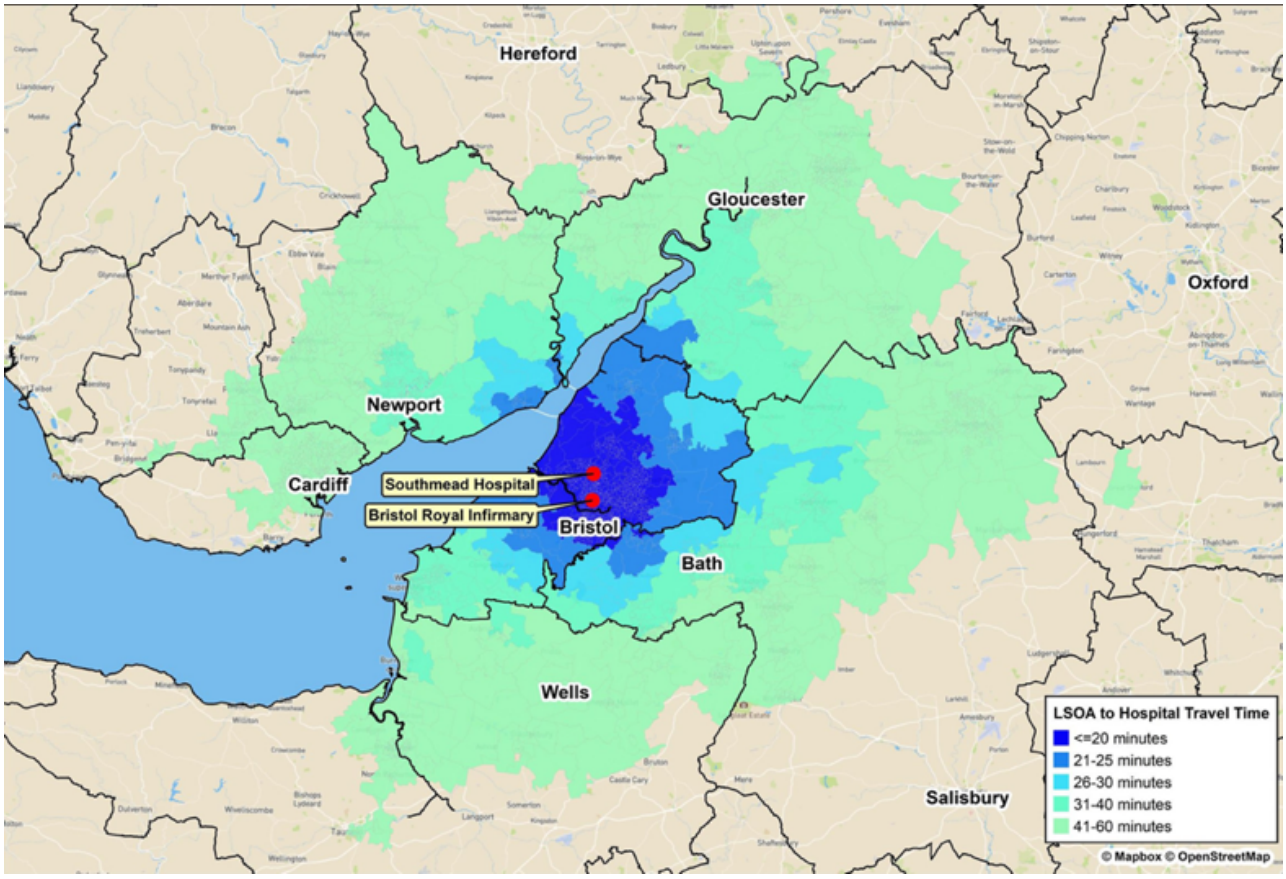


Figure 9: Map showing travel time by car to study hospitals. Taken from Campling et. al Epidemiol Infect. 2022 Jul 11;150:e150.[69]

Strengths & Limitations

This publication described a novel evidence-based method to define the denominator for the AvonCAP incidence study. The strength of this new method is that it is based on historical healthcare-seeking data. This provides an advantage compared with map-based methods,

which rely on multiple assumptions, all of which impact the final estimate. Had the study team used the 20-minute drive-time approach, as recommended by the CCG, it would have under-estimated the catchment population by 22% (age ≥18 years). This would have resulted in an over-estimation of hCAP incidence. Conversely, if a more simplistic map-based approach had been used, this would have over-estimated the denominator by 17% (age ≥18 years), resulting in an under-estimation of hCAP incidence.

There are, however, some limitations to this approach; firstly, it is dependent on adequate data for a particular disease i.e., a critical number of patients hospitalised with the disease being studied is required to provide confidence in the proportions for each GP surgery. This minimum number has not been quantified and was not necessary to establish for aLRTD due to its common presentation. Some practices, however, had small numbers, especially for younger adults, who are less likely to be hospitalised with aLRTD. Three years' worth of data (2017-2019) were combined, not only to minimise the effect of anomalous years, but also to increase the precision of the data.

This method was effective for aLRTD because aLRTD is treated at all acute hospitals i.e., patients generally do not specifically look for hospitals specialising in aLRTD, in the way they might do for other diseases, such as cancer. Challenges would exist with specialist / rare conditions due to low numbers and the potential unpredictability for where patients may travel.

In theory, this method could be used anywhere in England; however, reliability of the data would be negatively impacted in large cities with multiple hospitals and more transient populations.

Contribution to the Literature

To my knowledge this was the first peer-reviewed methodology using a patient-based, proportionate flow model to estimate hospital catchment populations for incidence studies in England. It has provided confidence in the denominator for the AvonCAP study, which has since published several incidence estimates.[68, 70] It also provides a standard for other incidence studies to work towards, ensuring due consideration is given when defining the denominator.

In addition to defining a hospital catchment for incidence estimates this methodology can support planning for healthcare commissioning. The Office for Health Improvement and Disparities (unit within the British Government) now use the same proportionate flow principle for payors within the NHS to determine how much money hospitals are reimbursed for the care

they provide; this is evidenced by their publication in June 2022[72] and helps to validate and provide a consensus view for this methodology.

This publication describes the importance of accurately estimating the denominator as well as the numerator for disease incidence studies. Although healthcare settings and systems differ by country the general principal of the approach described in this paper could be utilised outside of England, in those circumstances where patients have a choice as to which hospital they attend.

Looking forwards, this methodology sets out how, with the benefit of GP level data, it would be possible to facilitate the same principle of proportionate patient flow but apply it for individual comorbidities. This could produce aLRTD incidence estimates using prospective data, stratified by pneumococcal risk groups, which to my knowledge has not been done before.

4.1.2 Publication 5: Incidence of acute lower respiratory tract disease hospitalisations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective methodology[70]

Research in Context

The Nottingham study was the only source of prospective hCAP data in the UK, as previously described. As part of the feasibility process for the AvonCAP study it was critical to understand approximate patient numbers (and disease incidence) for hCAP in the proposed study hospitals. This publication describes the exploratory work conducted to determine the viability of the AvonCAP study.

All-cause aLRTD was studied rather than just pneumonia to provide a deeper insight into hospitalised respiratory illness. A literature search was conducted, which showed a paucity of data reporting aLRTD incidence in UK adults. Prior evidence suggested several factors meant previous estimates were likely underestimates, due to strict definitions required for each disease subset.[70]

Aims

To determine aLRTD incidence at a large secondary care hospital in Bristol using both prospective and retrospective approaches.[70]

Methods

Prospective Review: All adults aged ≥18 years resident within the BNSSG CCG admitted to the acute medical unit at North Bristol NHS Trust (NBT) between 19 Aug 2019 – 9 Sep 2019 were included in a survey of respiratory illness. Retrospective Review: All adult inpatient admissions at NBT recorded between March 2018 - February 2019 with relevant ICD-10 codes, were identified. Incidence Calculation: This was calculated using the prospective and retrospective numerators and the denominator was estimated using the methodology described in Publication 4.[69]

Results

aLRTD incidence estimates made for both the prospective and retrospective reviews, stratified by age and disease subgroup are shown Table 3.

Age	hCAP Incidence (per 100,000) Retrospective Analysis	hCAP Incidence (per 100,000) 21-day Prospective Review
≥18	591	645
18-49	116	99
50-64	315	433
65-74	1,289	1,698
75-84	2,442	2,339
≥85	4,215	4,164

Table 3: hCAP incidence estimates derived from both the retrospective and prospective approaches.[70]

Incidence estimates from each approach were strikingly similar, with incidence increasing with age.

Strengths & Limitations

A strength of this paper was that two different approaches were taken to estimate aLRTD incidence. Previous research had reported hCAP incidence *or* hospitalised lower respiratory tract (LRTI) incidence; this was the first attempt to estimate aLRTD incidence in the UK.

There were several limitations which need to be addressed. Firstly, the prospective component was based on 21-days of data collection, with the case count annualised. The 21-day period was carefully chosen to be representative of a whole year by analysing patient admissions, stratified by month, over the previous year. The period chosen for this analysis, 19th Aug – 9th Sep 2019 had a mean average number of admissions over the year, with a linear increase in admissions starting with a low in March to a peak in February, as shown in Figure 10.

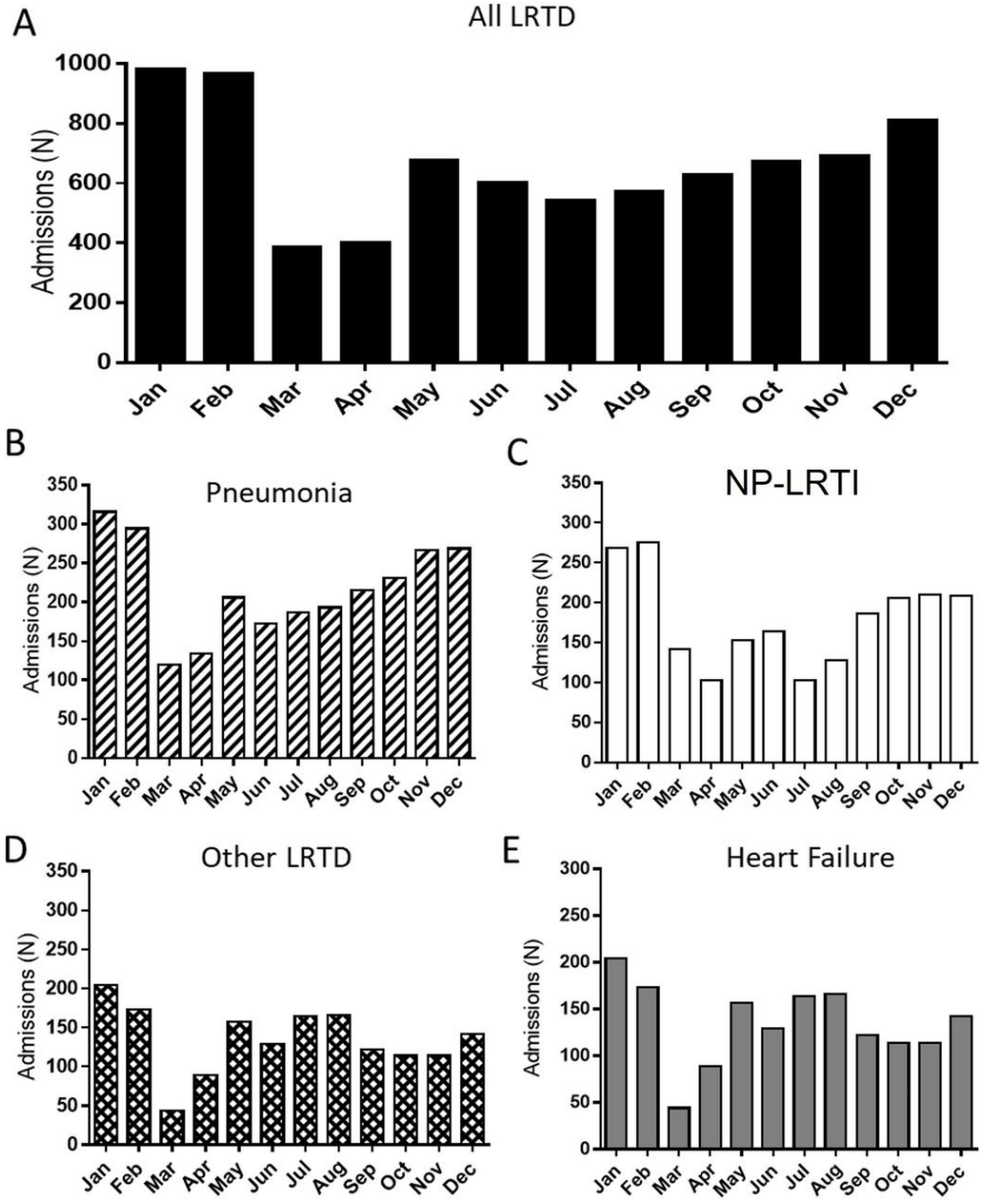


Figure 10: The aLRTD admissions identified by retrospective International Classification of Diseases 10th revision (ICD-10) diagnostic code analysis at North Bristol National Health Service Trust—UK 2018–2019. Monthly number of patients admitted, based on ICD-10 coding analysis, with (A) all acute lower respiratory tract disease (aLRTD) (black bars), (B) pneumonia (slashed bars), (C) non-pneumonic lower respiratory tract infection (NP-LRTI) (white bars), (D) other LRTD (cross-hash bars) and (E) heart failure (grey bars). Taken from Hyams et. al BMJ Open. 2022 Jun 15;12(6).[70]

However, many factors could have affected the number of admissions during this time-period. The retrospective component was based on ICD-10 coding data from a different year to the prospective data. The retrospective dataset would have included HAP because it difficult to distinguish between HAP and hCAP using coded data. This will likely have inflated the incidence in the retrospective, but not the prospective, analysis.

Contribution to the Literature

This paper reported the first hCAP incidence estimates using prospective data (645/100,000 for adults aged ≥18 years) in the UK, other than the Nottingham study which had reported an hCAP incidence of 158/100,000 in 2017/18 for adults aged ≥16 years.[12] The discussion section included a detailed explanation proposing why incidence estimates from Bristol were greater than those reported by the Nottingham study; these, included the process for patient enrolment and the choice of denominator. The output of this study supported the decision to proceed with the AvonCAP study.

Notably, this study was based on data prior to COVID-19, so it provides the only prospective pneumonia incidence estimates in the UK, other than Nottingham, without COVID-19 confounding the data. Furthermore, this was the first paper to estimate hCAP incidence using the novel approach to estimate denominators,[70] which has subsequently been used by the AvonCAP study.[68]

4.1.3 Publication 6: Incidence of community-acquired lower respiratory tract disease in Bristol, UK during the COVID-19 pandemic: A prospective cohort study[68]

Research in Context

This initial publication describing the AvonCAP study builds on Publication 5[70] and was the first large prospective study designed to measure hCAP incidence in the UK. The emergence of the COVID-19 pandemic in 2020 however, provided a unique opportunity to evaluate the impact of SARs-CoV-2 on aLRTD in the UK. The strict non-pharmaceutical interventions, introduced in response to the pandemic, had a profound influence on the management of and output of this study. Furthermore, although earlier studies had reported LRTI incidence, they were based on retrospective data.

Aims

To accurately estimate the incidence of aLRTD and its subsets, stratified by age, during the COVID-19 pandemic, and further stratify by confirmed COVID-19 disease.[1][68]

Methods

All adults aged ≥18 years admitted for acute care to NBT or UHBW with signs or symptoms of respiratory disease between 1st August 2020 - 15th November 2021 were screened for inclusion to the study. Cases infected with SARS-CoV-2 were defined by positive PCR tests conducted at UKHSA laboratories. Denominators were derived using a novel methodology, previously described.[68]

Results

12,557 admissions of aLRTD were recorded and 98% provided consent for the study. 3,178 (26%) of the aLRTD admissions were related to SARS-CoV-2, 6,909 (55%) were due to infection but without evidence of SARS-CoV-2, leaving 2,161 (17%) with no documented infection. Incidence was calculated over a period of 12 months, 1st Aug 2020 – 31st July 2021. aLRTD. Reported hCAP incidence was similar to the retrospective study, with an overall hCAP incidence, not related to SARS-CoV-2, for all adults aged ≥18 years and aged ≥65 years of 449.9/100,000 and 1,667.8/100,000 respectively.[68] This finding of continued high hCAP incidence during this time was unexpected due to the suppression of pneumococcal disease by non-pharmaceutical interventions.

[1] The study was designed prior to the COVID-19 pandemic therefore the COVID-19 aspects were included because of the pandemic.

Strengths & Limitations

This was a large prospective incidence study, meticulously designed to identify all eligible cases coupled with a robust methodology to estimate the denominator.[68] The two hospitals that participated in the study were geographically close to one another, which helped to facilitate a close working relationship and consistency between the sites with some study team members working across both sites.

From the perspective of determining hCAP incidence, a limitation of this study is that it took place during the COVID-19 pandemic, and so was affected by evolving non-pharmaceutical interventions, the use of COVID-19 vaccines, and changes to the dominant SARS-CoV-2 variant(s). The study is still ongoing, with new data due to be reported later this and next year (2024/25), which will provide an opportunity to compare admission rates by month and year to align with the emergence of different variants and other viral infections.[68]

Bristol is broadly representative of the UK population as subsequently evidenced by a retrospective analysis of HES data,[73] but it is not possible to definitively confirm this without other prospective sites in the UK. The demographic of the study population was largely white British (~75%) which is comparable with the UK overall, but not with other regions such as Greater London, West Midlands, or Greater Manchester.[74]

Contribution to the Literature

This study, designed to measure incidence of aLRTD, including hCAP reported an incidence of hCAP significantly greater than the Nottingham study as described above. Incidence estimates from this study were comparable with the previous pilot study which used both a retrospective and prospective approach.

An important contribution of this study - despite confounding by the impact of COVID-19 – was that it showed aLRTD stratified by disease-subset, due to other aetiologies was substantial. In fact, even during the alpha and delta waves of the pandemic, non-SARS-CoV-2 aLRTD accounted for a greater burden of disease than SARs-CoV-2. This is particularly notable given that it was widely reported that influenza and RSV disease incidence decreased dramatically during the pandemic.[75, 76] In addition to the primary infection due to these viruses it is accepted that they trigger secondary infections due to the pneumococcus.[75, 77]

Since the incidence of IPD in adults decreased during the pandemic,[24] the non-SARS-CoV-2 aLRTD would have been largely due to other pathogens, but due to the absence of microbiology / serology, it is only possible to hypothesise the aetiology. According to a study

conducted by UKHSA in adults aged ≥65 years prior to the pandemic, the most common respiratory pathogens causing hospital admissions after the pneumococcus, RSV and influenza were human metapneumovirus (hMPV) and Group A *Streptococcus*.[78] A study conducted between 2016 – 2021 in Israeli children aged ≤5 years showed that there was an almost complete elimination of hMPV elimination but a continuation of rhinovirus and adenovirus during the pandemic.[75] Irrespective of confirming the aetiology, this study showed that other pathogens were able to occupy this niche, which maintained a stable incidence of aLRTD.

4.2 Estimating Pneumonia Incidence - Summary

The AvonCAP feasibility study and AvonCAP study (Publications 5 and 6)[68, 70], expanded the evidence base for hCAP incidence. Decision makers now need to review both the Bristol and Nottingham datasets. Scientifically, AvonCAP incidence estimates, which are supported by the feasibility study, are more robust given that AvonCAP was specifically designed to measure incidence, however, to an extent this is offset given it was conducted during the COVID-19 pandemic. Despite COVID-19, the AvonCAP study demonstrated the considerable hospital burden of other aLRTD. The contribution to the literature of this study is not confined to the UK. Rather, this was the first prospective study of its kind outside of the USA and the UK's healthcare system is, in many respects, more comparable to those of other developed, (particularly developed European) countries than the USA.[79]

5 Risk Groups for Pneumococcal Disease

5.1 Risk Groups - Introduction

Adults in the UK with certain risk factors, defined in the Green Book[1] have been eligible for pneumococcal vaccination (with PPV23) since 2003. A small subset of these adults who are deemed to be at very high risk of pneumococcal disease are also eligible for PCV13.[1] This decision was taken in the absence of cost-effectiveness, but on the basis of expert opinion and clinical need, given the relatively small number of people who would be eligible.[80]

A substantial evidence gap existed when van Hoek & Miller modelled PCV13 use in at-risk adults.[29] Firstly, evidence for PCV13 vaccine efficacy, specifically in these risk groups, had not been demonstrated. Secondly, whilst it was known that adults with certain underlying comorbidities were at an elevated risk of pneumococcal infection compared to the rest of the population; however, this risk had not been quantified.

Van Hoek and colleagues at UKHSA had published a retrospective study to quantify the increased risk for risk groups for IPD in 2012, based on data between April 2002 – March 2009. Patient records from the national IPD surveillance programme, using laboratory-confirmed IPD, were linked with HES data.[81] Next, in 2012, the UKHSA published an economic analysis considering vaccinating adults in risk groups with PCV13.[82] The CAPiTA study, which later described PCV13 efficacy against pneumonia in adults, was still recruiting when this analysis was conducted, therefore the base-case only considered the impact PCV13 could have against preventing IPD. Overall, this analysis concluded that administration of PCV13 would not be a cost-effective intervention for all risk groups. However, it did conclude that vaccinating adults with chronic liver disease would be cost-effective. Furthermore, in a sensitivity analysis that included vaccine efficacy against pneumococcal pneumonia, the authors showed that PCV13 would be cost-effective for all risk groups, as defined in the Green Book. Due to the absence of efficacy evidence for PCV13, a conservative approach was adopted: to wait for results from CAPiTA. The decision to adopt a conservative approach was taken by the authors to ensure the publication met the criteria for *BMJ* guidelines for economic evaluations.[82, 83]

In 2015, after PCV13 efficacy data against VT pneumococcal pneumonia in adults from CAPiTA had been published, JCVI chose not to specifically re-model for risk groups. Instead, a decision was taken to focus on adults aged 65 years exactly, and an assumption was made

that 55% of 65-year-olds were not in a risk group.[29] This was based in part on the study by van Hoek et. al, described in the previous paragraph, which sought to quantify the risk of IPD stratified by underlying comorbidity.[81] The other component of this assumption came from a study in England and Wales evaluating the herd effect of PCV13 against IPD, 4 years after its introduction into the childhood schedule.[45]

The justification to not formally evaluate PCV13 for risk groups was based on an assumption regarding the indirect effect of the vaccine – as described earlier, van Hoek & Miller predicted the paediatric programme would lead to a "near elimination of adult VT pneumococcal disease." JCVI decided to continue to use PPV23 for adult risk groups, despite describing its limited efficacy against IPD and 0% efficacy against pneumococcal pneumonia.[29, 49]

5.1.1 Publication 7: The impact of certain underlying comorbidities on the risk of developing hospitalised pneumonia in England[84]

Research in Context

As described above, the UKHSA had quantified the increased risk of IPD for adults with pneumococcal risk factors but UK data quantifying the risk for pneumococcal pneumonia have not been established. It is generally accepted that comorbid conditions increase the risk of pneumonia. Researchers in Germany and the USA had previously produced all-cause hCAP risk group data, using retrospective ICD-10 coded data[85, 86] but UK-specific data were lacking.

The comparative analysis conducted between the Nottingham study and HES data, described in publication 2, identified that 99% of all hCAP was coded as J18 with 1% coded as J13 (see Table 4 for definition of relevant ICD-10 codes for pneumonia). Given the small proportion of hCAP patients coded as J13, most patients with pneumococcal pneumonia are coded as having unspecified pneumonia, J18.

ICD-10 Code	Description
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to *Streptococcus pneumoniae*
J14	Pneumonia due to *Haemophilus influenzae*
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, unspecified organism

Table 4: Definition of ICD-10 codes used to identify hCAP[87]

I set up a study to close this data gap to quantify the risk for adults with certain underlying comorbidities to be hospitalised with all-cause hCAP.

Aims

To quantify the increased likelihood of an adult in England with an underlying comorbidity to be admitted with hCAP compared with an otherwise healthy adult.[84]

Methods

This retrospective study extracted data from HES[2] between financial years 2012/13-2015/16. Six risk groups of interest were selected based on previously published research by the UKHSA[81], specifically; chronic respiratory disease (CRD), chronic heart disease (CHD), chronic kidney disease (CKD), chronic liver disease (CLD), diabetes mellitus (DM) and bone marrow transplant recipients. The comparator group was taken from healthy individuals admitted for a tooth extraction procedure.[84] Previously established ICD-10 codes for pneumonia used in the study conducted at the UKHSA (J12-J18), were used.[56] Figure 11 shows a schematic describing the study design.

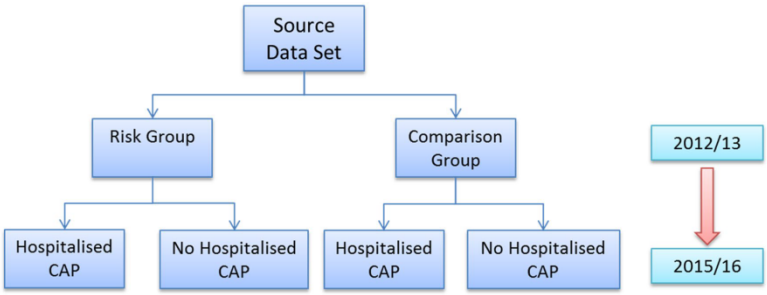


Figure 11: Study design. Taken from Campling et. al. Pneumonia (Nathan). 2019 Oct 11;11:4.[84]

Results

In total, 3,078,623 patient records were analysed, showing a significant increase in the likelihood of hCAP within a three-year period in those with any one of the defined comorbidities, ranging from 1.18 (CI 1.13, 1.23) for DM to 5.48 (CI: 5.28, 5.70) for CRD.[84]

Strengths & Limitations

This was the first time the risk of hCAP for adults with underlying comorbidities had been quantified for an English population. The study was based on a national, real-world dataset making it powerful and representative. It relied on hospital patients, making it challenging to find a perfect comparator (healthy) group.

[2] Data extraction, handling and analysis of raw data was conducted by HealthiQ Ltd under a license held with NHS Digital.

The structured and coded data used have inherent limitations: 1) all-cause pneumonia was analysed rather than pneumococcal pneumonia due to low usage of J13 and the propensity to use the non-specific code J18 instead, 2) the inability to confidently distinguish between hCAP and HAP, 3) the potential inaccuracy of coding due to numerous factors e.g., lack of diagnostic tests and – anecdotally - it is favourable financially for a hospital to code pneumonia vs other LRTIs.

Finally, because the study used all-cause CAP rather than pneumococcal CAP, an assumption was made but not tested: that the proportion of pneumococcal CAP recorded by the Nottingham study was applicable to all hCAP patients identified.

Contribution to the Literature

This publication quantified the increased likelihood adults with CRD, CHD, CKD, CLD, DM and bone marrow transplant recipients of hospitalisation with CAP in England. People with prior CRD were approximately five-times more likely to develop pneumococcal pneumonia than otherwise healthy people. Prior to this publication, evidence was only available from other countries, with different healthcare systems.

This study demonstrated the benefits of targeted measures to prevent pneumonia such as effectively managing underlying comorbidities, quitting smoking and vaccination (flu, pneumococcal and potentially SARS-CoV-2).[84] It therefore provides a rationale for the need to specifically consider the benefit of pneumococcal vaccines in adult risk groups, in addition to older adults.

The findings of this study were used to build the base case for two economic analyses for PCV20.[88, 89] In addition, a sensitivity analysis was conducted additionally considered sequelae further to hCAP.[88, 89]

This study provides a baseline datapoint for risk groups because it was conducted prior to the SARS-CoV-2 pandemic. It shone a light on vulnerable populations, a field that has since attracted much more attention. Leading this study resulted in me acquiring an in-depth knowledge of HES data, which I drew upon in subsequent studies. According to PubMed as of November 2024 this paper has been cited 12 times.

5.1.2 Publication 8: Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England[90]

Research in Context

Traditionally, pneumonia has been regarded as an acute disease, however by 2018 reports were emerging in the literature challenging this paradigm,[91, 92] suggesting it could also be viewed as a chronic disease with different phases.[93] Although the initial infectious insult is acute, patients can take up to six months to recover from the well-characterised symptoms of pneumonia.[94] As a study team, our hypothesis was that a patient who suffers an episode of pneumonia experiences a longer-term degradation in health along with a reduction in long-term survival.

The health economic models built in 2015 to evaluate PCV13, had assumed pneumonia as an acute illness. Providing the patient survived a hospitalisation for pneumonia, they were assumed to return to the healthy pool of individuals.[29] A broad objective of this study was to establish whether that aspect of the model was appropriate.[90]

Aims

This study set out to quantify healthcare resource utilisation, hospital costs and in-hospital mortality for patients with defined underlying comorbidities who were hospitalised with CAP compared to matched controls, not hospitalised with CAP.[63]

Methods

This retrospective cohort study used data extracted from the HES database[3] between financial years 2012/13-2015/16 – the study design is shown in figure 12. The same six groups of patients with defined comorbidities from Publication 7 were included (again identified by ICD-10 codes).[63] Figure 12 describes the study design.

[3] Data extraction, handling and analysis of raw data was conducted by HealthiQ Ltd under a license held with NHS Digital.

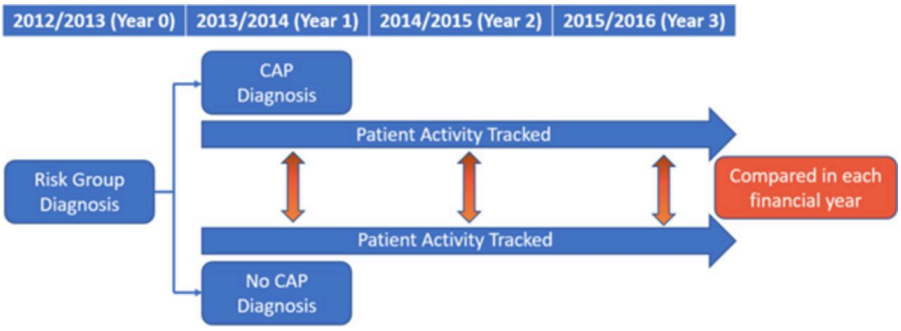


Figure 12: Study design. Taken from James Campling et al. BMJ Open Resp Res 2020;7:e000703[90]

Results

After adjusting for confounders, a significant increase was found for, in-hospital mortality, healthcare utilisation over the subsequent three years and hospital costs, in patients with hCAP. An increase in mortality of approximately four-fold was observed. This study provided evidence that adults with the comorbidities studied do not quickly return to their previous health status after an episode of hCAP.[90]

Strengths & Limitations

Hospital data from every NHS hospital in England over a four-year period were used; it therefore reflects real-world outcomes of adults with underlying comorbidities diagnosed with hCAP. To help overcome the vast number of variables that exist with this type of study, propensity score matching was used to match patients in the study and comparator groups. This was made possible due to the richness of data available.

This study relied entirely on coded data, which could open it up to criticism and questions around coding accuracy, as described previously for Publication 7 - i.e., use of J18 vs pathogen-specific pneumonia, and the challenge of excluding HAP.

The contribution an episode of pneumonia has on accelerating frailty, which, in turn, slows recovery is unclear. Furthermore, it is important to establish whether an episode of hCAP causes a decline in health status or if hCAP acts as a marker for a deteriorating health. Unfortunately, frailty measures are not captured within HES, so an alternative study design must be found.

Finally, from the perspective of the reader this manuscript was difficult to follow due to multiple concepts and components of the design. This was further compounded by investigating the prognosis of six risk groups simultaneously. If I were to repeat this, I would

focus on one key chronic comorbidity (CRD or CHD) to communicate the study and make the rest of the results available as supplementary data and / or report a multivariate analysis.

Contribution to the Literature

This study demonstrated that patients with underlying comorbidities, who are hospitalised with CAP are left with persistent sequelae, causing increased healthcare utilisation and increased healthcare costs. Crucially, in the population studied, we showed hCAP cases has an almost five-fold or higher increase of mortality within three years of presentation.

The benefits of targeted measures to prevent pneumonia, as described in publication 7, are also supported by this publication.

5.1.3 Publication 9: A review of evidence for pneumococcal vaccination in adults at increased risk of pneumococcal disease: risk group definitions and optimization of vaccination coverage in the United Kingdom[14]

Research in Context

The COVID-19 pandemic shone a light on some of the consequences of underlying comorbidities on an individual's health outcomes if they are diagnosed with a respiratory infection, the most notable of which was the increased likelihood of death. Several lessons were learnt from COVID-19 regarding how to operationalise identifying and administering vaccines to vulnerable people. I wanted to apply some of these learnings to pneumococcal disease.

Aims

The aim of this review was to use published literature to examine all relevant UK evidence for individuals defined as being at-risk of pneumococcal disease and to draw on any opportunities to implement lessons learnt from the COVID-19 pandemic to optimise vaccination.[14]

Methods

A targeted literature search was conducted using PubMed to identify publications the authors were not aware of while putting this review together.[14]

Results

This review described and discussed the UK's pneumococcal recommendations for risk groups and suggested they should be updated based on recent data. Vaccine uptake in risk groups was found to be sub-optimal. To address this, within the expert opinion section, the authors made several recommendations for the pneumococcal programme for risk groups, including relevant learnings from the COVID-19 pandemic.[14]

Strengths & Limitations

A strength of this review is that it was conducted by authors who are expert in their respective fields. All known risk groups were assessed and reviewed, providing a comprehensive analysis.

The available evidence for pneumococcal risk groups in the UK is not as robust as for older adults and is stronger for some disease areas than others. There was little scientific discussion describing the rationale or mechanism of action of pneumococcal disease for people with underlying comorbidities. Initially, there was a plan to incorporate disease pathophysiology, to

describe why people with comorbidities are at increased risk of pneumococcal disease, and what to define what contributes to the spectrum of risk. Unfortunately, time constraints meant this was not possible. Finally, as an author group, we were missing one of the most important groups responsible for immunisation, namely nurse immunisers. In hindsight this was remiss of us as they would have provided an invaluable practical perspective.

Contribution to the Literature

This review provided a detailed discussion with regards to adult pneumococcal vaccination in the UK. It highlighted the need for an update to the existing pneumococcal risk groups described in the Green Book, and provided suggestions to optimise the implementation of the immunisation programme.

This review provides evidence that could be referred to by UKHSA and policy makers in the future. There is also relevance for other countries, as one aspect we highlighted was the inconsistency in guidelines for at-risk populations around the world.

The issue of defining pneumococcal risk groups is currently under debate in the UK and as described in this article, many differences still exist between countries due to contrasting evidence. In the US, the ACIP committee have recently recommended that pneumococcal vaccination be offered to all adults aged 50 years and older.[95] Building on this review, and using a similar format, I have recently published a broader review article that describes risk group recommendations for pneumococcal, influenza, COVID-19 and RSV vaccines.[96]

5.2 Risk Groups for Pneumococcal Disease - Summary

The publications described in this section provide evidence regarding the disproportionate impact comorbid adults experience when hospitalised with pneumonia. The prediction that the JCVI made - that the herd effect would lead to the near elimination of VT pneumococcal disease, based on IPD data up to 2012/13, was shown to be incorrect.[24] It has subsequently been shown that VT pneumococcal disease actually started to increase among adults (including PCV13 VT serotypes, especially serotype 3) from 2013/14.[24] Furthermore, vaccine efficacy for PCV13 for adults in risk groups has since been described.[97]

Data quantifying the additional likelihood for risk groups to be hospitalised with CAP, as well as data showing the impact of being hospitalised with CAP for adults in the same risk groups, suggests it is now necessary to rethink the paradigm that pneumonia is solely an acute disease without sequelae. Scientifically, it is important to consider risk groups differently from the rest of the population in health economic models both in terms of their risk of pneumonia and subsequent sequelae.

6 Pneumonia Hospitalisation Costs

6.1 Publication 10: Hospitalization costs of adult community-acquired pneumonia in England [98]

Research in Context

The CEA published by van Hoek & Miller had assumed the cost of an admission for hCAP in 2015 was £715.[29] After carefully reviewing the evidence for this, it transpired that this was based on the lowest tariff available for an adult aged ≥18 years admitted for pneumonia, for an assumed period of 4 days with no complications or comorbidities.[98] This does not reflect the 'average' cost of treating pneumonia.

In 2017 I worked with a health economics colleague in the Health & Value team to estimate the cost of hCAP using HES data. This analysis reported a mean cost of £3,256 for all adults aged ≥65 years (including those with and without complications).[20]

I decided to conduct a formal study, using contemporary data, aiming to publish it the year before the next formal review of the adult pneumococcal programme was due to take place, i.e., shortly after PCV20 was licensed. The HES and Critical Care databases owned by NHS Digital are used by commissioners to reimburse hospitals for care delivered, making them appropriate sources for estimating hospital costs.

Aims

To estimate average hospital costs for patients admitted with hCAP.[98]

Methods

Data were extracted from the HES and Critical Care databases in 2019 for all adults hospitalised with CAP using ICD-10 codes J12-J18. Mean and median costs were estimated by matching with NHS tariff data, stratified by age, underlying comorbidity, critical care costs and aetiology.[98]

Results

Data from 187,251 patients across England supported this analysis, which cumulatively reported an annual (pre-COVID-19) bill to the NHS for treating hCAP of approximately £731 million. The mean cost/admission was estimated to be £3,904 which dropped to £3,402 when excluding critical care costs, which arose for 4.4% of admissions. Critical care costs were estimated to be £11,654 / episode, and there was variation in costs by co-morbidity and age.[98]

Strengths & Limitations

This study used the same hospital data used by commissioners to pay for hospital care in England over a 1-year period. The period studied was pre-COVID-19, and therefore reflective of costs in a non-pandemic era. The data are already over four years old but, due to the methodology used, it is relatively straightforward to escalate the costs with inflation according to the NHS tariff to provide up-to-date estimates. A major strength of this work is that I was able to describe the cause of the discrepancy between this study and costs previously used by van Hoek & Miller.[98] This was due to a number of factors including the complexity of patients included in the calculation along with a technical anomaly in how NHS reference costs had previously been reported.[98]

Limitations of this study largely stem from it using coded hospital data. All cases of pneumonia were included, even for those patients who had multiple admissions. These only accounted for a small proportion of patients, but likely were more complex, and therefore expensive cases. They were included so the total cost of CAP to the NHS / year could be described. These patients would have had a negligible impact on the mean average cost. Finally, cost estimates could not be stratified by pneumonia severity as these measures are not recorded in HES.[98]

Contribution to the Literature

This study was based on HES data, which are used for hospital reimbursement. The average cost of hCAP in England was £3,904, which is nearly 5.5 times greater than the cost assumed by van Hoek & Miller. This publication provides costs for hCAP stratified by age, comorbidity, causal pathogen, and critical care costs. It includes a clear description on how these costs were calculated and, as described above, why the estimate used by van Hoek & Miller was inaccurate. The estimates reported can easily be inflated to current day / future reference costs as needed. In addition to a range of researchers and policy makers in the UK (including the JCVI), this work has utility for commissioners and hospital executives to effectively allocate resource to manage hCAP patients. Finally, this paper provides a template model for how to calculate hospital costs for other diseases.

7 Review of the Literature

7.1 Publication 11: A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK[44]

Research in Context

The consensus view regarding the parameters used for health economic modelling for PCVs in adults was predicted upon van Hoek and Miller.[49] The rationale for this review was to formally document the evidence described, encompassed within this critical analysis, along with other emerging data. Writing this review provided an opportunity to explore and consolidate the evidence for modelling parameters.

Aims

To review contemporary data for pneumococcal disease and vaccines, which would form critical input parameters in modelling to assess the cost-effectiveness of higher-valency pneumococcal conjugate vaccines for UK adults.[44]

Methods

This review was largely based on literature familiar to the authors. A literature search was conducted using PubMed to identify further publications that the authors were not aware of.

Results

Data were critically appraised for invasive and non-invasive pneumococcal disease. The review examined hCAP incidence and described methodological shortcomings with the Nottingham study. There is a discussion regarding hospitalisation costs for pneumonia which highlighted a government guidance document for hospital tariffs. An in-depth discussion examined how although IPD incidence had substantially reduced during the COVID-19 pandemic, early data were indicating that the pneumococcal serotype distributions remained unchanged.

A large section of the review was dedicated to the topic of vaccine efficacy, effectiveness, and impact of the different vaccines. PCV13 had RCT-grade evidence for preventing pneumococcal CAP and IPD, however, PCV20 was an evolution of PCV13 with only immunogenicity data used to gain a license. PPV23 which was licensed in 1983, had a wealth of effectiveness data but these were inconsistent.[44]

Strengths & Limitations

This review sought to package together, in one place, all the data and evidence for assessing high valency PCVs (i.e., >13 serotypes) in the UK. A significant variable influencing pneumococcal epidemiology is the impact of the paediatric programme. Although this was acknowledged, a dedicated section on this was excluded for brevity. Another limitation of this review is that it largely used data that were published before the COVID-19 pandemic.

Contribution to the Literature

This review found that overall, the UK had rich and robust evidence to help make informed public health decisions, however, it flagged areas where data gaps still existed such as hCAP incidence and up-to-date hospitalised pneumonia costs. To an extent, these data gaps have since been addressed as described in publications 5, 6 and 9.

This publication provides a useful reference point by pulling together all the relevant data and points of consideration needed for making decisions on adult pneumococcal vaccines in the UK. It has been referenced by the Public Health Agency in Dublin in a manuscript they recently published which considered whether higher-valency PCVs should be used in Irish adults.[99]

A letter was written[100] to the journal editor regarding this review from the US-based Global Research and UK Medical Affairs groups at Merck & Co., who were unhappy with some of the language used to describe the effectiveness and impact of PPV23.[100] The wording for these sections however, had been chosen very carefully and only referred back to statements made by relevant UK institutions.[44]

8 Economic Analyses

In the UK the JCVI's threshold for cost-effectiveness for a vaccine is £20,000-£30,000 / Quality Adjusted Life Year (QALY). The JCVI are only able to provide positive advice for a vaccine that meets these criteria for being cost-effective.[47] If they provide advice to the Secretary of State for Health regarding a cost-effective vaccine, the health minister is legally bound to introduce the programme.[47]

The 2012 CEA published by Rozenbaum and colleagues stated that, in addition to CEAs they were also required to provide a Budget Impact Assessment (BIA) detailing the financial impact of new vaccine programme for HM Treasury.[82]

This section includes both a CEA and a BIA for PCV20, to which I contributed, based on the evidence described throughout this critical analysis.

8.1 Publication 12: Cost-effectiveness of using a 20-valent pneumococcal conjugate vaccine to directly protect adults in England at elevated risk of pneumococcal disease [88]

Research in Context

PCV20 was licensed for use in adults in the USA in 2021[101] and a UK license was granted in 2023.[50] Vaccines need to be shown to be cost-effective for the JCVI to advise the UK Government to recommend their use.[47] A cost-effectiveness analysis (CEA) for a higher-valent (>PCV13) pneumococcal conjugate vaccine in the UK had not been published.

Aims

To determine whether PCV20 vaccination would be a cost-effective intervention in all UK adults aged 65-99, and adults belonging to defined risk groups aged 18-64.[88]

Methods

A new bespoke deterministic model with a Markov-type process was built to assess the cost-effectiveness of PCV20 in all adults aged ≥65 years and for adults in a clinical risk group aged 18-64 years. Numerous scenarios were modelled i.e., PCV20 alone, PCV20 ⇒ PPV23, PPV23 alone, PPV23 ⇒ PPV23, PCV15 ⇒ PPV23. Input parameters were based on data described throughout this critical analysis.[88]

Results

PCV20 alone was found to be dominant, meaning it was the optimal schedule to employ. Further to this, not only did PCV20 meet the criteria of being cost-effective (<£20,000/QALY) it was shown to be cost-saving in terms of the base case and cost-effective in all sensitivity analyses.[88] (see Figure 13)

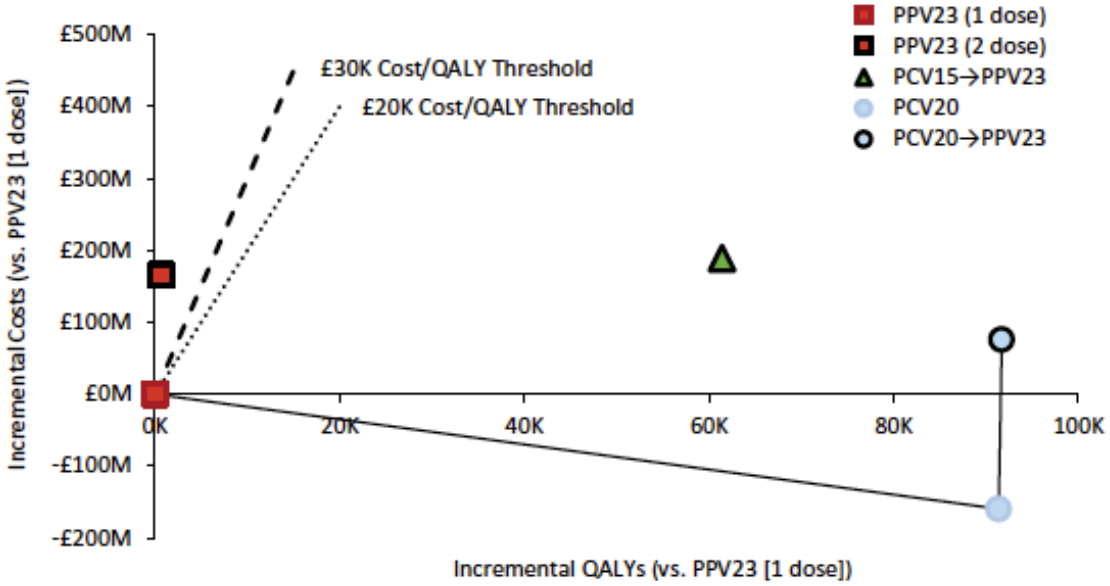


Figure 13: "Cost-effectiveness plane for alternative vaccination strategies among moderate- and high-risk adults aged 18–64 years and all adults aged 65–99 years in England (N = 15,635,909)." Taken from Mendes et. al, Expert Rev Pharmacoecon Outcomes Res. 2022 Dec;22(8):1285-1295.[88]

Strengths & Limitations

A strength of this CEA is that it was derived from robust parameters which had been tested and challenged over the previous 7 years, and the rationale for which was published. However, as with all mathematical modelling, although the parameters were based on contemporary, robust data, input parameters are themselves assumptions, any one of which could be wrong or could change. Probably the most important assumption made here was with respect to pneumococcal epidemiology, which is dynamic. Multiple pressures on the pneumococcus exist, which is currently evolving after the COVID-19 pandemic and with respect to the reduced 1+1 infant schedule. Finally, this model assumed vaccine uptake of PCV20 to be on a par with PPV23; however, practically, this will take time to achieve.

Contribution to the Literature

This was the first publication of a CEA for PCV20 in the UK. Subsequent CEAs will discuss parameter choice and compare results with this paper. In June 2021, Danelian and colleagues published the first of two CEAs commissioned by the JCVI. They concluded that “PCV20 was likely to be cost-effective” and “likely to avert more cases of pneumococcal disease in elderly adults in England than the current PPV23 vaccine.”[102]

Furthermore, UK CEAs are widely used and referred to by other countries – according to a PubMed search in November 2024 this paper has already been referenced 14 times, including CEAs for PCV20 in Belgium, Germany, Spain, Greece, The Netherlands, Norway, Japan, South Korea and Argentina.[103-111]

8.2 Publication 13: Public health and budgetary impact of 20-valent pneumococcal conjugate vaccine for adults in England [89]

Research in Context

A Budget Impact Analysis (BIA) is useful for payors to evaluate the budgetary implication of introducing a vaccine programme. A BIA calculates the total cost to the payor for acquiring and administering a vaccine and subtracts savings achieved from the public health benefit of the vaccine e.g., in context, any reduction in number of patients admitted to hospital with pneumonia.[89] PCV20 had been shown to be cost-effective,[88] therefore a BIA was conducted.

The CEA PCV20 for all at-risk adults included everyone aged ≥65 years and adults aged 18-64 with certain comorbidities.[88] Conscious of the potentially significant impact to the budget that this could have, patients who had already received PPV23 were excluded from the model i.e., PPV23 followed by PCV20.

Aims

To describe the net health budget impact of introducing PCV20 for at-risk adults to the UK national immunisation programme.[89]

Methods

A deterministic model with a Markov-type process was employed to establish the five-year costs associated with several pneumococcal vaccination strategies for at-risk adults in England.[89]

Results

After five years the total vaccination costs of replacing PPV23 with PCV20 would be £107.2m. It was estimated that 785 cases of IPD, 11,751 cases of hCAP, and 1,414 pneumococcal-related deaths would be prevented, and the intervention would reduce medical care costs by £48.5m, therefore giving a net cost of £58.7m. The budgetary impact was greatest after year one and declined each subsequent year. After year five, the programme became cost saving, with the cost of vaccinating the population less than the money saved through lower medical care costs.[89]

Strengths & Limitations

Like the CEA model, this model was based on carefully chosen input parameters described throughout this critical analysis. This BIA provided a conservative estimate of the budgetary impact of a PCV20 programme in at-risk adults. It was conservative, and therefore likely reported a greater budget impact (i.e., higher cost to government), because it included an assumed herd effect from a future paediatric programme. This herd effect would reduce the burden of VT pneumococcal disease in at-risk adults, thereby reducing the benefit of directly vaccinating adults.[89]

There were however limitations with this work. For simplicity, the model treats the NHS as only having one pot of money; in practice, however, NHS budgets are more complex. Vaccine acquisition and vaccine administration costs come out of one budget pot, whereas savings made by the NHS would be scattered across hospitals and commissioning organisations in England.

Contribution to the Literature

This publication concluded that if a PCV20 programme was introduced for at-risk adults there would be an initial cost to the payor. However, this cost would reduce each year. By the fifth year after introduction this cost would transform to a saving and for each subsequent year there would be a net saving to the payor. Not only is this an informative finding for the UK Government, but it will also likely be of interest to payors in other similar countries.

According to a PubMed search in November 2024 this paper had been referenced three times.

8.3 Economic Analyses – Summary

The evidence described throughout this critical analysis helped close the data gaps for modelling adult pneumococcal vaccines in the UK. Both economic models concluded that PCV20 would be a cost-saving intervention in England and, by inference the whole UK, for at-risk adults. Shortly after publication of these two models JCVI provided advice that PCV20 could be used in at-risk adults in the UK.

10 Discussion

This research aimed to close data gaps that existed when the JCVI reviewed PCV13 in 2015, specifically by quantifying the burden of pneumococcal disease, providing evidence for risk groups, and determining hospital costs for pneumonia. The 13 publications described herein are evidence that contemporary data were generated and now contribute to the scientific literature, with public health impact.

The objective of this research was to establish a more robust and comprehensive evidence base, increasing the likelihood that separate, independent health economic modelling studies of PCV20 are more likely to achieve similar conclusions. Publication 12 described a health economic model that concluded PCV20 was: (i) cost-saving in the base case and (ii) cost-effective, as a minimum, for all sensitivity analyses considered.[88] In June 2024 a separate model published by Danelian et al. also concluded that PCV20 was likely to be cost-effective in at-risk adults.[102] Furthermore, the JCVI have provided advice that PCV20 should be made available for at-risk adults.[112]

It is reassuring, from a scientific perspective that the structure of the CEA models developed to assess PCV13 in 2015 by both the JCVI and Pfizer were similar. The authors of a publication written by UKHSA stated that where robust evidence did not exist, they chose to select conservative parameters for modelling. They stated this was due to guidance provided by the BMJ for economic modelling publications, and given the potentially large financial implication for HM Treasury. [83] Conversely, in the same circumstance, Pfizer, who have a commercial interest in the outcome of the model, selected values based on data that met the threshold of being reasonable. In both cases, values for areas of ambiguity were determined more by opinion and less by evidence. Given the large degree of uncertainty that existed, it is not scientifically appropriate, to be overly critical of either the JCVI or Pfizer for their choice of parameters at the time. Furthermore, it is encouraging that - with the benefit of a more robust evidence base - both Pfizer and JCVI concluded that PCV20 is cost-effective for UK adults.[88, 112] The Danelian et al. publication refers to a number of publications described within this body of research and discusses some of the parameter choices in the context of publication 12.[102]

When viewed together, a strength of the publications discussed in this analysis is that they all contribute towards the evidence base, addressing the specific question of whether PCV20 is cost-effective for at-risk adults in the UK. The two review papers (Publications 9 and 11) comprise in-depth analyses, providing a comprehensive perspective of their respective

subjects. The rationale for publishing these review papers was to challenge and discuss the evidence, contributing towards forming a scientific consensus in areas of previous disagreement.

A strength of all 13 publications, viewed collectively, is the broad mix of genres encompassed, ranging from original primary research, using both prospective and retrospective data, to opinion pieces and targeted literature reviews. A weakness of my research is that only a small proportion was based on original research using prospective data. Although retrospective data usually are not regarded as highly as prospective data, they are still valuable, available rapidly and for a fraction of the resource / budget needed for prospective data.

PCV20 is now licensed and the vaccine is available in the UK privately,[113] but it is not yet available on the NHS due to the Government tendering processes. Assuming PCV20 is used this year (2024) or next, the current advice states that it should be used largely for pneumococcal vaccine-naïve adults. The only exception being for "individuals with asplenia, asplenic dysfunction or those with chronic renal disease," for whom five-yearly vaccination is already recommend.[1]

The JCVI minutes said: *"The Committee agreed that either PCV20 or PPV23 could be used for the adult pneumococcal programme. The Committee indicated a preference for higher valency vaccines (PCV20 and PPV23) due to the larger health benefit."* [Text advising against using PCV15.] *"The Committee also indicated that PCV20 was likely to prevent more disease than PPV23 and waning of immunity may occur at a slower rate."*

The routine use of repeating PPV23 vaccination is restricted in the UK to very specific risk groups due to the risk of hyporesponsivenes, a phenomenon that has also been observed with meningococcal polysaccharide vaccines.[1, 114] Hyporesponsivenes is characterised as the inability of polysaccharide vaccines to elicit a booster response, thereby resulting in a second dose of vaccine achieving only a similar or inferior antibody concentration compared with the primary dose.[114, 115] In adults, PPV23 induces a T-cell independent response and does not produce new memory B cells; moreover, PPV23 depletes existing, circulating memory B cells.[114] By contrast, PCVs, including PCV20, produce a T-cell dependent response, and there is evidence of an anamnestic response further to subsequent exposure to the antigen in adults.[50, 114, 115] Accordingly, more research is needed to demonstrate the need for, and benefit of, boosting in adults.

A related and important consideration, given that many older people in the UK have already been vaccinated with PPV23, is the phenomenon known as the Original Antigenic Sin. This is where, through two different vaccines against the same pathogen, the immune system is presented with similar but slightly different antigens, resulting in an inferior response elicited to the second antigen.[116] However, evidence suggests that Original Antigenic Sin does not impair the immune response to PCVs when given in sequence after PPV23.[117] Presumably, this is due to the conserved reference antigens used in each vaccine,[118] despite the difference in vaccine technology.

In circumstances where both a conjugate vaccine and PPV23 are recommended, it has been shown to be immunologically advantageous for the conjugate vaccine to be administered first; in these circumstances, PPV23 boosts the T-cell dependent response previously elicited by the PCV.[119] This is reflected in guidance in the Green Book and the SPC for PCV20.[1, 50]

Adults and children who were vaccinated with PPV23 up to 20 years ago are currently not eligible for PCV20 or future PCVs for the rest of their life. This issue must be reviewed to ensure the growing number of vulnerable adults can benefit from a PCV, especially when considering UKHSA's conclusions that the protection offered against IPD by PPV23 wanes within 2 years.[30, 120] This appears to be under consideration currently by the JCVI pneumococcal sub-committee. In the minutes of their meeting in February 2024 it was stated that re-vaccination for those in clinical risk groups should be considered and the cost-effectiveness of this should be analysed.[121]

The JCVI described a potentially dynamic environment over the coming years, with the likely approval of more high-valency PCVs.[112] This contrasts with the existing adult pneumococcal programme, which has been largely unchanged for ~20 years. There is a possibility that other higher-valency vaccines (PCV21 – currently in development by Merk & Co.)[122] will be approved later this year or next. Unlike the currently licensed PCVs which iteratively contained common, shared serotypes, PCV21 includes a new mixture of serotypes. PCV21 has 10 serotypes in common with PCV20 but the other 11 were selected to provide the broadest coverage possible.[122] Decisions regarding how best to deploy this growing number of vaccines will become more complex due to the disruption they will cause to pneumococcal epidemiology.

Interestingly, the JCVI June 2023 minutes also stated: *"The potential impact of an infant programme with a higher valency PCV would have to be incorporated into future discussions*

on the adult vaccination programme." The Pfizer cost-effectiveness model had, however, incorporated an assumption for an infant programme (with the caveat that at the time PCV20 was not licensed in the UK for paediatric use) three years after introducing the adult programme, with herd effect benefits starting after one year. This effect reduces the impact that direct PCV20 vaccination of adults would have in the model. If the adult programme commenced at the same time or sooner, it would have less of an impact.

There will likely be changes to the paediatric pneumococcal programme over the coming year(s), which will influence how adult vaccines are assessed in the future.[112] There are currently numerous unknowns regarding the potential herd effect of PCV20 given its lower immunogenicity elicited compared to PCV13 for the shared VT serotypes[123] i.e., how strong this response would be, and how many, and which serotypes it will protect against. Given the UK rollout delay, evidence may become available from other countries already using PCV20 e.g., the USA. In the meantime, modellers have already begun to consider future paediatric programmes. A recently published paper by Choi et al explored replacing PCV13 with either PCV15 or PCV20 concluded PCV20 would lead to a significant reduction in overall IPD.[124] Due to assumptions based on lower immunogenicity, serotype capsular switching and the rise of other non-PCV15 vaccine serotypes, they found that PCV15 would lead to an overall increase in disease compared to PCV13.[23]

The herd effect elicited by PCV13 for serotype 3 – now one of the most prevalent serotypes in adults – can, at best, be described as blunted and has been described by some groups as not being present at all.[24] Serotype 3 is unlike other PCV13 serotypes, in having a low case to carrier ratio and an ability to use its especially thick capsule to escape host-immunity.[125] According to the most contemporary published data, serotype 8 is the greatest cause of adult hCAP in the UK[126] and, crucially, the physical properties of serotype 8, regarding capsule thickness, closely resemble those of ST3.[14] Therefore it is possible that any herd effect PCV20 provides will not be as robust for ST8 as for other serotypes. This possibility, combined with the predicted limited herd effect PCV20 will have against serotype 3, strengthens the need for direct vaccination for at-risk adults.

Informally, at various scientific conferences, it has been suggested that for the paediatric programme, initially PCV20 could be introduced in a 2+1 schedule before switching to 1+1, due to the current lack of PCV20 1+1 immunogenicity data. Another suggestion is that PCV20 could be introduced for children in a 1+1 schedule, but with a catch-up programme for 1–4-year-olds to rapidly induce a herd effect. Evidence needed to support either of these approaches

would depend on new immunogenicity or vaccine efficacy data. Established corelates of direct protection against IPD in children, which are based on aggregated IgG concentrations measured by ELISA to PCV7 serotypes of 0.35 μg/mL, are now being challenged.[127] This is due to the antibody variability between serotypes and the observed reduction of immunogenicity in PCVs as the number of included serotypes increases.[127, 128] These corelates, which were derived from 3 clinical trials conducted across diverse populations, were used as evidence to support the 1+1 schedule in the UK.[52] The increasing complexity of interpreting immunogenicity data is further exacerbated when trying to predict the antibody titres required to elicit a herd effect, for which no base-line correlate exits.[52] Alternative approaches are therefore needed to act as surrogates for prediction of protection.

An experimental human challenge model has been developed, with an acceptable safety profile, that imitates "natural exposure" to the pneumococcus by inoculating healthy volunteers intranasally with controlled doses of the bacteria, thus facilitating evaluation of immune system responses.[125] Due to the time and cost requirements for vaccine efficacy and effectiveness studies, utilising experimental human challenge models could be used to help inform policy decisions and even guide the development of new vaccines.[129]

When the JCVI provided advice for PCV20 to be used in at-risk adults they also recommended that new vaccines against RSV should be used in the UK.[112] Emerging evidence generated as a consequence of the COVID-19 pandemic suggests a strong relationship exists between RSV infection and the pneumococcus; specifically, that pneumococcal infection often follows infection with RSV.[75] It is therefore plausible that the implementation of RSV vaccines could indirectly cause a reduction in pneumococcal infection. If RSV vaccines and PCV20 are introduced at the same time, it will be difficult to quantify the impact that each has on pneumococcal infection in the UK. However, comparisons could be made internationally in countries that do not implement both vaccines simultaneously. It is likely this issue will become even more complex going forwards, with new vaccines currently under development, including higher valency PCVs as well as combination vaccines for flu, COVID-19, and RSV.

Finally, the long-term impact of the paediatric herd effect on adults is not fully understood. Theoretically, if because of the herd effect, unvaccinated people are less frequently exposed to VT serotypes, when they are they exposed, they could experience more serious disease due to a lack of prior boosting through colonisation.

To keep pace with developments, the UKHSA are planning to initiate an acute respiratory infection surveillance programme. This will operate at selected centres across England, providing insight into pneumococcal pneumonia, RSV, COVID-19 and influenza.

Although the primary objective of the publications described in this critical analysis was to support PCV20, few specifically focused on PCV20; rather, most contribute holistically towards the evidence base for the burden and impact of aLRTD and therefore provide a broader contribution to the scientific literature. An example of this and the relevance of some of this work in the UK is evident by virtue of The NHS Long Term Plan referencing the Call-to-Action paper.[19, 62] Furthermore, a number of publications described are important beyond the UK and help to contribute to the ongoing scientific discussion regarding the evolving epidemiology of aLRTD both intra and post-pandemic. The prospective study in Bristol was uniquely set up to describe aLRTD admissions during the pandemic and reported that 55% were not due to SARS-CoV-2. This contrasts with a retrospective study conducted in Ontario, Canada which observed hospitalisations for viruses not related to COVID-19 dropped to near zero, although this study relied on ICD-10 coding and only focused on viral infections.[96, 130] The finding from Bristol raises several important questions that are yet to be answered i.e., which organisms were responsible for these infections, were they more dominant than SARS-CoV-2 in those patients and if so why, or was there something different about the population or the healthcare system in the Bristol region?

Work on defining local hospital catchment populations has a much greater benefit in the UK besides estimating disease that could be prevented by PCV20 including supporting incidence studies for different disease areas and helping provide a robust methodology for healthcare commissioning.[69, 72] It has also laid the foundation for determining risk group specific denominators, which will lead to aLRTD incidence estimates stratified by several comorbidities. More generally, this paper provides a framework for researchers in other countries to help define denominators when conducting disease incidence studies.

The work on pneumococcal risk groups was based on a cohort of patients with all-cause hCAP, therefore the findings are relevant for hCAP regardless of aetiology. These papers have led to further publications exploring the risk of hospitalisation due to respiratory infection due to a number of pathogens and the JCVI are now considering both which patients are at risk of vaccine preventable infection but also whether and when re-vaccination is appropriate.[121] Finally, the work conducted on direct hospital costs for hCAP clearly has much broader implications than just supporting PCV20 CEA models. It helps provide evidence for policy

makers, public health decision makers, commissioners and those responsible for running hospitals trusts. Although much of the utility of this work is largely confined to the UK it does provide an important data point to compare the NHS with other health systems around the world.

11 Conclusion

This body of research has contributed to advancing the scientific literature related to the pneumococcus by closing some of the data gaps responsible for limitations in the van Hoek & Miller CEA. The burden of pneumococcal disease is now better understood, evidence demonstrating the impact for adults in risk groups has been shown, and hCAP costs have been established. The impact of this on UK vaccine policy was demonstrated in July 2023 when the JCVI provided advice that all at-risk adults and all adults aged ≥65yr could receive PCV20.

This is an exciting, fast-moving period-of-time in the field of pneumococcal disease, which is still evolving after the COVID-19 pandemic. It is about to be further disrupted with the introduction of numerous innovative vaccines for both adults and infants over the coming years. It is imperative that investment in research and surveillance is not only maintained but increases to evaluate the new post-pandemic burden of disease and to monitor the evolution of serotype epidemiology across age groups, for both invasive and non-invasive disease, including defining hCAP incidence stratified by comorbidity. To help with current and future uncertainties with high-valency PCVs such as vaccine efficacy and their ability to impact on carriage and induce a herd effect, innovative approaches, such as human challenge models, should be explored and, where possible, utilised to provide corelates of protection.

12 References

1. UK Health Security Agency, *The Green book, chapter 25: pneumococcal*. 2023.
2. Chalmers, J.D., et al., *A systematic review of the burden of vaccine preventable pneumococcal disease in UK adults.* BMC Pulm Med, 2016. **16**(1): p. 77.
3. Habib, M., B.D. Porter, and C. Satzke, *Capsular serotyping of Streptococcus pneumoniae using the Quellung reaction.* J Vis Exp, 2014(84): p. e51208.
4. Knight, J.R., et al., *Determining the serotype composition of mixed samples of pneumococcus using whole-genome sequencing.* Microb Genom, 2021. **7**(1).
5. O'Brien, K.L., et al., *Chapter 12 - Pneumococcus, Pneumococcal Disease, and Prevention*, in *The Vaccine Book (Second Edition)*, B.R. Bloom and P.-H. Lambert, Editors. 2016, Academic Press. p. 225-243.
6. Bogaert, D., R. De Groot, and P.W. Hermans, *Streptococcus pneumoniae colonisation: the key to pneumococcal disease.* Lancet Infect Dis, 2004. **4**(3): p. 144-54.
7. Cleary, D.W., et al., *Changes in serotype prevalence of Streptococcus pneumoniae in Southampton, UK between 2006 and 2018.* Sci Rep, 2022. **12**(1): p. 13332.
8. Cheliotis, K.S., et al., *Influence of sex, season and environmental air quality on experimental human pneumococcal carriage acquisition: a retrospective cohort analysis.* ERJ Open Res, 2022. **8**(2).
9. Ferreira, D.M., et al., *Controlled Human Infection and Rechallenge with Streptococcus pneumoniae Reveals the Protective Efficacy of Carriage in Healthy Adults.* American Journal of Respiratory and Critical Care Medicine, 2013. **187**(8): p. 855-864.
10. Mitsi, E., et al., *Nasal Pneumococcal Density Is Associated with Microaspiration and Heightened Human Alveolar Macrophage Responsiveness to Bacterial Pathogens.* Am J Respir Crit Care Med, 2020. **201**(3): p. 335-347.
11. Hansen, K., et al., *Exploring the microbial landscape: uncovering the pathogens associated with community-acquired pneumonia in hospitalized patients.* Front Public Health, 2023. **11**: p. 1258981.
12. Pick, H., et al., *Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013-18.* Thorax, 2020. **75**(1): p. 38-49.
13. Brown, J.S., *Community-acquired pneumonia.* Clin Med (Lond), 2012. **12**(6): p. 538-43.
14. Campling, J., et al., *A review of evidence for pneumococcal vaccination in adults at increased risk of pneumococcal disease: risk group definitions and optimization of vaccination coverage in the United Kingdom.* Expert Rev Vaccines, 2023. **22**(1): p. 785-800.
15. NICE, *Pneumonia in adults: diagnosis and management. CG191.* 2023.
16. Arnold, F.W., et al., *Older Adults Hospitalized for Pneumonia in the United States: Incidence, Epidemiology, and Outcomes.* Journal of the American Geriatrics Society, 2020. **68**(5): p. 1007-1014.
17. Gessner, B.D., et al., *The rationale for use of clinically defined outcomes in assessing the impact of pneumococcal conjugate vaccines against pneumonia.* Expert Review of Vaccines, 2021. **20**(3): p. 269-280.
18. National Institue for Health and Care Excellence, *Pneumonia (community-aquired): antimicrobial presecribing*. 2019.
19. Chalmers, J., et al., *Community-acquired pneumonia in the United Kingdom: a call to action.* Pneumonia (Nathan), 2017. **9**: p. 15.

20. Jones, D., et al., *P63 Establishing the cost of hospitalised community acquired pneumonia (cap): a hospital episode statistics (hes) analysis.* Thorax, 2017. **72**(Suppl 3): p. A116-A116.
21. Lau, W.C.Y., et al., *Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom.* Vaccine, 2015. **33**(39): p. 5072-5079.
22. El Feghaly, R.E., et al., *New insights into the treatment of acute otitis media.* Expert Review of Anti-infective Therapy, 2023. **21**(5): p. 523-534.
23. Santos, L., *The impact of nutrition and lifestyle modification on health.* Eur J Intern Med, 2022. **97**: p. 18-25.
24. Bertran, M., et al., *Invasive pneumococcal disease 3 years after introduction of a reduced 1 + 1 infant 13-valent pneumococcal conjugate vaccine immunisation schedule in England: a prospective national observational surveillance study.* Lancet Infect Dis, 2024.
25. Ladhani, S.N., et al., *Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study.* Lancet Infect Dis, 2018. **18**(4): p. 441-451.
26. Westerink, M.A., H.W. Schroeder, Jr., and M.H. Nahm, *Immune Responses to pneumococcal vaccines in children and adults: Rationale for age-specific vaccination.* Aging Dis, 2012. **3**(1): p. 51-67.
27. Limited, M.S.D.U. *Summary of Product Characteristics: Pneumovax 23 solution for injection in pre-filled syringe*. 2022 [cited 2024 25 January]; Available from: https://www.medicines.org.uk/emc/product/9692.
28. Pletz, M.W., et al., *Pneumococcal vaccines: mechanism of action, impact on epidemiology and adaption of the species.* International Journal of Antimicrobial Agents, 2008. **32**(3): p. 199-206.
29. van Hoek, A.J. and E. Miller, *Cost-Effectiveness of Vaccinating Immunocompetent ≥65 Year Olds with the 13-Valent Pneumococcal Conjugate Vaccine in England.* PLoS One, 2016. **11**(2): p. e0149540.
30. Djennad, A., et al., *Effectiveness of 23-Valent Polysaccharide Pneumococcal Vaccine and Changes in Invasive Pneumococcal Disease Incidence from 2000 to 2017 in Those Aged 65 and Over in England and Wales.* EClinicalMedicine, 2018. **6**: p. 42-50.
31. Pilishvili, T. and N.M. Bennett, *Pneumococcal Disease Prevention Among Adults: Strategies for the Use of Pneumococcal Vaccines.* Am J Prev Med, 2015. **49**(6 Suppl 4): p. S383-90.
32. Tin Tin Htar, M., et al., *Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies.* PLoS One, 2017. **12**(5): p. e0177985.
33. Goldblatt, D. and E. Miller, *Pneumococcal pneumonia.* Thorax, 2020. **75**(1): p. 6-7.
34. Whitney, C.G., et al., *Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study.* The Lancet, 2006. **368**(9546): p. 1495-1502.
35. Dunne, E.M., et al., *Pneumococcal Vaccination in Adults: What Can We Learn From Observational Studies That Evaluated PCV13 and PPV23 Effectiveness in the Same Population?* Archivos de Bronconeumología, 2023. **59**(3): p. 157-164.
36. Geno, K.A., et al., *Pneumococcal Capsules and Their Types: Past, Present, and Future.* Clin Microbiol Rev, 2015. **28**(3): p. 871-99.

37. Miller, E., et al., *Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study.* Lancet Infect Dis, 2011. **11**(10): p. 760-8.
38. Tin Tin Htar, M., D. Christopoulou, and H.-J. Schmitt, *Pneumococcal serotype evolution in Western Europe.* BMC Infectious Diseases, 2015. **15**(1): p. 419.
39. Wyres, K.L., et al., *Pneumococcal capsular switching: a historical perspective.* J Infect Dis, 2013. **207**(3): p. 439-49.
40. Croucher, N.J., et al., *Population genomics of post-vaccine changes in pneumococcal epidemiology.* Nat Genet, 2013. **45**(6): p. 656-63.
41. Bonten, M.J., et al., *Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults.* N Engl J Med, 2015. **372**(12): p. 1114-25.
42. Tomczyk S, B.N., Stoecker C, et al, *Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged 65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). .* MMWR Morb Mortal Wkly Rep, 2014. **63**(63): p. 822-5.
43. Centers for Disease Control and Prevention. *Pneumococcal Vaccination: What Everyone Should Know*. 2023 [cited 2024 25 January]; Available from: https://www.cdc.gov/vaccines/vpd/pneumo/public/index.html#pay-for-vaccines.
44. Vyse, A., et al., *A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK.* Expert Rev Vaccines, 2021. **20**(10): p. 1311-1325.
45. Waight, P.A., et al., *Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study.* Lancet Infect Dis, 2015. **15**(5): p. 535-43.
46. Lansbury, L., et al., *Pneumococcal serotypes and risk factors in adult community-acquired pneumonia 2018-20; a multicentre UK cohort study.* Lancet Reg Health Eur, 2024. **37**: p. 100812.
47. Joint Committee on Vaccination and Immunisation, *Code of Practice June 2013*. 2013.
48. UK Government, *Immunisation against infectious disease*, Department of Health and Social Care, Editor. 2021.
49. Joint Committee on Vaccination and Immunisation, *Minute of the meeting on 7 October 2015*. 2015.
50. Pfizer. *Summary of Product Characteristics - Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)*. 2023.
51. Flasche, S., et al., *The Potential for Reducing the Number of Pneumococcal Conjugate Vaccine Doses While Sustaining Herd Immunity in High-Income Countries.* PLoS Med, 2015. **12**(6): p. e1001839.
52. Goldblatt, D., et al., *Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1 + 1) compared with two primary doses and a booster (2 + 1) in UK infants: a multicentre, parallel group randomised controlled trial.* Lancet Infect Dis, 2018. **18**(2): p. 171-179.
53. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.* Jama, 2000. **283**(15): p. 2008-12.

54. Rodrigo, C., et al., *Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia.* Eur Respir J, 2015. **45**(6): p. 1632-41.
55. Walters, J.A., et al., *Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2017. **1**(1): p. Cd001390.
56. Trotter, C.L., et al., *Increasing hospital admissions for pneumonia, England.* Emerg Infect Dis, 2008. **14**(5): p. 727-33.
57. Woodhead, M.A., et al., *Prospective study of the aetiology and outcome of pneumonia in the community.* Lancet, 1987. **1**(8534): p. 671-4.
58. Spencer, S.A. and M.P. Davies, *Hospital episode statistics: improving the quality and value of hospital data: a national internet e-survey of hospital consultants.* BMJ Open, 2012. **2**(6).
59. Campling J , J.D., Ellsbury G, *S6 Establishing the true incidence of hospitalised community acquired pneumonia (cap) in the uk: a hospital episode statistics (hes) analysis.* Thorax, 2017. **72: A7**.
60. Pelton, S.I., A.M. Loughlin, and C.D. Marchant, *Seven valent pneumococcal conjugate vaccine immunization in two Boston communities: changes in serotypes and antimicrobial susceptibility among Streptococcus pneumoniae isolates.* Pediatr Infect Dis J, 2004. **23**(11): p. 1015-22.
61. Davies, N.G., et al., *Modeling the effect of vaccination on selection for antibiotic resistance in Streptococcus pneumonia e.* Sci Transl Med, 2021. **13**(606).
62. NHS England, *The NHS Long Term Plan*. 2019.
63. Vyse, A., et al., *The proportion of contemporary invasive pneumococcal disease and pneumococcal pneumonia in UK adults reflected by serotypes included in the 13-valent pneumococcal conjugate vaccine and next generation higher valency pneumococcal conjugate vaccines in development.* Vaccine, 2020. **38**(51): p. 8068-8070.
64. Fletcher, M.A., et al., *Pneumococcal empyema and complicated pneumonias: global trends in incidence, prevalence, and serotype epidemiology.* Eur J Clin Microbiol Infect Dis, 2014. **33**(6): p. 879-910.
65. Campling, J., et al., *S6 Establishing the true incidence of hospitalised community acquired pneumonia (cap) in the uk: a hospital episode statistics (hes) analysis.* Thorax, 2017. **72**(Suppl 3): p. A7-A7.
66. Lim, W.S., et al., *BTS guidelines for the management of community acquired pneumonia in adults: update 2009.* Thorax, 2009. **64**(Suppl 3): p. iii1-iii55.
67. University of Bristol. *Pfizer's Vaccine Centre of Excellence launches at the University of Bristol*. 2021; Available from: https://www.bristol.ac.uk/news/2021/may/vaccine-centre-of-excellence-.html#:~:text=%22We're%20proud%20to%20have,the%20use%20of%20vaccines%20worldwide.
68. Hyams, C., et al., *Incidence of community acquired lower respiratory tract disease in Bristol, UK during the COVID-19 pandemic: A prospective cohort study.* Lancet Reg Health Eur, 2022. **21**: p. 100473.
69. Campling, J., et al., *A novel approach to estimate the local population denominator to calculate disease incidence for hospital-based health events in England.* Epidemiol Infect, 2022. **150**: p. e150.

70. Hyams, C., et al., *Incidence of acute lower respiratory tract disease hospitalisations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective methodology.* BMJ Open, 2022. **12**(6): p. e057464.
71. UK Government, *The NHS Constitution for England*, D.o.H.a.S. Care, Editor. 2023.
72. Office for Health Improvement and Disparities. *NHS Acute (Hospital) Trust Catchment Populations - 2022 Rebase Experimental Statistics*. 2023; Available from: https://app.powerbi.com/view?r=eyJrIjoiODZmNGQ0YzItZDAwZi00MzFiLWE4NzAtMzVmNTUwMThmMTVlIiwidCI6ImVlNGUxNDk5LTRhMzUtNGIyZS1hZDQ3LTVmM2NmOWRlODY2NiIsImMiOjh9.
73. Campling, J., et al., *S111 Adult hospitalised community acquired pneumonia incidence in Bristol: comparison of retrospective ICD-10 based analysis and prospective study data.* Thorax, 2022. **77**(Suppl 1): p. A68-A69.
74. Garlick, S., *Ethnic group, England and Wales: Census 2021*, O.f.N. Statistics, Editor. 2022, gov.uk.
75. Dagan, R., et al., *The COVID-19 pandemic as an opportunity for unravelling the causative association between respiratory viruses and pneumococcus-associated disease in young children: a prospective study.* EBioMedicine, 2023. **90**: p. 104493.
76. Binns, E., et al., *Influenza and respiratory syncytial virus during the COVID-19 pandemic: Time for a new paradigm?* Pediatr Pulmonol, 2022. **57**(1): p. 38-42.
77. Dagan, R., D. Danino, and D.M. Weinberger, *The Pneumococcus–Respiratory Virus Connection—Unexpected Lessons From the COVID-19 Pandemic.* JAMA Network Open, 2022. **5**(6): p. e2218966-e2218966.
78. Sharp, A., et al., *Estimating the burden of adult hospital admissions due to RSV and other respiratory pathogens in England.* Influenza Other Respir Viruses, 2022. **16**(1): p. 125-131.
79. Reibling, N., M. Ariaans, and C. Wendt, *Worlds of Healthcare: A Healthcare System Typology of OECD Countries.* Health Policy, 2019. **123**(7): p. 611-620.
80. Joint Committee on Vaccination and Immunisation. *JCVI statement on the wider use of pneumococcal conjugate vaccines in the UK*. 2013; Available from: https://assets.publishing.service.gov.uk/media/5a7cd74ded915d71e1e4df62/JCVI_statement_on_pneumococcal_vaccination_for_clinical_risk_groups_Final.pdf.
81. van Hoek, A.J., et al., *The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England.* J Infect, 2012. **65**(1): p. 17-24.
82. Rozenbaum, M.H., et al., *Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis.* Bmj, 2012. **345**: p. e6879.
83. Drummond, M.F. and T.O. Jefferson, *Guidelines for authors and peer reviewers of economic submissions to the BMJ.* BMJ, 1996. **313**(7052): p. 275-283.
84. Campling, J., et al., *The impact of certain underlying comorbidities on the risk of developing hospitalised pneumonia in England.* Pneumonia (Nathan), 2019. **11**: p. 4.
85. Pelton, S.I., et al., *Rates of pneumonia among children and adults with chronic medical conditions in Germany.* BMC Infect Dis, 2015. **15**: p. 470.
86. Shea, K.M., et al., *Rates of pneumococcal disease in adults with chronic medical conditions.* Open Forum Infect Dis, 2014. **1**(1): p. ofu024.
87. World Health Organisation. *International Statistical Classification of Diseases and Related Health Problems 10th Revision*. 2019; Available from: https://icd.who.int/browse10/2019/en.

88. Mendes, D., et al., *Cost-effectiveness of using a 20-valent pneumococcal conjugate vaccine to directly protect adults in England at elevated risk of pneumococcal disease.* Expert Rev Pharmacoecon Outcomes Res, 2022. **22**(8): p. 1285-1295.
89. Mugwagwa, T., et al., *Public health and budgetary impact of 20-valent pneumococcal conjugate vaccine for adults in England.* Expert Rev Vaccines, 2022. **21**(9): p. 1331-1341.
90. Campling, J., et al., *Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England.* BMJ Open Respir Res, 2020. **7**(1).
91. Mangen, M.-J.J., et al., *The impact of community-acquired pneumonia on the health-related quality-of-life in elderly.* BMC Infectious Diseases, 2017. **17**(1): p. 208.
92. Andrade, L.F., et al., *Health related quality of life in patients with community-acquired pneumococcal pneumonia in France.* Health and Quality of Life Outcomes, 2018. **16**(1): p. 28.
93. Dela Cruz, C.S., et al., *Future Research Directions in Pneumonia. NHLBI Working Group Report.* Am J Respir Crit Care Med, 2018. **198**(2): p. 256-263.
94. NHS England. *RightCare community-acquired pneumonia scenario*. 2023; Available from: https://www.england.nhs.uk/long-read/rightcare-community-acquired-pneumonia-scenario/.
95. Centers for Disease Control, *CDC Recommends Lowering the Age for Pneumococcal Vaccination from 65 to 50 Years Old.* CDC Website, 2024.
96. Reynard, C., et al., *Adult risk groups for vaccine preventable respiratory infections: an overview of the UK environment.* Expert Rev Vaccines, 2024. **23**(1): p. 1052-1067.
97. Suaya, J.A., et al., *Post hoc analysis of the efficacy of the 13-valent pneumococcal conjugate vaccine against vaccine-type community-acquired pneumonia in at-risk older adults.* Vaccine, 2018. **36**(11): p. 1477-1483.
98. Campling, J., et al., *Hospitalization costs of adult community-acquired pneumonia in England.* J Med Econ, 2022. **25**(1): p. 912-918.
99. Humphreys, H., et al., *Invasive pneumococcal surveillance to assess the potential benefits of extended spectrum conjugate vaccines (PCV15/PCV20) in older adults.* Epidemiol Infect, 2023. **151**: p. e27.
100. Dawson, R., et al., *Response to Vyse et al., "A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK".* Expert Review of Vaccines, 2022. **21**(6): p. 869-870.
101. US Food & Drug Administration, *June 10, 2021 Approval Letter - Prevnar 20.* 2021.
102. Danelian, G., et al., *The impact and cost-effectiveness of pneumococcal immunisation strategies for the elderly in England.* Vaccine, 2024. **42**(18): p. 3838-3850.
103. Marbaix, S., et al., *Cost-utility of 20-valent pneumococcal conjugate vaccine compared to no vaccination and recommended alternative vaccines among Belgian adults.* Expert Review of Vaccines, 2023. **22**(1): p. 1008-1021.
104. Kühne, F., et al., *Cost-effectiveness of use of 20-valent pneumococcal conjugate vaccine among adults in Germany.* Expert Review of Vaccines, 2023. **22**(1): p. 921-932.
105. Cantarero, D., et al., *Cost-utility analysis of the use of the 20-valent anti-pneumococcal vaccine (PCV20) in adults older than 60 years in Spain.* Vaccine, 2023. **41**(36): p. 5342-5349.

106. Gourzoulidis, G., et al., *Health and economic outcomes of 20-valent pneumococcal conjugate vaccine compared to 15-valent pneumococcal conjugate vaccine strategies for adults in Greece.* Frontiers in Public Health, 2023. **11**.
107. de Boer, P.T., et al., *Higher-valency pneumococcal conjugate vaccines in older adults, taking into account indirect effects from childhood vaccination: a cost-effectiveness study for the Netherlands.* BMC Medicine, 2024. **22**(1): p. 69.
108. Malene B, M., et al., *Cost-effectiveness of 20-valent pneumococcal conjugate vaccine compared with 23-valent pneumococcal polysaccharide vaccine among adults in a Norwegian setting.* Cost Effectiveness and Resource Allocation, 2023. **21**(1): p. 52.
109. Nakamura, S., et al., *Cost-effectiveness analysis of adult pneumococcal conjugate vaccines for pneumococcal disease in Japan.* Expert Review of Vaccines, 2024. **23**(1): p. 546-560.
110. Kang, D.-W., et al., *Cost-effectiveness of the 20-valent pneumococcal conjugate vaccine versus the 23-valent pneumococcal polysaccharide vaccine for older adults in South Korea.* Vaccine, 2024. **42**(4): p. 871-878.
111. Rey-Ares, L., et al., *Cost-Effectiveness of 20-Valent Pneumococcal Conjugate Vaccine in Argentinean Adults.* Infectious Diseases and Therapy, 2024. **13**(6): p. 1235-1251.
112. Joint Committee on Vaccination and Immunisation, *Minute of the meeting held June 2023*. 2023.
113. Boots. *Pneumonia Vaccination Service*. 25 March 2024]; Available from: https://www.boots.com/online/pharmacy-services/pneumonia-vaccination-service.
114. Clutterbuck, E.A., et al., *Pneumococcal conjugate and plain polysaccharide vaccines have divergent effects on antigen-specific B cells.* J Infect Dis, 2012. **205**(9): p. 1408-16.
115. O'Brien, K.L., M. Hochman, and D. Goldblatt, *Combined schedules of pneumococcal conjugate and polysaccharide vaccines: is hyporesponsiveness an issue?* Lancet Infect Dis, 2007. **7**(9): p. 597-606.
116. Fazekas de St, G. and R.G. Webster, *Disquisitions of Original Antigenic Sin. I. Evidence in man.* J Exp Med, 1966. **124**(3): p. 331-45.
117. Sun, Y., Y. Hwang, and M.H. Nahm, *Avidity, potency, and cross-reactivity of monoclonal antibodies to pneumococcal capsular polysaccharide serotype 6B.* Infect Immun, 2001. **69**(1): p. 336-44.
118. Bentley, S.D., et al., *Genetic Analysis of the Capsular Biosynthetic Locus from All 90 Pneumococcal Serotypes.* PLOS Genetics, 2006. **2**(3): p. e31.
119. Namkoong, H., et al., *Theory and strategy for Pneumococcal vaccines in the elderly.* Human Vaccines & Immunotherapeutics, 2016. **12**(2): p. 336-343.
120. Andrews, N.J., et al., *Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales.* Vaccine, 2012. **30**(48): p. 6802-8.
121. Pneumococcal subcommittee, J.C.o.V.a.I., *Minute JCVI Pneumococcal subcommittee 22 February 2024.* 2024.
122. Merck & Co., *Merck Announces V116, an Investigational, 21-valent Pneumococcal Conjugate Vaccine Specifically Designed for Adults, Met Key Immunogenicity and Safety Endpoints in Two Phase 3 Trials*. 2023.
123. Essink, B., et al., *Pivotal Phase 3 Randomized Clinical Trial of the Safety, Tolerability, and Immunogenicity of 20-Valent Pneumococcal Conjugate Vaccine in Adults Aged ≥18 Years.* Clinical Infectious Diseases, 2021. **75**(3): p. 390-398.

124. Choi, Y.H., et al., *Potential impact of replacing the 13-valent pneumococcal conjugate vaccine with 15-valent or 20-valent pneumococcal conjugate vaccine in the 1 + 1 infant schedule in England: a modelling study.* The Lancet Public Health, 2024. **9**(9): p. e654-e663.
125. Robinson, R.E., et al., *Human Infection Challenge with Serotype 3 Pneumococcus.* American Journal of Respiratory and Critical Care Medicine, 2022. **206**(11): p. 1379-1392.
126. Hyams, C., et al., *Surveillance of pneumococcal serotypes in adults hospitalised with acute lower respiratory tract infection in Bristol, UK.* Vaccine, 2024. **42**(7): p. 1599-1607.
127. Ryman, J., et al., *Predicting vaccine effectiveness against invasive pneumococcal disease in children using immunogenicity data.* npj Vaccines, 2022. **7**(1): p. 140.
128. Andrews, N.J., et al., *Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study.* The Lancet Infectious Diseases, 2014. **14**(9): p. 839-846.
129. Hazenberg, P., et al., *Serotype 3 Experimental Human Pneumococcal Challenge (EHPC) study protocol: dose ranging and reproducibility in a healthy volunteer population (challenge 3).* BMJ Open, 2024. **14**(1): p. e075948.
130. Habbous, S., et al., *Changes in hospitalizations and emergency department respiratory viral diagnosis trends before and during the COVID-19 pandemic in Ontario, Canada.* PLoS One, 2023. **18**(6): p. e0287395.

13 Appendices

Appendix 1 - Publications

A1.1 – Table of Publications Describing My Contribution

Publication	My Contribution
Publication 1: Chalmers JD, **Campling J**, Dicker A, Woodhead M, Madhava H. A systematic review of the burden of vaccine preventable pneumococcal disease in UK adults. *BMC Pulmonary Medicine.* 2016 May 11;16(1):77. doi: 10.1186/s12890-016-0242-0.	I led the collaboration between Pfizer and the University of Dundee to conduct this review. I helped develop the protocol, reviewed the list of studies identified for extraction, reviewed and contributed to the analysis and contributed to and edited the manuscript.
Publication 2: Chalmers J, **Campling J,** Ellsbury G, Hawkey PM, Madhava H, Slack M. Community-acquired pneumonia in the United Kingdom: a call to action. *Pneumonia.* 2017 Oct 5;9:15. doi: 10.1186/s41479-017-0039-9.	I convened a meeting where I presented findings of my analysis comparing HES data with the results of a prospective pneumonia study in Nottingham to the expert group to initiate the discussion. I also contributed to the writing / editing and approval of this manuscript.
Publication 3: Vyse A, **Campling J,** Czudek C, Ellsbury G, Slack M. The proportion of contemporary invasive pneumococcal disease and pneumococcal pneumonia in UK adults reflected by serotypes included in the 13-valent pneumococcal conjugate vaccine and next generation higher valency pneumococcal conjugate vaccines in development. *Vaccine.* 2020 Dec 3;38(51):8068-8070. doi: 10.1016/j.vaccine.2020.10.090. Epub 2020 Nov 12.	I contributed towards the concept, design and manuscript writing / editing.
Publication 4: **Campling J**, Begier E, Vyse A, Hyams C, Heaton D, Southern J, Finn A, Madhava H, Gessner BD, Ellsbury G. A novel approach to estimate the local population denominator to calculate disease incidence for hospital-based health events in England. *Epidemiology and Infection.* 2022 Jul 11;150:e150. doi: 10.1017/S0950268822000917.	I conceived this study and contributed towards all aspects of this publication.
Publication 5: Hyams C, Begier E, Garcia Gonzalez M, Southern J, **Campling J**, Gray S, Oliver J, Gessner BD, Finn A. Incidence of acute lower respiratory tract disease hospitalisations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective	I shared my experience of working with the research team in Nottingham highlighting some of the challenges they faced with both their numerator and denominator. I also contributed to the analysis, including estimating the

methodology. *British Medical Journal Open*. 2022 Jun 15;12(6):e057464. doi: 10.1136/bmjopen-2021-057464.	denominators and writing / editing the manuscript.
Publication 6: Hyams C, Challen R, Begier E, Southern J, King J, Morley A, Szasz-Benczur Z, Gonzalez MG, Kinney J, **Campling J**, Gray S, Oliver J, Hubler R, Valluri S, Vyse A, McLaughlin JM, Ellsbury G, Maskell NA, Gessner BD, Danon L, Finn A; Avon CAP Research Group. Incidence of community acquired lower respiratory tract disease in Bristol, UK during the COVID-19 pandemic: A prospective cohort study. *Lancet Regional Health Europe.* 2022 Oct;21:100473. doi: 10.1016/j.lanepe.2022.100473.	I shared my knowledge and experience from working with the study team in Nottingham to help design this study, particularly with regards to the denominator estimate. I also contributed to the analysis, including estimating the denominators and writing / editing the manuscript.
Publication 7: **Campling J,** Jones D, Chalmers JD, Jiang Q, Vyse A, Madhava H, Ellsbury G, Slack M. The impact of certain underlying comorbidities on the risk of developing hospitalised pneumonia in England. *Pneumonia.* 2019 Oct 11;11:4. doi: 10.1186/s41479-019-0063-z.	I conceived this study and contributed towards all aspects of this publication.
Publication 8: **Campling J**, Jones D, Chalmers J, Jiang Q, Vyse A, Madhava H, Ellsbury G, Rabe A, Slack M. Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England. *British Medical Journal Open Respiratory Research*. 2020 Oct;7(1):e000703. doi: 10.1136/bmjresp-2020-000703.	I conceived this study and contributed towards all aspects of this publication.
Publication 9: **Campling J,** Vyse A, Liu HH, Wright H, Slack M, Reinert RR, Drayson M, Richter A, Singh D, Barlow G, Kassianos G, Ellsbury G. A review of evidence for pneumococcal vaccination in adults at increased risk of pneumococcal disease: risk group definitions and optimization of vaccination coverage in the United Kingdom. *Expert Review Vaccines*. 2023 Jan-Dec;22(1):785-800. doi: 10.1080/14760584.2023.2256394.	I conceived this study and contributed towards all aspects of this publication.
Publication 10: **Campling J,** Wright HF, Hall GC, Mugwagwa T, Vyse A, Mendes D, Slack MPE, Ellsbury GF. Hospitalization costs of adult community-acquired pneumonia in England. *Journal of Medical Economics.* 2022 Jan-Dec;25(1):912-918. doi: 10.1080/13696998.2022.2090734.	I conceived this study and contributed towards all aspects of this publication.

Publication 11: Vyse A, **Campling J,** Czudek C, Ellsbury G, Mendes D, Reinert RR, Slack M. A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK. Expert Rev Vaccines. 2021 Oct;20(10):1311-1325. doi: 10.1080/14760584.2021.1984888.	I contributed to the study concept, design, analysis and manuscript writing / editing.
Publication 13: Mendes D, Averin A, Atwood M, Sato R, Vyse A, **Campling J,** Weycker D, Slack M, Ellsbury G, Mugwagwa T. Cost-effectiveness of using a 20-valent pneumococcal conjugate vaccine to directly protect adults in England at elevated risk of pneumococcal disease. Expert Rev Pharmacoecon Outcomes Res. 2022 Dec;22(8):1285-1295. doi: 10.1080/14737167.2022.2134120.	I contributed throughout the planning phase of this study regarding some aspects of the model structure but mainly with regards to the input parameters. I also contributed to analysis and the preparation, review and approval of the manuscript.
Publication 14: Mugwagwa T, Averin A, Atwood M, Sato R, Vyse A, **Campling J,** Weycker D, Slack M, Ellsbury G, Mendes D. Public health and budgetary impact of 20-valent pneumococcal conjugate vaccine for adults in England. Expert Rev Vaccines. 2022 Sep;21(9):1331-1341. doi: 10.1080/14760584.2022.2104250.	I contributed throughout the planning phase of this study regarding some aspects of the model structure but mainly with regards to the input parameters. I also contributed to analysis and the preparation, review and approval of the manuscript.

A1.2 - Evidence of My Contribution to Publications

Subject: Re: contribution
Date: Friday 5 April 2024 at 16:47:49 British Summer Time
From: James Campling (MED - Postgraduate Researcher)
To: James Chalmers (Staff)

Dear James,

Thank you for this – much appreciated.

Kind Regards,

James

From: James Chalmers (Staff) <j.chalmers@dundee.ac.uk>
Date: Friday, 5 April 2024 at 13:36
To: James Campling (MED - Postgraduate Researcher) <James.Campling@uea.ac.uk>
Subject: contribution

Re: contribution to research papers

Chalmers JD, **Campling J**, Dicker A, Woodhead M, Madhava H. A systematic review of the burden of vaccine preventable pneumococcal disease in UK adults. *BMC Pulmonary Medicine.* 2016 May 11;16(1):77. doi: 10.1186/s12890-016-0242-0.

James led the collaboration between Pfizer and the University of Dundee to conduct this review. He helped to develop the protocol, reviewed the list of studies identified for extraction, reviewed, and contributed to the analysis and contributed to and edited the manuscript.

Chalmers J, **Campling J,** Ellsbury G, Hawkey PM, Madhava H, Slack M. Community-acquired pneumonia in the United Kingdom: a call to action. *Pneumonia.* 2017 Oct 5;9:15. doi: 10.1186/s41479-017-0039-9.

James convened a meeting where he presented findings of his analysis comparing HES data with the results of a prospective pneumonia study in Nottingham to the expert group to initiate the discussion. He also contributed to the writing / editing and approval of this manuscript.

Pfizer Limited
Walton Oaks, Dorking Road, Walton on the Hill,
Tadworth, Surrey KT20 7NS, UK
Telephone: +44 (0)1304 616161

Worldwide Biopharmaceutical Businesses

5 April 2024

To Whom it may concern,

I hereby confirm that **James Campling** contributed as a co-author to the peer-reviewed publications listed below. His specific contributions to these papers were as follows:

1) Vyse A, **Campling J,** Czudek C, Ellsbury G, Slack M. The proportion of contemporary invasive pneumococcal disease and pneumococcal pneumonia in UK adults reflected by serotypes included in the 13-valent pneumococcal conjugate vaccine and next generation higher valency pneumococcal conjugate vaccines in development. *Vaccine.* 2020 Dec 3;38(51):8068-8070. doi: 10.1016/j.vaccine.2020.10.090. Epub 2020 Nov 12.

James contributed towards the concept, design and manuscript writing / editing.

2) Vyse A, **Campling J,** Czudek C, Ellsbury G, Mendes D, Reinert RR, Slack M. A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK. Expert Rev Vaccines. 2021 Oct;20(10):1311-1325. doi: 10.1080/14760584.2021.1984888.

James contributed to the study concept, design, analysis and manuscript writing / editing.

3) Vyse A, **Campling J,** Czudek C, Ellsbury G, Mendes D, Reinert RR, Slack MPE. Response to Dawson et al: Letter to the Editor on "A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK". Expert Rev Vaccines. 2022 Jun;21(6):871-872. doi: 10.1080/14760584.2022.2047024.

James contributed to the writing / editing.

Andrew Vyse

Dr. Andrew Vyse
Clinical Epidemiologist

Subject: PhD thesis contribution
Date: Thursday 4 April 2024 at 16:06:19 British Summer Time
From: Catherine Hyams
To: James Campling (MED - Postgraduate Researcher)

Dear James

Please feel free to forward this on to whomever it concerns re your contribution to papers:

Paper 1: Hyams C, Begier E, Garcia Gonzalez M, Southern J, **Campling J**, Gray S, Oliver J, Gessner BD, Finn A. Incidence of acute lower respiratory tract disease hospitalisations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective methodology. *British Medical Journal Open*. 2022 Jun 15;12(6):e057464. doi: 10.1136/bmjopen-2021-057464.
James shared his experience of working with the research team in Nottingham highlighting some of the challenges they faced with both their numerator and denominator. He also contributed to the analysis, including estimating the denominators and writing / editing the manuscript.

Paper 2: Hyams C, Challen R, Begier E, Southern J, King J, Morley A, Szasz-Benczur Z, Gonzalez MG, Kinney J, **Campling J**, Gray S, Oliver J, Hubler R, Valluri S, Vyse A, McLaughlin JM, Ellsbury G, Maskell NA, Gessner BD, Danon L, Finn A; Avon CAP Research Group. Incidence of community acquired lower respiratory tract disease in Bristol, UK during the COVID-19 pandemic: A prospective cohort study. *Lancet Regional Health Europe.* 2022 Oct;21:100473. doi: 10.1016/j.lanepe.2022.100473.

James shared his knowledge and experience from working with the study team in Nottingham to help design this study, particularly with regards to the denominator estimate. He also contributed to the analysis, including estimating the denominators and writing / editing the manuscript.

Let me know if you need anything else

VBW and Good Luck!

Catherine

Dr. Catherine Hyams

PostDoctoral Clinical Research Fellow
Principal Investigator AvonCAP study
University of Bristol | NBT and UHBW NHS Trusts
catherine.hyams@bristol.ac.uk | catherine.hyams@nbt.nhs.uk
skype: cathyams

Pfizer Limited
Walton Oaks, Dorking Road, Walton on the Hill,
Tadworth, Surrey KT20 7NS, UK
Telephone: +44 (0)1304 616161

Pfizer

Worldwide Biopharmaceutical Businesses

5 April 2024

To Whom it may concern,

I hereby confirm that **James Campling** contributed as a co-author to the peer-reviewed publications described below. His specific contributions to these papers were as follows:

1) Ellsbury G, **Campling J**, Madhava H, Slack M. Identifying UK travellers at increased risk of developing pneumococcal infection: a novel algorithm. J Travel Med. 2021 Aug 27;28(6):taab063. doi: 10.1093/jtm/taab063.

James contributed to the concept for creating the algorithm, designing the algorithm including defining the search strategy. He also contributed to the analysis, writing / editing the manuscript and responding to reviewer feedback.

2) **Campling J**, Begier E, Vyse A, Hyams C, Heaton D, Southern J, Finn A, Madhava H, Gessner BD, Ellsbury G. A novel approach to estimate the local population denominator to calculate disease incidence for hospital-based health events in England. *Epidemiology and Infection*. 2022 Jul 11;150:e150. doi: 10.1017/S0950268822000917.

James conceived this study and led on the design, analysis, manuscript writing / editing and responding to reviewer feedback.

3) **Campling J**, Jones D, Chalmers JD, Jiang Q, Vyse A, Madhava H, Ellsbury G, Slack M. The impact of certain underlying comorbidities on the risk of developing hospitalised pneumonia in England. *Pneumonia*. 2019 Oct 11;11:4. doi: 10.1186/s41479-019-0063-z.

James conceived this study and led on the design, analysis, manuscript writing / editing and responding to reviewer feedback.

4) **Campling J**, Jones D, Chalmers J, Jiang Q, Vyse A, Madhava H, Ellsbury G, Rabe A, Slack M. Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England. *British Medical Journal Open Respiratory Research.* 2020 Oct;7(1):e000703. doi: 10.1136/bmjresp-2020-000703.

James conceived this study and led on the design, analysis, manuscript writing / editing and responding to reviewer feedback.

5) **Campling J**, Vyse A, Liu HH, Wright H, Slack M, Reinert RR, Drayson M, Richter A, Singh D, Barlow G, Kassianos G, Ellsbury G. A review of evidence for pneumococcal vaccination in adults at increased risk of pneumococcal disease: risk group definitions and optimization of vaccination coverage in the United Kingdom. *Expert Review Vaccines.* 2023 Jan-Dec;22(1):785-800. doi: 10.1080/14760584.2023.2256394.

James conceived this study and led on the design, analysis, manuscript writing / editing and responding to reviewer feedback.

6) **Campling J**, Wright HF, Hall GC, Mugwagwa T, Vyse A, Mendes D, Slack MPE, Ellsbury GF. Hospitalization costs of adult community-acquired pneumonia in England. *Journal of Medical Economics.* 2022 Jan-Dec;25(1):912-918. doi: 10.1080/13696998.2022.2090734.

James conceived this study and led on the design, analysis, manuscript writing / editing and responding to reviewer feedback.

Dr. Gillian Ellsbury
Medical Director – Primary Care
Pfizer UK

Pfizer Limited
Walton Oaks, Dorking Road, Walton on the Hill,
Tadworth, Surrey KT20 7NS, UK
Telephone: +44 (0)1304 616161

Worldwide Biopharmaceutical Businesses

5 April 2024

To Whom it may concern,

I hereby confirm that **James Campling** contributed as a co-author to the peer-reviewed publications listed below. His specific contributions to these papers were as follows:

1) Mendes D, Averin A, Atwood M, Sato R, Vyse A, **Campling J,** Weycker D, Slack M, Ellsbury G, Mugwagwa T. Cost-effectiveness of using a 20-valent pneumococcal conjugate vaccine to directly protect adults in England at elevated risk of pneumococcal disease. Expert Rev Pharmacoecon Outcomes Res. 2022 Dec;22(8):1285-1295. doi: 10.1080/14737167.2022.2134120.

James contributed throughout the planning phase of this study regarding some aspects of the model structure but mainly with regards to the input parameters. James also contributed to the analysis and the preparation, review and approval of the manuscript.

2) Mugwagwa T, Averin A, Atwood M, Sato R, Vyse A, **Campling J,** Weycker D, Slack M, Ellsbury G, Mendes D. Public health and budgetary impact of 20-valent pneumococcal conjugate vaccine for adults in England. Expert Rev Vaccines. 2022 Sep;21(9):1331-1341. doi: 10.1080/14760584.2022.2104250.

James contributed throughout the planning phase of this study regarding some aspects of the model structure but mainly with regards to the input parameters. James also contributed to the analysis and the preparation, review and approval of the manuscript.

Dr. Tendai Mugwagwa
Director, Value & Evidence
GAV Value & Evidence Strategy
Pfizer inc

Tendai Mugwagwa

A1.3 – Copy of My Publications Included in this Critical Analysis

Chalmers et al. BMC Pulmonary Medicine (2016) 16:77
DOI 10.1186/s12890-016-0242-0

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

A systematic review of the burden of vaccine preventable pneumococcal disease in UK adults

James D. Chalmers[1*], James Campling[2], Alison Dicker[1], Mark Woodhead[3] and Harish Madhava[2]

Abstract

Background: Invasive pneumococcal disease (IPD) and pneumococcal pneumonia are common and carry a significant morbidity and mortality. Current strategies to prevent pneumococcal disease are under review in the United Kingdom (UK). We conducted a systematic review to evaluate the burden of vaccine type adult pneumococcal disease specifically in the UK.

Methods: A systematic review conducted and reported according to MOOSE guidelines. Relevant studies from 1990 to 2015 were included. The primary outcome was the incidence of vaccine type pneumococcal disease, focussing on the pneumococcal polysaccharide vaccine (PPSV), the 13-valent conjugate vaccine (PCV13) and the 7-valent conjugate vaccine (PCV7).

Results: Data from surveillance in England and Wales from 2013/14 shows an incidence of 6.85 per 100,000 population across all adult age groups for IPD, and an incidence of 20.58 per 100,000 population in those aged >65 years. The corresponding incidences for PCV13 serotype IPD were 1.4 per 100,000 and 3.72 per 100,000. The most recent available data for community-acquired pneumonia (CAP) including non-invasive disease showed an incidence of 20.6 per 100,000 for adult pneumococcal CAP and 8.6 per 100,000 population for PCV13 serotype CAP. Both IPD and CAP data sources in the UK suggest an ongoing herd protection effect from childhood PCV13 vaccination causing a reduction in the proportion of cases caused by PCV13 serotypes in adults. Despite this, applying the incidence rates to UK population estimates suggests more than 4000 patients annually will be hospitalised with PCV13 serotype CAP and more than 900 will be affected by IPD, although with a trend for these numbers to decrease over time.
There was limited recent data on serotype distribution in high risk groups such as those with chronic respiratory or cardiac disease and no data available for vaccine type (VT) CAP managed in the community where there is likely to be a considerable unmeasured burden.

Conclusion: The most recent available data suggests that VT pneumococcal disease continues to have a high burden in UK adults despite the impact of childhood PCV13 vaccination. IPD estimates represent only a fraction of the total burden of pneumococcal disease.

Study registration: PROSPERO CRD42015025043

Keywords: Vaccine, Pneumonia, Infection, Epidemiology, Mortality

* Correspondence: jchalmers@dundee.ac.uk
[1]School of Medicine, University of Dundee, Dundee DD1 9SY, UK
Full list of author information is available at the end of the article

Background

Streptococcus pneumoniae is a Gram-positive bacterium and a commensal of the human nasopharynx [1]. Failure of natural immunity to *S. pneumoniae* leads to pneumococcal infection and in some cases to invasive pneumococcal disease (IPD) [1–3]. The most frequent manifestation of pneumococcal disease, however, is pneumococcal pneumonia where the pneumococcus may be responsible for up to 60 % of cases of community-acquired pneumonia (CAP) [4]. Hospitalised CAP carries a mortality rate of 5–15 % rising to more than 30 % in patients admitted to the intensive care unit [5, 6]. The highest rates of pneumococcal disease are observed in infants, the elderly, patients with chronic respiratory disease and in patients with immune compromise [7–10]. This is despite the availability of effective antimicrobial treatments against *S. pneumonia*e, emphasising the importance of preventing pneumonia wherever possible [11, 12]. The impact of pneumococcal disease in the UK is substantial with approximately 6000 cases of IPD reported annually and 192,281 hospital admissions for pneumonia in 2013/14 in England of which up to 50 % may be pneumococcal [13, 14]. The cost to the UK National Health Service is estimated at more than £1 billion [15].

Pneumococcal disease is, at least partially, a vaccine preventable disease. The 23-valent pneumococcal polysaccharide vaccine (PPSV) has been recommended in the UK for patients at high risk of pneumococcal disease since 2003, including adults over the age of 65 years. A systematic review and meta-analysis of the data supporting PPSV show that it protects against IPD in adults in high income countries (OR 0.20 95 % CI 0.10–0.39, $n = 27886$), but limitations include uncertainty over its protection against IPD in patients with chronic illnesses (OR 1.56 95 % CI 0.35–0.694 $n = 3230$), protection against non-invasive pneumococcal CAP and its duration of protection [16].

The 13-valent pneumococcal conjugate vaccine (PCV13, Prevenar-13) has been evaluated for the prevention of vaccine type IPD in children and in elderly subjects [17, 18]. The recent CAPITA trial conducted in the Netherlands demonstrated the efficacy of PCV13 for the prevention, in those aged ≥65, of vaccine type pneumococcal CAP and also non-invasive CAP caused by vaccine serotypes [18]. An analysis based on the frequency of IPD and CAP caused by *S. pneumoniae* in the Netherlands concluded that PCV13 was cost-effective [19].

PCV13 is not currently part of the UK adult vaccination programme, neither for elderly patients aged >65 years nor for specific high risk groups. Determining whether PCV13 would be cost-effective in the UK requires accurate information on the burden of vaccine preventable pneumococcal disease in the UK.

We conducted a systematic review to determine the incidence and burden of vaccine preventable pneumococcal disease in the adult UK population.

Methods

This manuscript reports a systematic review of observational studies and was conducted and is reported according to the MOOSE (meta-analysis and systematic review of observational studies in epidemiology) guidelines [20]. The review protocol was registered on PROSPERO (CRD42015025043).

Search strategy

A librarian searched electronic databases from 1990 until September 2015 for relevant studies using PUBMED and EMBASE. A combination of text words and controlled vocabulary terms related to the subject of interest (pneumococcal disease) and possible outcome measures was used to develop a sensitive search strategy. Terms entered were (Streptococc* [tiab] OR pneumococc* [tiab]) AND (Serotype [Title/Abstract] OR serogroup [Title/Abstract) AND (incidence OR frequency OR prevalence OR distribution). Further searches were conducted for specific data on risk groups and UK regions as described in the relevant sections below. No language restrictions were applied to the search. The search was supplemented by reviews of reference lists, bibliographies and the investigators files where appropriate.

Inclusion criteria

The review included observational cohort studies (including prospective, retrospective, registry and surveillance designs) reporting any of the following study outcomes; 1) Original data reporting of the incidence of vaccine type and non-vaccine type pneumococcal disease; 2) Inclusion or enrolment of patients in the United Kingdom; 3) Sufficient data to generate or infer incidence of disease in the general population or specific risk groups.

For data extraction, articles were independently reviewed by two investigators. Non relevant studies were excluded based on title and abstract review alone.

Outcomes

The primary outcome was the incidence of vaccine type pneumococcal disease in the adult UK population, expressed as an incidence per 100,000 population. Secondary measures included the proportion of pneumococcal disease caused by PCV13 vaccine serotypes, other vaccine serotypes and the proportion of cases of CAP caused by vaccine serotypes was recorded. In addition the proportion of cases of vaccine type pneumococcal pneumonia in risk groups expressed as incidence per 100,000 population where possible. Risk groups include patients with splenectomy, chronic respiratory disease, chronic heart disease, chronic kidney disease and diabetes. Immunosuppression included any disorder leading to significant immune suppression (whether inherited or acquired) including HIV and iatrogenic immune suppression (incl. chemotherapy and corticosteroids).

Vaccine type pneumococcal disease

Vaccine type (VT) pneumococcal disease was defined as being caused by one of the following serotypes: 4, 6B, 9 V, 14, 18C, 19 F, 23 F, 1, 3, 5, 6A, 7 F and 19A (PCV13 VT pneumococcal disease) OR pneumococcal disease caused by one of the following serotypes: 4, 6B, 9 V, 14, 18C, 19 F, 23 F, 1, 3, 5, 7 F, 19A, 2, 8, 9 N, 10A, 11A, 12 F, 15B, 17 F, 20, 22 F and 33 F. (PPSV VT pneumococcal disease).

Results were stratified according to the period of the study, following PPSV introduction (2003), following PCV7 introduction (2007) and following PCV13 introduction (2010).

Results

The primary search identified 2,431 papers, with an additional 51 papers identified from other sources. 38 cohorts were eligible for inclusion. The characteristics of the included studies are described in the online supplement (Additional file 1: Tables E1-E5). The process of literature review is summarised in Fig. 1.

Incidence of vaccine type pneumococcal disease in adults in the UK

The most recent published data for the incidence of VT pneumococcal disease is from 2013/14 in England and Wales, reported by Waight et al. [21] This data is limited to IPD.

Among all age groups (including children) PCV13 vaccine serotype IPD had an incidence of 1.40 per 100,000 population whilst PCV7 vaccine serotype IPD had an incidence of 0.2 per 100,000 population [21].

The same authors reported that this represents a statistically significant reduction in PCV13 vaccine serotype IPD compared to 2008–2010 (incidence 4.48 per 100,000 population), Incidence Rate Ratio (IRR) 0.31 (0.28–0.35) [21]. There was a corresponding increase in non-vaccine serotypes from 4.19 per 100,000 to 5.25 per 100,000 during the same period, IRR 1.25 (1.17–1.35). Regional data for the North East of England from 2006 to 2010 showed that PCV13 was responsible for 58 % of IPD cases across all age groups with a reported incidence of 7.8 per 100,000 falling to 5.2 per 100,000 in 2009/10. The corresponding figures for PCV7 serotypes were 3.9 per 100,000 in 2006/7 falling to 1.3 per 100,000 in 2009/10 [22].

The contribution of PCV13 serotypes to total IPD was relatively stable from 1996 to 2005, accounting for 76 % of cases in 1996, and 69 % in 2005 in a study from the Thames Valley region [23]. In the study of Waight et al., PCV13 serotypes accounted for 44.1 % of IPD across all age groups (42.4 % among adults aged 15 years and older) in 2008–10 falling to 20.4 % across all age groups (20.8 % among adults aged 15+) in 2013/14 [21].

Data from Scotland has also been reported [24–27]. Feikin et al. reported reductions in PCV7 serotypes following the introduction of the childhood vaccination schedule in 2007, with an IRR of 0.90 (0.61–1.35) in year one, 0.58 (0.38–0.88) in year 2, 0.29 (0.17–0.50) in year 3 and 0.16 (0.08–0.34) in year 4 post vaccine introduction [27]. These

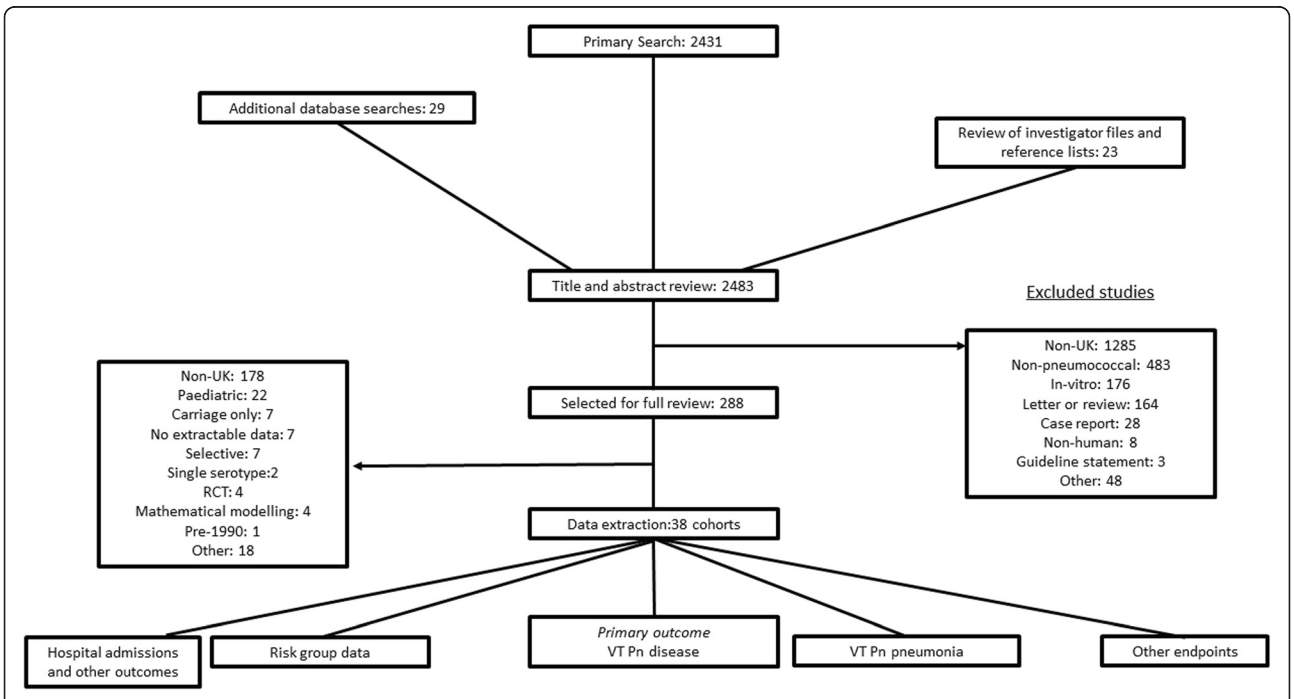


Fig. 1 Process of literature review. Abbreviations UK = United Kingdom, RCT = randomized controlled trial, Pn = pneumococcal VT = vaccine type

reductions were equivalent to those reported in other countries included in this analysis [27].

These data are limited to IPD. The search identified few studies that addressed non-invasive pneumococcal disease or that specifically addressed CAP. A series of studies conducted in Nottingham UK prospectively recruited patients admitted to hospital with CAP and used a validated multiplex immunoassay to determine 14 pneumococcal serotypes in urine [28–30]. The study of Rodrigo et al., which only included adults, found an incidence of PCV13 serotype CAP of 21.7 per 100,000 population in 2008/2009 reducing to 8.6 per 100,000 population in 2012–2013 [29]. The corresponding rates for PCV7 VT pneumococcal CAP was 11.1 per 100,000 in 2008/9 reducing to 2.3 per 100,000 in 2012–13 [29]. This was associated with a significant reduction in overall CAP from 90.7 cases per 100,000 in 2008/9 to 65.4 per 100,000 in 2012/13 [29]. This data is only applicable to hospitalised cases of CAP as outpatients were not included. Our systematic review identified no recent studies of the incidence of VT CAP managed in the community.

In terms of PPSV vaccine coverage of IPD, the proportion of pneumococcal disease cases caused by serotypes present in the vaccine, has remained stable over time. From 1995 to 1999, for those aged 5–64 years, 97.8 % of isolates were covered by the PPSV vaccine [31]. The study by Sleeman et al., identified slightly lower vaccine coverage (89.9 %) in Oxford whilst in those aged >65 years, vaccine coverage was 97.2 % [31]. Foster et al. reported coverage of 91 % for PPSV serotypes for invasive pneumococcal disease in 1995 which remained stable at 89 % in 2005 [23]. During the similar period of 1993–1999 in Scotland, Kyaw et al. reported vaccine coverage of 95 % in adults age 5–64 years and 96 % in those older than 65 [32]. This remained stable over time, with 94.9 % coverage in 2003 from a Scottish study by Clarke et al. [33] Andrews et al. reported the incidence of IPD following the introduction of the PPSV programme to all adults in 2003 [34]. From 1998 to 2004/5 they report an incidence of 17.58 per 100,000 adults, with a stable incidence of 17.95 per 100,000 in 2005/6 and 17.2 in 2006–2010, among those aged 65–74 years [34]. They noted a small reduction in incidence of PPSV serotype IPD following the introduction of PCV7 but not following introduction of PPSV- IRR following PPSV in the over 80's was 0.99 (0.90–1.08) while following introduction of PCV7 the IRR was 0.77 (0.71–0.83) [28]. The incidence rate remains substantial at 38.17 per 100,000 population in the over 80's following PCV7 introduction [34]. Regional data confirms these patterns, with data from Hull and East Yorkshire (2002–2009) showing 89 % coverage for PPSV serotypes. This varied from 94.4 % in 2002 to 81.4 % in 2009, with the change arising entirely due to reductions in PCV7 serotypes [35].

Burden of vaccine type pneumococcal community-acquired pneumonia

The majority of studies only reported data for IPD, and few specifically reported data for CAP. The only prospective study to report data on the contribution of VT pneumococcal CAP were from adults admitted to hospital in Nottingham, UK from 2008 to 2013 [29].

The proportion of cases of CAP caused by *S. pneumoniae* extracted from Rodrigo et al. [29] and the proportion of CAP cases caused by PCV7 and PCV13 are shown in Fig. 2.

This study reported a decline over 5 years in the incidence of all-cause CAP from 91 cases per 100,000 in 2008/9 falling to 65 cases per 100,000 in 2012/13. Pneumococcal pneumonia declined over the same period from 35 to 21 cases per 100,000 population. The proportion of cases of pneumococcal pneumonia caused by vaccine serotypes is shown below (Fig. 3). Overall, PCV13 serotypes accounted for 41–62 % of pneumococcal pneumonia during the study period, with the majority of these cases caused by the additional serotypes in PCV13 compared to PCV7 (namely 1,3,5,6A,7 F and 19A) [29]. This study found that only 13.3 % of pneumococcal aetiology was identified by blood cultures, consistent with comparison of population estimates which suggest the incidence of non-invasive CAP is 5 to 10 fold higher than IPD. [21, 29] Interestingly, although concerns have been raised that herd protection may not reduce the incidence of serotype 3, this study showed a marked reduction in serotype 3 CAP incidence from 2008 to 2013 [29].

The British Society for Antimicrobial Chemotherapy (BSAC) reported surveillance data from respiratory tract isolates of *S. pneumoniae*, although these represented sputum specimens without a clear clinical diagnosis of CAP [36]. Farrell et al. reported from 1997 to 2007 that PCV13 serotypes accounted for 58.6 % of respiratory tract isolates. The corresponding figure for PPSV was approximately 72.2 %, accounting for some serotypes not being reported as they were of low incidence [36].

Pneumococcal meningitis

Limited data were also available for pneumococcal meningitis, with data from Johnson et al., showing that from 1998 to 2005, PCV13 serotypes accounted for 83.6 % of cases of pneumococcal meningitis in England and Wales [37]. PPSV serotypes accounted for 94 % of cases of pneumococcal meningitis [37].

Absolute number of cases of PCV13 serotype CAP and IPD

The most recent Office for National Statistics estimates of the UK population are 54.3 m people in England, 64.5 m people across the whole of the UK, with 11.4 m people

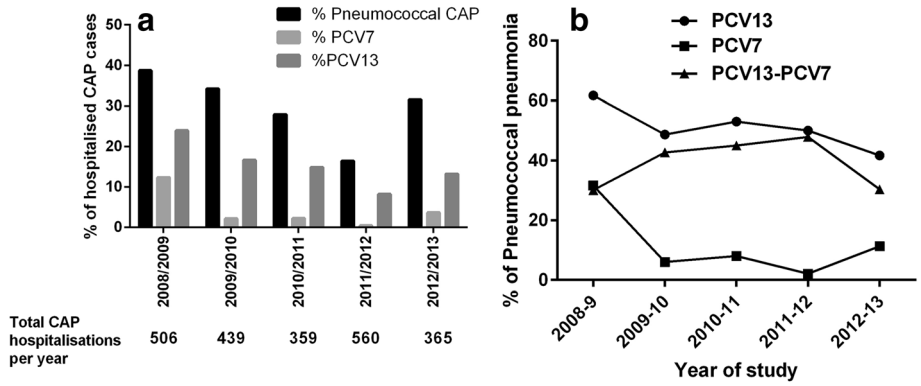


Fig. 2 **a** Proportion of cases of adult hospitalised community-acquired pneumonia caused by *S.pneumoniae*, PCV7 serotypes and PCV13 serotypes respectively. **b** Proportion of pneumococcal CAP cases caused by different vaccine serotypes. Abbreviations. PCV = pneumococcal conjugate vaccine, CAP = community-acquired pneumonia

aged >65 years [38]. Putting the incidence data into context therefore, the most recent data would indicate that 934 cases of PCV13 serotype IPD would be expected in adults per year [21]. This would include approximately 420 cases in patients aged >65 years [21]. Assuming the results of Rodrigo et al. are applicable to the adult UK population as a whole, there would be 10,696 hospitalised cases of Pneumococcal CAP annually, with 4465 cases due to PCV13 serotypes [29]. This would include an estimated 2418 cases annually due to PCV13 serotypes in patients aged ≥65 years. There was no data to estimate the number of non-hospitalised (outpatient) cases due to vaccine serotypes. These estimates are shown in Fig. 3. The figure suggests that the true incidence from 2014/15 onwards is likely to be lower than reported above due to a decreasing trend in absolute numbers with time.

Incidence of vaccine type pneumococcal disease in specific risk groups in the UK

Adults aged >65 years

Among adults aged >65 years Waight et al. reported an incidence of PCV13 serotype IPD of 10.33 per 100,000 population in 2008–10 reducing to 3.72 per 100,000 in 2013/14 [21]. PCV7 serotypes reduced from 4.58 per 100,000 in 2008–10 to 0.53 per 100,000 population in 2013/14, giving an IRR of 0.11 (0.08–0.18). This study demonstrated a highly significant reduction in all 5 additional serotypes while there were no significant reductions in the non-PCV13 serotypes [21].

From the study of Rodrigo et al., the overall contribution of pneumococcal CAP to overall CAP incidence varied from year to year from 17.1 to 37.3 % of cases [29]. The proportion of cases due to PCV7 reduced substantially

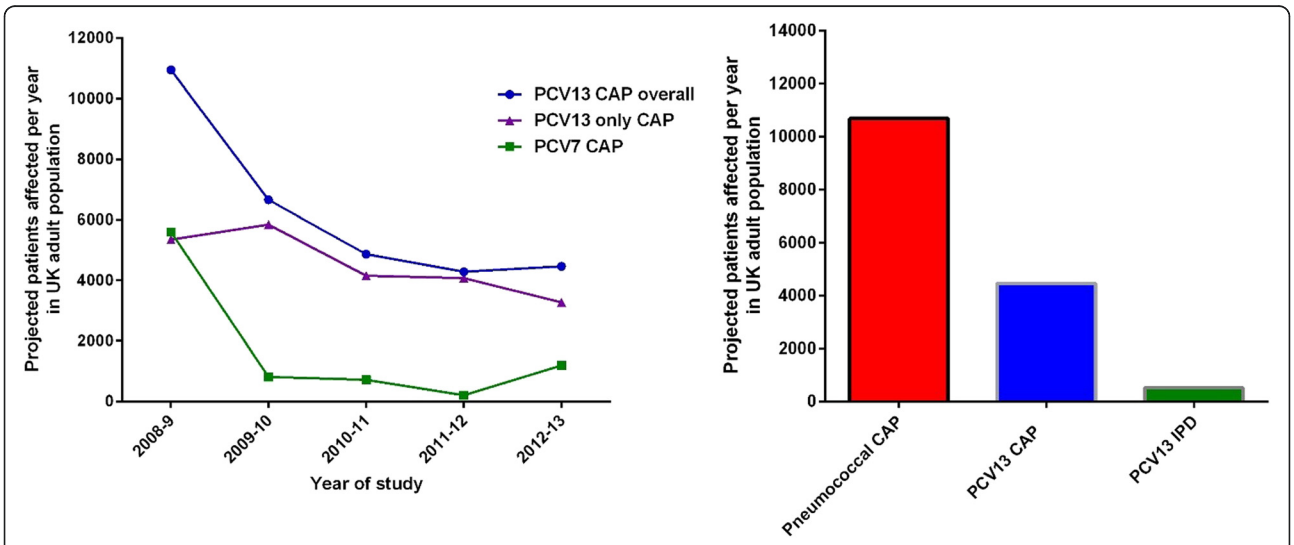


Fig. 3 Projected number of patients affected by VT pneumococcal disease based on the most recent UK data identified in the systematic review [21, 29]. PCV13 only CAP refers to serotypes contained in PCV13 that are not contained in PCV7. Abbreviations: CAP = community-acquired pneumonia, IPD = invasive pneumococcal disease

from 13.4 % of all CAP cases in 2008/9 to 0.3 % in 2011/12. Rates of CAP due to PCV13 also reduced significantly from 2008/09 onwards, from 24.8 % of CAP cases to 7.5 % of cases in 2011/12 and 12.6 % of cases in 2012/13 [29]. The largest reductions were seen in those aged >85 years [29].

Risk groups

Van Hoek reported data on the impact of clinical risk factors for IPD in England [39]. The authors examined specific risk groups including those with asplenia, chronic respiratory disease (including COPD), chronic heart disease, chronic renal disease, chronic liver disease, diabetes, immunosuppression, cochlear implants and cerebrospinal fluid leaks [39]. They used data from a 2009 survey of PPSV uptake in general practice to estimate the proportion of patients with these risk factors in England and identified 44.8 % of patients aged >65 years having had at least one risk factor, with chronic heart disease the most common. [39] The incidence of IPD was greatly increased in patients with risk factors, particularly chronic liver disease, immunosuppression and chronic respiratory disease. In the older age group (>65 years), the incidence in patients without risk factors was 17.9 per 100,000, increasing to 48 per 100,000 with one or more risk factor. This was higher still at 91 per 100,000 if the co-morbidity was COPD, and 129 per 100,000 in chronic liver disease [39].

A similar pattern was observed in younger adults (16–64 years). The baseline incidence without risk factors was 5.2 per 100,000, rising to 39 per 100,000 in risk groups, with the higher incidence 172 per 100,000 in those with chronic liver disease and 91 per 100,000 in chronic respiratory disease. The study was conducted prior to the introduction of PCV13. From 2005 to 2009, there was good coverage of PPSV in the risk groups (90 % in 2005/6 falling to 83 % in 2008/9, compared to 95 and 91 % in non-risk groups respectively), and also good coverage of PCV13 (73 % of IPD cases in 2005/6 falling to 61 % in 2008/9, compared to 75 and 64 % over the same period in non-risk groups) [39]. The introduction of PCV7 had a clear effect in both risk and non-risk groups, with the % vaccine coverage falling from 45 % in 2005/6 to 21 % in 2008/9, with no significant differences between risk and non-risk groups [39].

The search identified no specific data on the incidence of non-invasive pneumococcal infection in risk groups [10, 40–42]. A summary of the risk group incidence estimates are shown in Fig. 4. Table 1 below summarises incidence data from 3 studies with the most recent incidence data for IPD, CAP and risk groups in the UK.

Immunosuppressed patients

There are few studies of pneumococcal disease in immunosuppressed patients and most surveillance data are unable to identify these subgroups of patients. The above study by Van Hoek identified that immunosuppression was the single greatest risk factor for IPD among risk groups in the UK population [39]. The incidence was 209 per 100,000 for immunosuppressed patients aged >65 years (odds ratio 11.7 compared to patients >65 without immunosuppression). The equivalent data for younger adults was 88 per 100,000 (odds ratio 17.1 compared to adults 16–64 without immunosuppression [39]. HIV is also a risk factor for IPD. [42] The above study identified an incidence of 95 per 100,000 in the elderly (age >65 years) although this is based on only 2 cases. The incidence rate was 316 per 100,000 in adults aged 16–64 years (odds ratio 61.2 compared to patients without HIV) [39].

Yin et al. reported a study of IPD among HIV positive individuals from 2000 to 2009. This included 63,109 HIV positive adults of which 951 developed IPD. [43] This resulted in estimates of IPD incidence of 245 per 100,000 HIV positive adults. The study reported that in the final year of data (2009), 23 % of causative serotypes were covered by PCV7, a 54 % reduction compared to prior to PCV7 introduction. For PPSV, the coverage was 89 % in 2000–2006 and 91 % in 2009 [43].

Impact of vaccine type pneumococcal disease on outcomes

We identified minimal data on the pre-specified markers of disease impact such as hospitalisation rates, length of hospital stay, intensive care unit admissions, attributable mortality and healthcare costs.

Van Hoek examined differences in site of infection and mortality association with different vaccine serotypes in England and Wales. Serotypes 35 F, 6C and 18C were most frequently associated with meningitis in the elderly, and serotype 1 was most strongly associated with empyema hospitalisation [44].

The highest case fatality rates among patients aged 5–64 years were reported for serotype 31 (33 %), 11A (30 %) and 19 F (21 %). Serotype 31 is not included in either the PPSV or PCV13, while 11A is included in PPSV and not PCV13. Among the elderly (>65 years) the highest case fatality rates were for serotypes 19 F (41 %), 31 (40 %) and 3 (39 %) [44].

Scottish data was reported by Inverarity et al. for the period 1992–2007. The highest 30-day mortality rate was for serogroup 3 (24 %), followed by 19 and 23 (18 and 15 % respectively). Serotype data was not available for the majority of the study [26].

Risk groups greatly influence the risk of mortality in IPD. As reported by Van Hoek, the mortality in patients aged >65 years without other risk factors was 29.1 % (compared to 5.4 % in patients aged 16–64 years) [39]. Among the elderly, one or more risk factors increased mortality by approximately 20 %, chronic heart disease

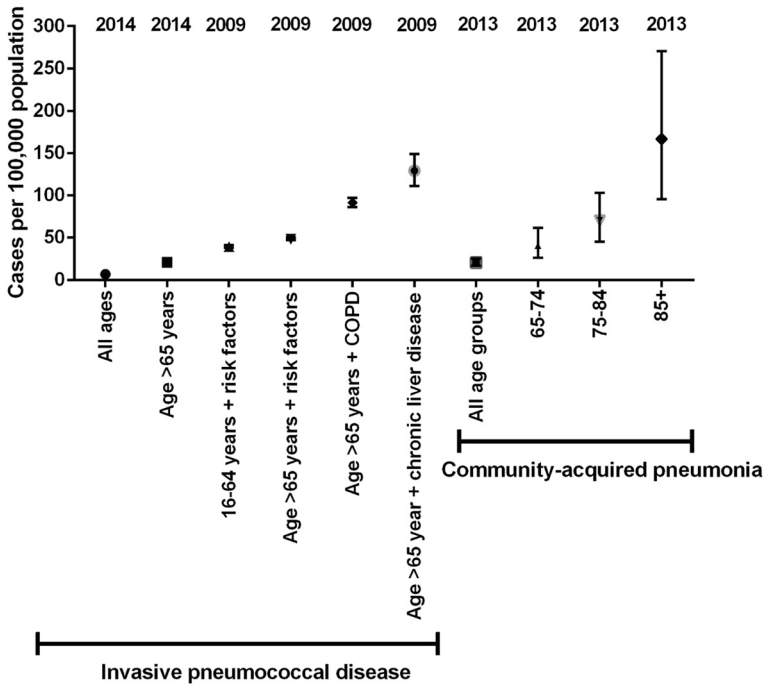


Fig. 4 The most recent incidence data available for each pre-specified population grouped according to invasive pneumococcal disease and community-acquired pneumonia. Data derived from Waight et al., Rodrigo et al. and van Hoek et al. [21, 29, 39]. The dates across the top indicate the most recent year in which data were available

increased risk by 40 %, kidney disease by 90 % and chronic liver disease was associated with a near 3 fold increased risk of death [39]. Even larger impacts were seen in the younger age group, where having one or more co-morbidity increased mortality by an odds ratio of 3.9 (3.4–4.4) [39].

Table 1 Selected population IPD and CAP disease burden estimates for PCV13 serotype CAP

Study	Population	Year	Incidence/100,000
Waight et al [21]	England and Wales IPD – all ages	2013/14	1.40
Waight et al [21]	England and Wales IPD- age >65 years	2013/14	3.72
Rodrigo et al [29]	Nottingham (multicentre) CAP- adults all ages	2012/13	8.60
Rodrigo et al [29]	Nottingham (multicentre) CAP- Age >65 years	2012/13	16.75
Van Hoek et al [39]	England Risk groups[a] Adult	2008/9	37.10[b]
Van Hoek et al [39]	England Risk groups[a] ≥65 years	2008/9	39.84[b]

CAP refers to non-invasive and invasive pneumococcal community acquired pneumonia

[a]risk groups include asplenia/splenic dysfunction/chronic respiratory disease/chronic heart disease/chronic kidney disease/chronic liver disease/diabetes/immunosuppression/cochlear implants/cerebrospinal fluid leaks [39]

[b]data extracted based on reported 83 % coverage of total IPD incidence by PCV13 during 2008/9

Discussion

Our systematic review identifies a high burden of pneumococcal disease in adults in the UK, while also revealing substantial ongoing changes in the epidemiology of pneumococcal disease. The most recent data from 2013/14 shows an incidence of 6.85 per 100,000 population across all age groups for IPD, and an incidence of 20.58 per 100,000 population in those aged >65 years [21]. The corresponding incidences for PCV13 serotype IPD were 1.4 per 100,000 and 3.72 per 100,000. The most recent available data for CAP including non-invasive disease showed an incidence of 20.6 per 100,000 for hospitalised adults with pneumococcal CAP and 8.6 per 100,000 population for hospitalised PCV13 serotype CAP [21, 29]. We have estimated that if these most recent estimates are applicable to UK population as a whole, there would be at least 10,000 cases of hospitalised pneumococcal CAP, with 4000 caused by PCV13 serotypes and more than 900 cases of PCV13 serotype IPD. The estimates of burden for non-invasive disease are likely to be an underestimate due to the absence of data from CAP managed in the community.

These data have limitations as discussed below, but suggest that pneumococcal disease and PCV13 vaccine type pneumococcal CAP continue to have a significant burden in adults, even after the introduction of PCV13 in children.

There is, however, an ongoing trend of reduced incidence of PCV13 serotype IPD and CAP in the UK, demonstrated both in the study of Waight et al., who demonstrated a 69 % incidence reduction between 2008 and 2014, and in the study by Rodrigo et al. who demonstrated a reduction of 48 % in PCV7 CAP, and a 13 % reduction in the additional serotypes contained in PCV13 [21, 29].

Pneumococcal vaccination is now a core part of public health policy [3, 45]. The pneumococcal polysaccharide vaccination covers 23 common serotypes and has been available since 1983. It was introduced into the routine vaccination schedule in England and Wales in 2003/4 for patients aged 80 and over, followed by patients aged 75 and over in 2004/5 and all patients aged 65 and over in 2005/6. The 7-valent conjugate vaccine was introduced in children in 2007, followed by the introduction of the 13-valent conjugate vaccine for children in 2010 [3].

S. pneumoniae is capable of causing IPD and non-invasive pneumococcal pneumonia [46]. We identified a large body of evidence on the incidence of IPD in the UK thanks to ongoing surveillance programmes in England, Wales and Scotland.

Patients aged >65 years have the highest incidence of pneumococcal disease and non-invasive pneumococcal pneumonia and are therefore the primary target of vaccination programmes [18]. Although high uptake of paediatric conjugate vaccines has led to a reduction in cases of adult IPD through herd protection, there remains a substantial burden of IPD and pneumococcal pneumonia in adults [47, 48].

The CAPITA trial was a randomized double blind placebo controlled trial conducted in the Netherlands which demonstrated efficacy in the reduction of vaccine type pneumococcal CAP in those adults >65 years receiving the 13-valent conjugate vaccine [18]. In the per-protocol population, vaccine efficacy for the prevention of a first episode of vaccine-type CAP was 46 %, and protection persisted for at least 4 years. There are, however, important differences between the UK and the Netherlands. The Netherlands has no PPSV programme, while uptake of the PPSV vaccination in the UK is among the best in Europe [45]. In addition, as noted above, the PCV13 vaccine has been used in the UK since 2010 for children, while the CAPITA trial results were obtained in a population where PCV7 was introduced for newborns in 2006 and replaced by PCV10 in 2011 [49]. Therefore our data allows a degree of comparison between the epidemiology of pneumococcal disease in the UK and the Netherlands. In 2008 in the Netherlands, 68.4 % of IPD episodes in patients aged 65 years or older were caused by PCV13 serotypes, compared to 42.3 % in 2013 [49]. The corresponding figures from Waight et al. for England and Wales were 44.1 and 20.3 % [21]. Rodrigo et al. reported that 40.6 % of cases of pneumococcal CAP were PCV13 VT in 2012/13 [29].

The impact of pneumococcal vaccination programmes in children has been accompanied by a concern about serotype replacement and the potential implication of this on public health [50–52]. Waight et al. reported a significant increase in non-vaccine serotype IPD following the introduction of PCV13 (IRR 1.25 95 % CI 1.17–1.35 comparing 2008–10 to 2013/14) [21]. Data reported, only in abstract form to date, from the BSAC surveillance project provides further evidence that this is occurring [53]. Using data from up to 40 clinical laboratories in the UK and Ireland, they showed for bacteraemic pneumococcal disease, 76 % of cases were PCV13 serotypes prior to PCV7 introduction (data from Jan 04-Dec 06) falling to 21 % (Jan-Dec 14). The corresponding data for respiratory isolates was 59 % falling to 17 % [53]. The most frequent serotypes for both bacteraemia and lower respiratory tract infection in 2004–6 were covered by PCV13, but in 2014 were not, with serotypes 8, 22 F and 12 F being most frequent in bacteraemia and 15A and 23B most frequent in LRTI [53]. They report associated significant increases in penicillin, tetracycline and multidrug resistance which appears to be mostly due to expansion of serotype 15A [53]. Antimicrobial resistance is an increasing problem in CAP generally and these data emphasise the importance of ongoing surveillance and consideration of the indirect impact of childhood vaccination [50–52, 54].

This study identified important gaps in the literature regarding the burden of pneumococcal disease in the UK. There was limited data outside of surveillance of IPD. Data for non-invasive pneumococcal pneumonia was limited to hospitalised patients in a single UK city, in Nottingham, England and a series of respiratory tract isolates forming part of the British Society for Antimicrobial Chemotherapy surveillance studies [31, 36, 53] which would include patients with CAP, but would also include respiratory/sputum isolates from patients with other respiratory tract infections such as exacerbations of COPD [55], bronchiectasis (where *S. pneumoniae* can be a coloniser) [56] and upper airway commensals. There are important differences both in terms of serotypes responsible for invasive vs non-invasive disease, in disease outcomes and in vaccine effectiveness against non-invasive disease vs invasive disease. Inclusion of additional data on non-invasive CAP in the UK would be valuable. Our available data suggests that there are up to 10 cases of non-invasive pneumococcal CAP for each case of IPD and so studies restricted to IPD are likely to greatly underestimate the burden of pneumococcal disease.

None of the studies identified in the systematic review were conducted in the community and so the burden of

pneumococcal disease in the community is unknown. Multiple studies suggest that *S. pneumoniae* remains the most common cause of CAP in outpatients, where the majority of CAP is managed [57–60]. Although the mortality rate of CAP in the community is low at less than 1 %, the impact is significant at a population level in terms of lost days of work, reduced productivity and long term complications [60, 61]. More data on the burden of disease in the community is needed, as hospital based studies may underestimate the true impact.

At the other end of the severity spectrum, we identified little data on the pneumococcal vaccine serotypes associated with the most severe pneumonia causing intensive care unit admission. Although Van Hoek et al. reported data on the mortality attributable to different serotypes using record linkage, similar data for ICU admission was not available [39]. Mortality and severe pneumonia requiring ICU admission are not necessarily synonymous as the majority of pneumonia related deaths occur outside the ICU with up to 50 % occurring due to co-morbidities rather than directly due to pneumonia [61–63].

The incidence of CAP, and pneumococcal disease in particular is greatly increased in at risk populations such as patients with COPD, chronic heart failure and immunosuppression [42]. COPD patients have a greatly increased frequency of pneumonia at 22.4 per 1000 person years due to a combination of reduced local immunity, co-morbidities and the impact of immunosuppression through inhaled corticosteroids [64, 65]. Additional risk factors identified through analysis of UK health records include diabetes, chronic heart disease, chronic renal disease, asplenia, chronic liver disease, sickle cell disease, HIV, previous stroke, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, dementia, osteoporosis and malignancy [66]. IPD data suggests a greatly increased risk of IPD in patients with one or more risk factors, particularly chronic liver disease, COPD and immunosuppression with evidence of "risk stacking" with the incidences greatest in patients with more risk factors, or a combination of increasing age and high risk co-morbidities [39]. Mortality from IPD is also greatly increased in patients from high risk groups, ranging from a 20 % increase in risk of death among elderly patients with COPD, to an estimated 1000 % increased risk of death among patients aged 16–64 years with chronic liver disease, compared to patients of the same age without liver disease [39].

The UK population is ageing, and therefore the burden of CAP and pneumococcal disease in general is expected to increase even with the impact of childhood and adult vaccine programmes.

There are important regional variations in the incidence of CAP in the UK. Millet et al. demonstrated a significantly lower incidence of LRTI and CAP in London and the South East of England compared to the North, Yorkshire and the Midlands in both men and women [67]. This may be partly explained by differences in socioeconomic deprivation which is a major risk factor for CAP. Given the large differences observed in this study between regions, estimates of risk averaged across the whole of the UK should be interpreted in the local context. [67]

Conclusion

VT pneumococcal disease continues to have a significant burden in adults in the UK. IPD data will underestimate the impact of pneumococcal disease because the majority of cases of CAP are non-invasive. Nevertheless, both IPD and CAP data sources in the UK suggest an ongoing herd protection effect from childhood PCV13 causing a reduction in the proportion of cases caused by PCV13 serotypes in adults. Despite this, the most recent data suggests that PCV13 serotypes account for 12.6 % of all cases of CAP and 41 % of pneumococcal CAP. This data will be useful in evaluating the clinical and economic case for adult PCV13 vaccination in the UK.

Ethical approval

Not required.

Availability of data

Data available from the authors on request.

Additional file

Additional file 1: Table of included studies. (DOCX 26 kb)

Abbreviations

BSAC: British Society of Anti-microbial chemotherapy; CAP: community acquired pneumonia; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; IPD: invasive pneumococcal disease; IRR: incident rate ratio; LRTI: lower respiratory tract infection; MOOSE: meta analysis of observational studies of epidemiology; NHS: National Health Service; PCV13: pneumococcal conjugate vaccine- 13-valent; PCV7: pneumococcal conjugate vaccine- 7-valent; PPSV: pneumococcal polysaccharide vaccine; RCT: randomized controlled trial; UK: United Kingdom; VT: vaccine type.

Competing interests

JDC reports grant support from AstraZeneca, Bayer Healthcare, Aradigm corporation and Pfizer Ltd. outside the submitted work. JC and HM are full time employees of Pfizer Ltd, UK. AD and MW declare that they have no competing interests.

Authors' contributions

JDC conceived the study, supervised the literature review, reviewed papers/abstract and wrote the manuscript. JC contributed to study design, literature review and wrote the manuscript. AD supervised the literature review, reviewed papers and abstracts and wrote the manuscript. MW contributed to study design and wrote the manuscript. HM conceived the study, contributed to study design and wrote the manuscript. All authors read and approved the final manuscript.

Funding
Supported by Pfizer Ltd, UK.

Author details
[1]School of Medicine, University of Dundee, Dundee DD1 9SY, UK. [2]Pfizer Ltd, Dorking Road, Tadworth KT20 7NS, UK. [3]Manchester Royal Infirmary, Manchester M13 9WL, UK.

Received: 15 February 2016 Accepted: 1 May 2016
Published online: 11 May 2016

References

1. Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. Lancet Infect Dis. 2004;4:144–54.
2. Krone CL, van de Groep K, Trzcinski K, et al. Immunosenescence and pneumococcal disease: an imbalance in host-pathogen interactions. Lancet Respir Med. 2014;2:141–53.
3. Miller E, Andrews NJ, Waight PA, et al. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. Lancet Infect Dis. 2011;11:760–8.
4. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009;64 Suppl 3:iii1–55.
5. Chalmers JD, Mandal P, Singanayagam A, et al. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. Intensive Care Med. 2011;37:1409–20.
6. Chalmers JD, Singanayagam A, Akram AR, et al. Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia. Systematic review and meta-analysis. Thorax. 2010;65:878–83.
7. Trotter CL, Stuart JM, George R, et al. Increasing hospital admissions for pneumonia, England. Emerg Infect Dis. 2008;14:727–33.
8. Klemets P, Lyytikainen O, Ruutu P, et al. Invasive pneumococcal infections among persons with and without underlying medical conditions: implications for prevention strategies. BMC Infect Dis. 2008;8:96.
9. Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, et al. Epidemiology of community-acquired pneumonia in older adults: a population-based study. Respir Med. 2009;103:309–16.
10. Torres A, Peetermans WE, Viegi G, et al. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax. 2013;68:1057–65.
11. Jiang Y, Gauthier A, Keeping S, et al. Cost-effectiveness of vaccinating the elderly and at-risk adults with the 23-valent pneumococcal polysaccharide vaccine or 13-valent pneumococcal conjugate vaccine in the UK. Expert Rev Pharmacoecon Outcomes Res. 2014;14:913–27.
12. Mooney JD, Weir A, McMenamin J, et al. The impact and effectiveness of pneumococcal vaccination in Scotland for those aged 65 and over during winter 2003/2004. BMC Infect Dis. 2008;8:53.
13. Public Health England. Pneumococcal disease: guidance, data and analysis. https://www.gov.uk/government/collections/pneumococcal-disease-guidance-data-and-analysis#epidemiology. Accessed 15 Feb 2016.
14. Hospital Episode Statistics. http://www.hscic.gov.uk/hes. Accessed 15 Feb 2016.
15. Melegaro A, Edmunds WJ, Pebody R, et al. The current burden of pneumococcal disease in England and Wales. J Infect. 2006;52:37–48.
16. Moberley S, Holden J, Tatham DP, et al. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;1:CD000422.
17. Lucero MG, Dulalia VE, Nillos LT et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database Syst Rev. 2009;CD004977.
18. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372:1114–25.
19. Mangen MJ, Rozenbaum MH, Huijts SM et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J. 2015. http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=fab1e230-2a90-4c64-8fb0-d948ea4ee5c5&cKey=27e4cf22-da30-4347-997c-d31f6cb1e2ea&mKey=%7B7A574A80-EAB1-4B50-B343-4695DF14907E%7D. Accessed 15 Feb 2016.
20. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008–12.
21. Waight PA, Andrews NJ, Ladhani SN, et al. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015;15:535–43.
22. Chapman KE, Wilson D, Gorton R. Serotype dynamics of invasive pneumococcal disease post-PCV7 and pre-PCV13 introduction in North East England. Epidemiol Infect. 2013;141:344–52.
23. Foster D, Knox K, Walker AS, et al. Invasive pneumococcal disease: epidemiology in children and adults prior to implementation of the conjugate vaccine in the Oxfordshire region, England. J Med Microbiol. 2008;57:480–7.
24. Lamb KE, Flasche S, Diggle M, et al. Trends in serotypes and sequence types among cases of invasive pneumococcal disease in Scotland, 1999–2010. Vaccine. 2014;32:4356–63.
25. Kyaw MH, Clarke S, Jones IG, et al. Non-invasive pneumococcal disease and antimicrobial resistance: vaccine implications. Epidemiol Infect. 2002;128:21–7.
26. Inverarity D, Lamb K, Diggle M, et al. Death or survival from invasive pneumococcal disease in Scotland: associations with serogroups and multilocus sequence types. J Med Microbiol. 2011;60:793–802.
27. Feikin DR, Kagucia EW, Loo JD, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. PLoS Med. 2013;10, e1001517.
28. Rodrigo C, Bewick T, Sheppard C, et al. Pneumococcal serotypes in adult non-invasive and invasive pneumonia in relation to child contact and child vaccination status. Thorax. 2014;69:168–73.
29. Rodrigo C, Bewick T, Sheppard C, et al. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. Eur Respir J. 2015;45:1632–41.
30. Rodrigo C, Bewick T, Sheppard C, et al. Clinical features of adults with seven-valent-conjugated-vaccine-serotype pneumococcal pneumonia. Vaccine. 2014;32:1460–5.
31. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. J Infect Dis. 2001;183:239–46.
32. Kyaw MH, Clarke S, Edwards GF, et al. Serotypes/groups distribution and antimicrobial resistance of invasive pneumococcal isolates: implications for vaccine strategies. Epidemiol Infect. 2000;125:561–72.
33. Clarke SC, Scott KJ, McChlery SM. Serotypes and sequence types of pneumococci causing invasive disease in Scotland prior to the introduction of pneumococcal conjugate polysaccharide vaccines. J Clin Microbiol. 2004;42:4449–52.
34. Andrews NJ, Waight PA, George RC, et al. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine. 2012;30:6802–8.
35. Elston JW, Santaniello-Newton A, Meigh JA, et al. Increasing incidence of invasive pneumococcal disease and pneumonia despite improved vaccination uptake: surveillance in Hull and East Yorkshire, UK, 2002–2009. Epidemiol Infect. 2012;140:1252–66.
36. Farrell DJ, Felmingham D, Shackcloth J, et al. Non-susceptibility trends and serotype distributions among Streptococcus pneumoniae from community-acquired respiratory tract infections and from bacteraemias in the UK and Ireland, 1999 to 2007. J Antimicrob Chemother. 2008;62 Suppl 2:ii87–95.
37. Johnson AP, Waight P, Andrews N, et al. Morbidity and mortality of pneumococcal meningitis and serotypes of causative strains prior to introduction of the 7-valent conjugant pneumococcal vaccine in England. J Infect. 2007;55:394–9.
38. Population estimates for UK, England and Wales, Scotland and Northern Ireland, Mid 2014. http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk–england-and-wales–scotland-and-northern-ireland/mid-2014/index.html.
39. van Hoek AJ, Andrews N, Waight PA, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012;65:17–24.
40. Seminog OO, Goldacre MJ. Risk of pneumonia and pneumococcal disease in people hospitalized with diabetes mellitus: English record-linkage studies. Diabet Med. 2013;30:1412–9.
41. Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analyses. J Epidemiol Community Health. 2012;66:1177–81.

42. Torres A, Blasi F, Dartois N, et al. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. Thorax. 2015;70:984–9.
43. Yin Z, Rice BD, Waight P, et al. Invasive pneumococcal disease among HIV-positive individuals, 2000–2009. AIDS. 2012;26:87–94.
44. van Hoek AJ, Andrews N, Waight PA, et al. Effect of serotype on focus and mortality of invasive pneumococcal disease: coverage of different vaccines and insight into non-vaccine serotypes. PLoS ONE. 2012;7:e39150.
45. Pneumococcal Polysaccharide Vaccine (PPV) coverage report, England, April 2014 to March 2015. Public Health England, 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/448406/hpr2615_ppv.pdf. Accessed 15 Feb 2016.
46. Gladstone RA, Jefferies JM, Faust SN, et al. Continued control of pneumococcal disease in the UK - the impact of vaccination. J Med Microbiol. 2011;60:1–8.
47. van Hoek AJ, Sheppard CL, Andrews NJ, et al. Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England. Vaccine. 2014;32:4349–55.
48. Collins AM, Wright AD, Mitsi E, et al. First human challenge testing of a pneumococcal vaccine. Double-blind randomized controlled trial. Am J Respir Crit Care Med. 2015;192:853–8.
49. van Deursen AM, van Mens SP, Sanders EA, et al. Invasive pneumococcal disease and 7-valent pneumococcal conjugate vaccine, the Netherlands. Emerg Infect Dis. 2012;18:1729–37.
50. Gladstone RA, Jefferies JM, Tocheva AS, et al. Five winters of pneumococcal serotype replacement in UK carriage following PCV introduction. Vaccine. 2015;33:2015–21.
51. Bottomley C, Roca A, Hill PC, et al. A mathematical model of serotype replacement in pneumococcal carriage following vaccination. J Royal Soc Inter Royal Soc. 2013;10:20130786.
52. Choi YH, Jit M, Gay N, et al. 7-Valent pneumococcal conjugate vaccination in England and Wales: is it still beneficial despite high levels of serotype replacement? PLoS ONE. 2011;6:e26190.
53. Reynolds R, Mushtaq S, Fry N et al. Expansion of multi-resistant (non-vaccine) serotype 15A in both invasive and respiratory streptococcus pneumoniae infections in the UK and Ireland. ICAAC 2015. http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=fab1e230-2a90-4c64-8fb0-d948ea4ee5c5&cKey=27e4cf22-da30-4347-997c-d31f6cb1e2ea&mKey=%7B7A574A80-EAB1-4B50-B343-4695DF14907E%7D. Accessed 15 Feb 2016.
54. Chalmers JD, Rother C, Salih W, et al. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. Clin Infect Dis. 2014;58:330–9.
55. Bafadhel M, Haldar K, Barker B, et al. Airway bacteria measured by quantitative polymerase chain reaction and culture in patients with stable COPD: relationship with neutrophilic airway inflammation, exacerbation frequency, and lung function. Int J Chron Obstruct Pulmon Dis. 2015;10:1075–83.
56. Chalmers JD, Smith MP, McHugh BJ, et al. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2012;186:657–65.
57. Cilloniz C, Ewig S, Polverino E, et al. Community-acquired pneumonia in outpatients: aetiology and outcomes. Eur Respir J. 2012;40:931–8.
58. Almirall J, Boixeda R, Bolibar I, et al. Differences in the etiology of community-acquired pneumonia according to site of care: a population-based study. Respir Med. 2007;101:2168–75.
59. Woodhead MA, Macfarlane JT, McCracken JS, et al. Prospective study of the aetiology and outcome of pneumonia in the community. Lancet. 1987;1:671–4.
60. Akram AR, Chalmers JD, Hill AT. Predicting mortality with severity assessment tools in out-patients with community-acquired pneumonia. QJM. 2011;104:871–9.
61. Eurich DT, Marrie TJ, Minhas-Sandhu JK, et al. Ten-year mortality after community-acquired pneumonia. A prospective cohort. Am J Respir Crit Care Med. 2015;192:597–604.
62. Bauer TT, Welte T, Strauss R, et al. Why do nonsurvivors from community-acquired pneumonia not receive ventilatory support? Lung. 2013;191:417–24.
63. Mortensen EM, Coley CM, Singer DE, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med. 2002;162:1059–64.
64. Mullerova H, Chigbo C, Hagan GW, et al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir Med. 2012;106:1124–33.
65. Singanayagam A, Chalmers JD, Hill AT. Inhaled corticosteroids and risk of pneumonia: evidence for and against the proposed association. QJM. 2010;103:379–85.
66. Vinogradova Y, Hippisley-Cox J, Coupland C. Identification of new risk factors for pneumonia: population-based case–control study. Br J Gen Pract. 2009;59:e329–38.
67. Millett ER, Quint JK, Smeeth L, et al. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PLoS ONE. 2013;8:e75131.

Chalmers et al. Pneumonia (2017) 9:15
DOI 10.1186/s41479-017-0039-9

Pneumonia

COMMENTARY Open Access

Community-acquired pneumonia in the United Kingdom: a call to action

James Chalmers[1,5*], James Campling[2], Gillian Ellsbury[2], Peter M. Hawkey[3], Harish Madhava[2] and Mary Slack[4]

Abstract

Pneumococcal disease has a high burden in adults in the United Kingdom (UK); however, the total burden is underestimated, principally because most cases of community-acquired pneumonia (CAP) are non-invasive. Research into pneumonia receives poor funding relative to its disease burden (global mortality, disability-adjusted life years, and years lived with disability), ranking just 20 out of 25 for investment in infectious diseases in the UK. The current accuracy of data for establishing incidence rates is questionable, and it is a reflection of the paucity of research that much of the background information available derives from nearly 30 years ago. Given the relationship between CAP and mortality (pneumonia accounts for 29,000 deaths per annum in the UK, and 5–15% of patients hospitalised with CAP die within 30 days of admission), and the increasing threat of antimicrobial resistance associated with inappropriate antibiotic prescribing, such neglect of a highly prevalent problem is concerning. In this Call to Action, we explore the poorly understood burden of CAP in the UK, discuss the importance of an accurate diagnosis and appropriate treatment, and suggest how national collaboration could improve the management of an often life-threatening, yet potentially preventable disease.

Keywords: Antimicrobial resistance, *Clostridium Difficile*, Community-acquired pneumonia, Immunization, Pneumococcal disease, Pneumonia burden, Pneumonia diagnostics, Pneumonia epidemiology, *Streptococcus Pneumoniae*

Background

By any measure, pneumonia has a huge impact on the United Kingdom (UK) and European healthcare systems, being associated with high rates of hospital admission and length of stay. Across Europe, annual inpatient care accounts for healthcare expenditure of €5.7 billion, outpatient care for €0.5 billion, and medication for €0.2 billion. The reported incidence of invasive pneumococcal disease (IPD) in the UK is 6.85 per 100,000 annually [1]. In addition, 5–15% of patients hospitalised with community-acquired pneumonia (CAP) will die within 30 days of admission, rising to 30% for those admitted to the intensive care unit [2]. This is particularly worrying because pneumonia is responsible for more hospital admissions and bed days than any other lung disease in the UK, and results in 29,000 deaths per annum—the third greatest cause of death from lung disease after chronic obstructive pulmonary disease (COPD; second greatest cause) and lung cancer (leading cause). Furthermore, the UK ranks 21 out of 99 countries for age-standardized mortality due to pneumonia [3]. CAP also has long-term implications for subsequent mortality; 1-, 5-, and 7-year mortality rates in patients who recovered from CAP in the Netherlands were significantly higher at 17%, 43%, and 53%, respectively, than the mortality rates seen in age- and sex-matched population controls (4%, 19%, and 24%). Malignancy (27%), COPD (19%), and cardiovascular disease (16%) were the most common causes of death [4].

Conditions such as cardiovascular disease have seen mortality rates drop significantly over the past 10 years [5] in line with major research initiatives and funding allocation, but little progress has been observed in pneumonia epidemiology, pathophysiology, or therapy. Indeed, in an analysis of UK infectious disease research funding (1997–2013), pneumonia received poor investment relative to its disease burden (global mortality, disability-adjusted life years, and years lived with

* Correspondence: jchalmers@dundee.ac.uk
[1]University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK
[5]Division of Molecular & Clinical Medicine, School of Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK
Full list of author information is available at the end of the article

disability), ranking just 20 out of 25 infectious diseases [6]. In this article, we argue that, despite its obvious impact and burden, pneumonia is a substantially underestimated, neglected, and underfunded condition in the UK. Many possible reasons exist for this unfortunate position; none of them, we would argue, is acceptable.

Streptococcus pneumoniae is the leading cause of community-acquired pneumonia in the UK and Europe [7]. The results of a recent systematic review [2] show that (i) vaccine-type pneumococcal disease still has a high burden in UK adults, and (ii) the total burden of pneumococcal disease in the UK is underestimated, principally because most cases of CAP are non-invasive. Given the relationship between CAP and mortality, and the increasing threat of antimicrobial resistance (AMR) associated with inappropriate antibiotic prescribing, this neglect of a highly prevalent problem is concerning.

Here, we explore the poorly understood burden of CAP in the UK, discuss the importance of an accurate diagnosis and appropriate treatment, and suggest how national collaboration could improve the management of an often life-threatening, yet potentially preventable disease.

Community-acquired pneumonia is an immediate and growing concern

Pneumonia disproportionately affects older people [8], with an overall CAP incidence of approximately 7.99/1000 person-years in patients aged 65 years or older, and a doubling of incidence between individuals aged 65–69 and 85–89 years, according to 1997–2011 data from the UK Clinical Practice Research Datalink, associated with the Hospital Episode Statistics (HES) database [9]. Given that the UK population is aging (it is estimated that 23% will be aged ≥65 years by 2035 vs. 17% in 2010) [10], the economic burden of caring for elderly patients with pneumonia can only increase in the absence of steps to minimize the incidence of the disease [7].

Pneumonia and lower respiratory tract infections are major causes of morbidity and mortality among those aged 65 years or older [9], and CAP in the elderly can aggravate underlying comorbidities (e.g. cardiovascular disease, renal disease, liver disease, and malignancy) with serious consequences [11]. Furthermore, long-term quality of life is substantially affected by CAP, and pneumococcal pneumonia increases the risk of pneumonia-related mortality three-fold versus non-pneumococcal pneumonia in elderly patients [7].

Given the growing burden of disease, mechanisms to reduce societal- and healthcare-associated costs must be a priority. Prevention aside, the identification of individuals who could be managed in the outpatient setting could not only virtually eliminate hospital costs but also decrease risk of infection with potentially resistant nosocomial bacteria [7]. However, a study by Woodhead et al. [12] (1987), conducted almost 30 years ago, was the last to investigate the relative proportions of patients with CAP accessing primary and secondary care in the UK. This study found that 22% of CAP was treated in hospital, with the remainder treated in primary care [12]. For the UK National Health Service (NHS), avoiding emergency admissions is a major concern due to the high costs versus other forms of care; however, most clinical commissioning groups (formerly known as primary care trusts) still have high rates of emergency admissions [13].

Increased socioeconomic deprivation is associated with increased incidences of both CAP and lower respiratory tract infection. Regional variations exist; rates of CAP in the UK are approximately 70% higher in the most deprived quintile (North England) than in the least deprived quintile (London and South East coast) [9].

Finally, CAP has an indirect socioeconomic impact; the same historical cohort study [12] mentioned above found that approximately half of patients in employment required more than two weeks off work. Data are lacking on the current effect of pneumonia on work days lost to CAP in the UK. In Europe, this cost is estimated to be €3.6 billion annually [7].

How are policy makers and healthcare funders making informed decisions?

CAP is a cause for serious concern, yet it is largely ignored in the political and healthcare arenas. This situation could reflect a lack of understanding of the extent of the problem. The current accuracy of data for establishing incidence rates is questionable; we believe the statistics quoted above are an underestimate. This view is supported by data from other developed countries (see Fig. 1). It is a reflection of the paucity of research that much of the UK background information available derives from nearly 30 years ago.

In more detail, the recent prospective cohort study of adults (aged ≥16 years) with CAP admitted to two large teaching hospitals (acute admission units, hospital wards and critical care units) in Nottingham, UK, used a standardized proforma to collect daily information on patient demographics, clinical information, microbiological investigations, radiological findings and outcome measures [14]. Inclusion criteria comprised symptoms suggestive of lower respiratory tract infection (at least one of breathlessness, cough, sputum, or fever), with new infiltrates on chest radiography consistent with pneumonia, and treatment by the admitting clinical team for CAP. Exclusion criteria were post-obstruction pneumonia due to lung cancer, active tuberculosis (discharged from hospital within the preceding 10 days), and aspiration pneumonia. The overall incidence rates for

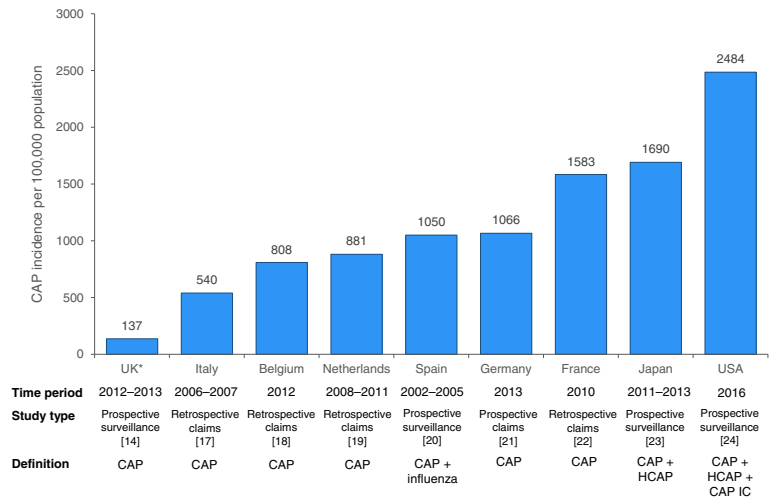


Fig. 1 Incidence rates of CAP around the world. *Age group 65–74 years only. CAP, community-acquired pneumonia; CAP IC, community-acquired pneumonia in children; HCAP, healthcare-acquired pneumonia

patients who were hospitalized with CAP and pneumococcal CAP over 5 years (2008–2013) were 79.9 and 23.4 cases per 100,000 population, respectively. However, this study was not strictly designed to determine the overall incidence of CAP. It did not, for example, include data for patients (i) who did not consent for study; (ii) from whom a urine sample was not obtained; (iii) who were discharged from hospital within 10 days previously; (iv) who were admitted via a route not involving acute admission units, hospital wards and critical care units, or (v) who attended Accident and Emergency (A&E) but were not admitted. Furthermore, a substantial discrepancy exists between the number of patients aged 16 years or older and eligible for inclusion in the Nottingham study (n = 2702) [14] and HES data for the corresponding population (n = 11,059) [15]; there is also a large difference in CAP incidence rates from these two sources. Miscoding of HES data is a well-recognized limitation of the database, but that notwithstanding, the four-fold scale of this range is alarming, not least because it is unclear which of the two values is more accurate. Such a discrepancy might represent the difference between, for example, an incidence in Nottingham of 50,000 and 200,000 CAP cases per annum. These data together with known, extensive regional variations associated with socioeconomic deprivation [9] and higher European incidence rates (Fig. 1) would tend to reduce confidence in published UK incidence rates. HES data are used by Public Health England (PHE) to help guide policy [16], but the problems outlined above mean that decisions are based on data which might lack adequate strength and/or consistency.

A comparison of rates across Europe suggests that the incidence of CAP is seriously underestimated in the UK (Fig. 1), lending credence to the suggestion that the Nottingham study data may represent an incomplete assessment of the incidence of CAP in the UK, which the HES data might help to clarify. The authors considered opinion is that even the latter numbers are likely to be an underestimate. By considering possible routes via which patients with CAP access healthcare in the UK (Fig. 2), it becomes clear that across the country, the capture of CAP incidence in primary care is difficult, and the capture of CAP incidence in secondary care is incomplete. One of the fundamental drivers of this problem is the lack of a specific ICD-10 (10th revision of the International Statistical Classification of Diseases and Related Health Problems) diagnostic code for CAP, with the result that coding is not complete and patients are spread across multiple diagnostic codes.

The consequence of underestimating the incidence, and therefore the importance, of CAP is that its impact on major healthcare outcomes such as AMR, *Clostridium difficile* infection (CDI), healthcare costs and winter pressures are, in turn, greatly underestimated. Such incomplete data on the incidence of CAP have major implications for all involved in healthcare, but particularly for those responsible for healthcare policy at governmental and local levels, who base far-reaching decisions on such information. It is our view that we cannot tackle the consequences of CAP until we raise the profile of CAP among the public, policy makers, and research funders.

Inappropriate antibiotic treatment of community-acquired pneumonia aggravates the development of antimicrobial resistance

Hospitalization for CAP is increasing; from 1998 to 2008, the incidence of CAP-associated admissions in

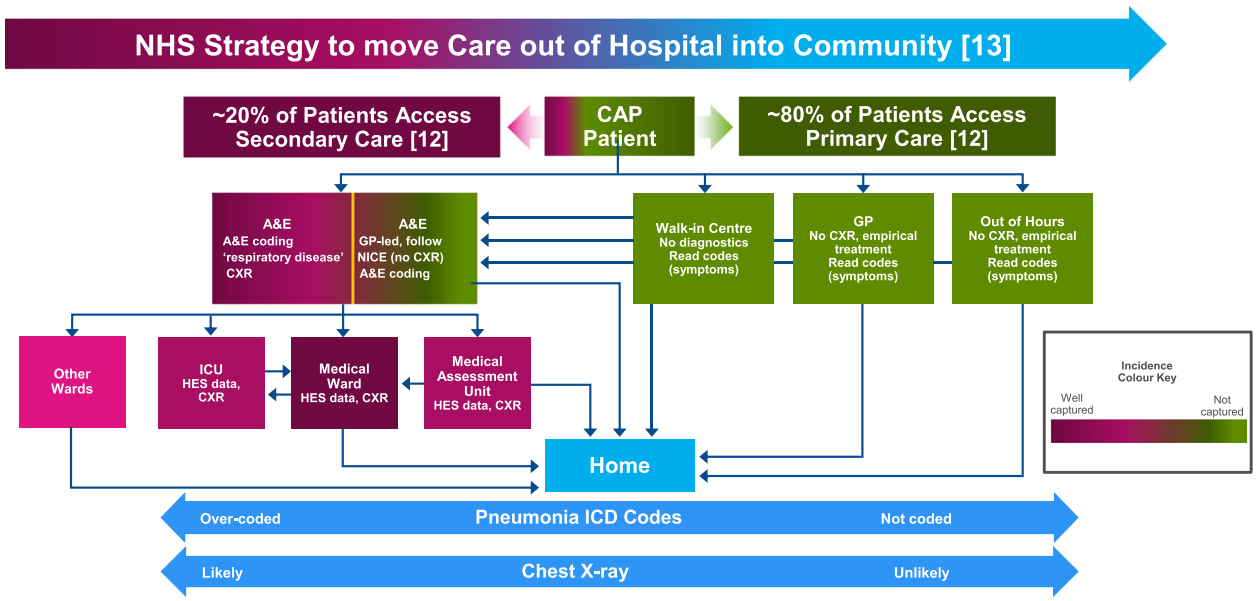


Fig. 2 Simplified schematic of the UK care pathway for adult patients with CAP accessing healthcare, and estimated capture of incidence rates. A&E, accident and emergency; CAP, community-acquired pneumonia; CXR, chest X-ray; GP, general practitioner; HES, hospital episode statistics; ICU, intensive care unit; NICE, National Institute for Health and Care Excellence

Oxfordshire (UK) rose by 4.2% per year, accelerating to 8.8% per year from 2009 to 2014 [8]. Trotter et al. [17] also showed a marked increase (34%) in pneumonia hospitalizations between 1997 and 1998 and 2004–2005 in the UK. Consequently, because antibiotics are most commonly indicated for respiratory tract infections in UK hospitals (comprising 31% of prescriptions) [18], it seems likely that increasing rates of hospital admissions for CAP will also result in a rise in antibiotic prescribing, contributing to the development of AMR [8].

In Europe, AMR has been observed in all pathogens associated with CAP, including *S. pneumoniae*, which is the single most common causative agent isolated [7]. CDI is strongly associated with broad-spectrum antibiotic use in CAP and is often nosocomial. [19, 20] A study [20] in two Edinburgh hospitals found that (i) all of the broad-spectrum antibiotics commonly used in CAP (amoxicillin/clavulanic acid, cephalosporins, and quinolones) were associated with a high level of risk for CDI, and (ii) shortened antibiotic treatment duration can reduce disease incidence, risk of developing AMR, side effects, length of stay and hospital costs.

Improved antimicrobial stewardship and the development of novel measures to tackle AMR are urgently needed. A pathogen-directed antibiotic strategy (e.g. use of penicillin rather than amoxicillin-clavulanate to treat likely or confirmed pneumococcal disease) has demonstrated comparable clinical efficacy to an empirical broad-spectrum antibiotic strategy in patients with CAP [21]. Appropriate treatment with pathogen-directed antibiotics is likely to help reduce the risk of AMR, but we lack robust, cost-effective and widely available diagnostics. A perception exists that antimicrobial-resistant pathogens are increasing in UK and international CAP patients, leading to increased use of broad-spectrum antibiotics. Without prospective studies using modern diagnostics and determining the true incidence of CAP and its associated pathogens, antibiotic policies are reliant on superannuated microbiological data, or international data that may not be applicable to the UK. A systematic review has shown that current criteria used to identify potentially antibiotic resistant pathogens in the USA are not applicable to UK or European CAP patients [22].

There is an urgent need to develop rapid, accurate, point-of-care diagnostics capable of (i) differentiating between viral and bacterial infections in CAP in the community setting to minimize unnecessary antibiotic prescription [23], and (ii) identifying bacterial infections to guide pathogen-directed antibiotic treatment. Point-of-care diagnostics will have added benefit in helping to establish both the true incidence of CAP and the understanding of bacterial versus viral burden in the disease. Initiatives such as the "Longitude Prize" [24] are an important factor in promoting diagnostic research.

A 2013 Cochrane review [25] has shown that 23-valent pneumococcal polysaccharide vaccination prevents IPD and non-invasive pneumococcal pneumonia, but does not have an impact on all-cause CAP. It is essential to increase vaccine coverage (e.g. against the

Table 1 Call to Action in the UK

Implement core research into CAP incidence and development of diagnostic tests	• Prospective, national community study of the true incidence of CAP in primary care o Incorporating representative centres from each major UK geographical region • Prospective national study of the true incidence of CAP in secondary care o Involving ~5 representative centres; one in each major UK geographical region • Develop simple, accurate, and affordable point-of-care diagnostic(s) for: o Differentiating viral vs. bacterial CAP to avoid unnecessary antibiotic use o Identifying causative pathogen to guide pathogen-directed antibiotic therapy
Investigate the true impact of CAP on AMR	• Role/scale of inappropriate antibiotic prescribing in the treatment of CAP in both primary and secondary care • Contribution of inappropriate prescribing in CAP to the development of AMR • Establish the effectiveness of antibiotic stewardship programs in terms of improved CAP outcomes and reduced AMR • Comprehensive molecular diagnostic studies in patients with CAP to establish the incidence of antibiotic resistant pathogens and novel approaches to identify those requiring broad-spectrum antibiotic therapies
Implement appropriate immunization	• Institute appropriate vaccination strategy, including groups at risk, according to national recommendations

most common causative agents, *S. pneumoniae* and influenza) [7]) to at least prevent IPD and non-invasive pneumonia, thereby potentially reducing antibiotic use (including that for treating pneumonia-associated secondary infection) and minimizing selective pressure leading to AMR [23]. The WHO Global Action Plan on Antimicrobial Resistance advocates the development and use of new or improved vaccines to prevent diseases becoming problematic due to AMR [26]. Furthermore, the UK Joint Committee on Vaccinations and Immunisation (JCVI) has recognized the strategic importance of immunization in addressing AMR, recommending that cost-effectiveness analyses of vaccination programs should include the potential benefits of reduced antimicrobial use [27].

Data from the Nottingham study [14], together with serotype-specific surveillance data for IPD (July to June from 2002 to 2003 to 2013–2014) collated by Public Health England, published by Waight et al. [1] and analyzed for cost effectiveness by Van Hoek et al. [28], were instrumental in the JCVI decision that 13-valent pneumococcal conjugate vaccine would not be universally recommended for those aged 65 years and older in England. The vaccine is therefore only offered to those aged 10 years or older who have been identified as being at particularly high risk of, and high mortality from, IPD (e.g. those receiving bone marrow transplants, or with acute or chronic leukaemia) [29]. Necessarily, determining the efficacy and cost effectiveness of vaccination programs requires accurate information on the burden of disease. As noted previously, data on CAP incidence are poorly captured in the UK, not least because most cases of CAP are non-invasive [2].

Call to action

As a first step, we draw attention to pneumonia as an underestimated, neglected, and underfunded condition in the UK, and call for all healthcare practitioners, researchers, health planners, and policy makers at both primary and secondary care level to react swiftly, as outlined in Table 1. National prospective studies of the true incidence of CAP in both primary and secondary care (including reasons for patients being overlooked or lost to follow-up), immediate review of CAP diagnostic methods, and effective preventative strategies (e.g. adequate vaccination programs) are urgently needed to ensure that all patients (especially the elderly) receive optimal care and treatment to minimize the impact of CAP, reduce its medical and socioeconomic burden, and restrict the development of AMR.

Abbreviations

A&E: accident & emergency; AMR: antimicrobial resistance; CAP IC: community-acquired pneumonia in children; CAP: community acquired pneumonia; CDI: *Clostridium difficile* infection; CXR: chest X-ray; GP: general practitioner; HCAP: healthcare-acquired pneumonia; HES: Hospital Episode Statistics; ICD-10: International Statistical Classification of Diseases and Related Health Problems – 10th revision; ICU: intensive care unit; IPD: invasive pneumococcal disease; JCVI: Joint Committee on Vaccinations and Immunisation; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PHE: Public Health England; WHO: World Health Organization

Acknowledgements

Not applicable.

Funding

Dr. James Chalmers, Prof. Peter Hawkey and Prof. Mary Slack received honoraria from Pfizer in connection with the development of this manuscript. Pfizer also provided funding for the following: Hospital Episode Statistics (HES) data processing and analysis by Harvey Walsh Ltd. under an NHS digital re-use agreement, medical writing support by Richard Watt of Sudler Medical Communications, and journal publication charges.

Availability of data and materials

The datasets used and/or analysed for the current article are available from the corresponding author on reasonable request.

Authors' contributions

All authors were involved in draft content development, and in reading and approval of the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
Dr. James Chalmers has received research grant support from AstraZeneca, Pfizer, GlaxoSmithKline, Boehringer-Ingelheim and Bayer Healthcare and has participated in advisory boards or lectures for Griffols, AstraZeneca, Pfizer, Napp, Boehringer-Ingelheim and Bayer Healthcare.
Prof. Peter Hawkey has received support from Pfizer to present at educational meetings and to attend advisory board meetings, as well as research funding and/or speaker support from: AstraZeneca, Beckton Dickinson, Eumedica; MSD, Novartis, Novacta, Roche, Department of Health UK, NIHR, and PHE. He is also Director of Modus Medica, a medical education/consultancy.
Prof. Mary Slack has received personal fees from GSK, Pfizer, AstraZeneca and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards (outside the scope of the submitted work). She has also worked as a contractor for Pfizer.
James Campling, Gillian Ellsbury and Harish Madhava are full-time employees of Pfizer; no other conflicts of interest to declare.

Publisher's Note

Author details
[1]University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK. [2]Pfizer Ltd, Tadworth KT20 7NS, UK. [3]Institute of Microbiology and Infection, University of Birmingham, B15 2TT, Birmingham, UK. [4]School of Medicine, Griffith University, Campus, Gold Coast, QLD 4222, Australia. [5]Division of Molecular & Clinical Medicine, School of Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK.

Received: 14 June 2017 Accepted: 7 September 2017
Published online: 05 October 2017

References

1. Waight WA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MPE, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015;15:535–43.
2. Chalmers JD, Campling J, Dicker A, Woodhead W, Madhava H, et al. A systematic review of the burden of vaccine preventable pneumococcal disease in UK adults. BMC Pulm Med. 2016;16:77.
3. British Lung Foundation. The battle for breath – the impact of lung disease in the UK. 2016. Available from: https://www.blf.org.uk/what-we-do/our-research/the-battle-for-breath-2016. Accessed Apr 2017.
4. Bruns AH, Oosterheert JJ, Cucciolillo MC, El Moussaoui R, Groenwold RH, Prins JM, et al. Cause-specific long-term mortality rates in patients recovered from community-acquired pneumonia as compared with the general Dutch population. Clin Microbiol Infect. 2011;17:763–8.
5. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe W, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J. 2016;0:1–14.
6. Head MG, Fitchett JR, Nageshwaran V, Kumari N, Hayward A, Atun R. Research investments in global health: a systematic analysis of UK infectious disease research funding and global health metrics, 1997–2013. EBioMedicine. 2015;3:180–90.
7. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67:71–9.
8. Quan TP, Fawcett NJ, Wrightson JM, Finney J, Wyllie D, Jeffery K, et al. Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998–2014. Thorax. 2016;71:535–42.
9. Millett CR, Quint JK, Smeeth L, et al. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PLoS One. 2013;8:e75131.
10. Office for National Statistics. Statistical Bulletin – Older People's Day, 2011. Available from: http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/dcp171778_235000.pdf. Accessed Nov 2016.
11. Kaplan V, Clermont G, Griffin MF, Kasal J, Scott Watson R, Linde-Zwirble WT, et al. Pneumonia. Still the old man's friend? Arch Intern Med. 2003;163:317–23.
12. Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology of pneumonia in the community. Lancet. 1987;1:671–4.
13. Purdy S. Avoiding hospital admissions. What does the research evidence say? The King's Fund, 2010. Available from: www.kingsfund.org.uk/sites/files/kf/Avoiding-Hospital-Admissions-Sarah-Purdy-December2010.pdf. Accessed Nov 2016.
14. Rodrigo C, Bewick T, Sheppard C, Greenwood S, Mckeever TM, Trotter CL, et al. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. Eur Respir J. 2015;45:1632–41.
15. Hospital Episode Statistics (HES) data. 2016. Reused with the permission of NHS digital. All rights reserved.
16. Thorrington D, Andrews N, Stowe J, Miller E et al. The hospitalised burden of pneumonia in England in the conjugate vaccine era. 10th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-10) Glasgow, UK, Jun 26–30, 2016. Poster presentation Available from: http://s3-eu-west-1.amazonaws.com/poster-isppd2016/original/ISPPD-0692.pdf. Accessed May 2017.
17. Trotter CL, Stuart JM, George R, et al. Increasing hospital admissions for pneumonia. England Emerg Infect Dis. 2008;14:727–33.
18. Health Protection Agency. English National Point Prevalence Survey on Healthcare-associated Infections and Antimicrobial use, 2011. London: Public Health England, 2012. Available from: http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317134304594. Accessed Nov 2016.
19. Slimings C, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile* infection: update of systematic review and meta-analysis. J Antimicrob Chemother. 2014;69:881–91.
20. Chalmers JD, Akram AR, Singanayagam A, et al. Risk factors for *Clostridium difficile* infection in hospitalized patients with community-acquired pneumonia. J Inf Secur. 2016b;73:45–53.
21. Van der Eerden MM, Vlaspolder F, De Graaff CS, Groot T, Bronsveld W, Jansen HM, et al. Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study. Thorax. 2005;60:672–8.
22. Chalmers JD, Roither C, Salih W, et al. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. Clin Infect Dis. 2014;58:330–9.
23. Review on Antimicrobial Resistance. Tackling drug-resistant Infections globally: Final report and recommendations, 2016. Available from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf. Accessed Nov 2016.
24. Longitude Prize, 2014. Available from: https://longitudeprize.org/challenge/antibiotics. Accessed Nov 2016.
25. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;1:CD000422.
26. WHO. Global Action Plan on Antimicrobial Resistance, 2015. Available from: http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf. Accessed Dec 2016.
27. Joint Committee on Vaccinations and Immunisation. Minutes of the meeting on 1 October 2014. Available at: https://app.box.com/s/iddfb4ppwkmtjusir2tc/1/2199012147/22846051967/1. Accessed Dec 2016.
28. Van Hoek AJ, Miller E. Cost-effectiveness of vaccinating immunocompetent ≥65 year olds with the 13-valent pneumococcal conjugate vaccine in England. PLoS One. 2016;11(2):e0149540.
29. Joint Committee on Vaccinations and Immunisation. Interim JCVI statement on adult pneumococcal vaccination in the UK. Available at: https://www.gov.uk/government/publications/jcvi-interim-statement-on-adult-pneumococcal-vaccination. Accessed Jul 2017.

Vaccine 38 (2020) 8068–8070

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

The proportion of contemporary invasive pneumococcal disease and pneumococcal pneumonia in UK adults reflected by serotypes included in the 13-valent pneumococcal conjugate vaccine and next generation higher valency pneumococcal conjugate vaccines in development

Andrew Vyse [a,*], James Campling [a], Carole Czudek [a], Gillian Ellsbury [a], Mary Slack [b]

[a] Pfizer Ltd, Walton Oaks, Tadworth KT20 7NS, UK
[b] School of Medicine, Griffith University, Gold Coast Campus, Queensland 4222, Australia

ARTICLE INFO

Article history:
Received 1 September 2020
Received in revised form 27 October 2020
Accepted 29 October 2020
Available online 12 November 2020

Keywords:
Pneumococcal
Disease
Conjugate
Vaccine
Serotype
Distribution
Adult

The UK introduced a pneumococcal conjugate vaccine (PCV) that covered seven serotypes (PCV-7) for routine infant immunisation in 2006 which was replaced with a 13 valent PCV (PCV-13) in 2010 [1]. This resulted in major reductions in the vaccine type pneumococcal disease burden across all age ranges due to both direct and indirect protection [2]. PCV-13 is also licensed in the UK for the prevention of invasive pneumococcal disease (IPD) and pneumococcal pneumonia in adults but is currently only recommended for very high-risk adults in the UK. At present all UK adults aged 65+ years and those considered at increased risk of pneumococcal infection are routinely offered a single dose of the 23-valent pneumococcal polysaccharide vaccine (PPV-23) with re-vaccination recommended for patients with chronic renal disease and asplenia/splenic dysfunction [1]. However, PPV-23 has only limited short term effectiveness against IPD in UK adults aged 65+ years with no impact achieved at the population level [3]. There is also a lack of consistent evidence showing PPV-23 effectiveness against adult community acquired pneumonia (CAP), which reflects a much larger disease burden compared to adult IPD with the pneumococcus an important cause [4]. Since 2013/14 there has been a rapid increase in IPD in older UK adults aged 65+ years that is especially attributed to several PPV-23 non PCV-13 (PPV-23non13) serotypes [2]. Next generation higher valency PCVs (PCV-15 and PCV-20) that include some PPV-23non13 serotypes are now in advanced stages of development [5,6]. These are anticipated to shortly become available for use in adults and may offer new opportunities to protect UK adults against pneumococcal disease. The serotypes included in currently available pneumococcal vaccines (PCV-13, PPV-23) and next generation higher valency PCVs (PCV-15, PCV-20) are shown in Table 1.

Two key articles describe the contemporary epidemiology and pneumococcal disease burden in UK adults with insight into individual pneumococcal serotype. These data enable the proportion of serotypes included in PCV-13, PCV-15 and PCV-20 currently contributing to adult pneumococcal disease to be determined. The first article presents routine national IPD surveillance data from England and Wales from 2000 to 2017. For adults aged 65+ years the number of IPD cases occurring in 2016/17 are described for 27 individual serotypes, including all those in PCV-13, PCV-15 and PCV-20 [2]. The second presents data from a prospective study of hospitalised CAP in adults aged 16+ years living in Greater Notting-

* Corresponding author.

https://doi.org/10.1016/j.vaccine.2020.10.090

Table 1
The comparative serotype composition of currently available pneumococcal vaccines (PCV-13, PPV-23) and next generation higher valency PCVs (PCV-15, PCV-20).

	4	6 B	9 V	14	18 C	19 F	23 F	1	5	7 F	3	6 A	19 A	22 F	33 F	10 A	15 B	8	11 A	12 F	2	9 N	17 F	20
PPV-23	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■
PCV-13	■	■	■	■	■	■	■	■	■	■	■	■	■											
PCV-15	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■									
PCV-20	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■				

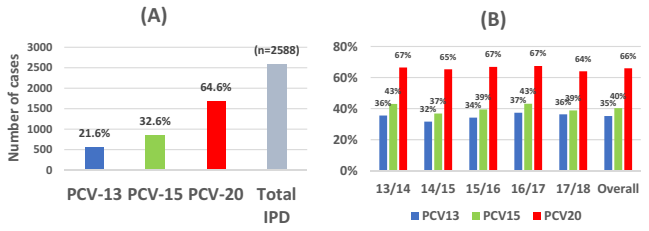


Fig. 1. The proportion of cases due to serotypes included in PCV-13, PCV-15 and PCV-20 in (A) IPD in adults aged 65+ years living in England and Wales in 2016/17 (B) community acquired pneumococcal pneumonia in adults aged 16+ years in Greater Nottingham between 2013/14 and 2017/18.

ham (a local region consisting of the city of Nottingham and the adjoining urban areas of Nottinghamshire and Derbyshire in the East Midlands of England) from 2013 to 2018 where the 24 pneumococcal serotypes included in PCV-13 and PPV-23 were individually identified from cases of pneumococcal CAP using a 24-valent multiplex urinary assay [7].

In adults aged 65+ years the proportion of IPD due to serotypes included in PCV-13, PCV-15 and PCV-20 was 22%, 33% and 65% respectively in 2016/17 (Fig. 1). Between 2013/14 and 2017/18 the mean proportion of pneumococcal CAP in adults aged 16+ years due to the serotypes included in PCV-13, PCV-15 and PCV-20 was 35%, 40% and 66% respectively (36%, 39% and 64% in 2017/18) (Fig. 1). Further stratification by individual serotype into narrower age bands was not possible.

The majority of IPD in adults aged 65+ years in 2016/17 caused by serotypes in PCV-13 was due to serotype 3 (53% of PCV-13 type IPD, 12% of total IPD). Other notable PCV-13 serotypes in this age group were 19A (28% of PCV-13 type IPD, 6% total IPD) and 19F (6% of PCV-13 type IPD, 1% of total IPD). Trends show that incidence due to serotype 19A and especially serotype 3 has been increasing post 2013/14 in older adults. However, IPD due to the remaining PCV-13 serotypes declined and comprised only 3% of the total IPD burden in those aged 65+ years in 2016/17. Other serotypes not included in PCV-13 that contributed most notably to the IPD burden in older adults in 2016/17 were serotypes 8 (16%), 12F (9%) and 9N (7%) with the incidence due to these serotypes also rising considerably post 2013/14. Whilst serotypes 22F and 33F collectively caused 11% of the IPD burden in adults aged 65+ years in 2016/17 incidence for each has remained relatively stable post 2013/14 [2].

Overall the serotype distribution for pneumococcal CAP in English adults aged 16+ years in Greater Nottingham broadly reflected the distribution for IPD seen nationally in England and Wales for adults aged 65+ years in 2016/17. Serotypes 3, 8 and 12F were similarly prominent causes of pneumococcal CAP (comprising a mean of 17%, 16% and 5% respectively across the study period). The proportion of serotype 3 pneumococcal CAP increased across the study period from 13% in 2013/14 to 19% in 2017/18 with pneumococcal CAP due to serotypes 8 and 12F also increasing during this period. The proportion of serotype 33F pneumococcal CAP declined from 4.5% in 2013/14 to 0.3% in 2017/18 but for serotype 22F remained stable at ~3% across the study period. However, in contrast to IPD, adult serotype 9N CAP showed no evidence of a recent increase [7].

Collectively these data suggest the additional serotypes included in PPV-23 not currently in next generation PCVs (serotypes 2, 9N, 17F and 20) cause only a small proportion of the contemporary adult pneumococcal disease burden in the UK. This was 6% of pneumococcal CAP across the five-year study period (4% in 2017/18). Serotypes 9N, 17F and 20 all contributed similarly to this adult pneumococcal CAP burden with serotype 2 extremely rare. The relevant IPD burden in adults aged 65+ years in 2016/17 is only presented for serotypes 9N and 17F which collectively caused 8% of total IPD [2,7].

Despite strong indirect protection induced by the UK routine infant PCV-13 immunisation programme these data suggest a significant proportion of the contemporary pneumococcal disease burden in UK adults is still caused by PCV-13 serotypes [2,7]. However, this is largely due to a small number of vaccine serotypes (19F, 19A and most notably 3) and is possibly because higher thresholds of protection are required for these [8]. It has also been hypothesized that routine infant PCV-13 programmes may induce only more limited levels of indirect protection for these serotypes specifically [8]. Therefore, directly vaccinating adults aged 65+ years with next generation higher valency PCVs may also be needed to optimally address the full vaccine preventable pneumococcal disease burden. Whilst paediatric formulations of PCV-15 and PCV-20 are currently at an earlier stage of development, waiting for these to become available and relying on subsequent indirect protection alone to protect adults may leave an important persisting burden of pneumococcal disease in those aged 65+ years due to certain vaccine serotypes where indirect protection is more limited.

These data indicate a substantial proportion of the current adult pneumococcal disease burden in the UK is caused by serotype 3, and the ability of PCVs to specifically protect against serotype 3 disease is being questioned [2,7,8]. However, a recent analysis of data from a large randomised controlled clinical trial (RCT) showed PCV-13 efficacy against serotype 3 pneumonia in adults aged 65+ years to be 61.5% (95%CI 17.6–83.4) [9]. This suggests that PCVs that include serotype 3 will provide some direct protection for older adults against serotype 3 disease [4].

Compared to PCV-13 the serotype composition of the new higher valency PCVs being developed reflect increasing proportions of the current adult pneumococcal disease burden in the UK, particularly when serotypes that have recently been rapidly increasing in the UK (e.g. serotypes 8 and 12F) are included. At present the serotypes included in PCV-20 reflect a large proportion (~65%) of the adult pneumococcal disease burden in the UK, indicating PCV-20 could potentially have a substantial impact. However, addition of serotypes 22F and 33F alone provides only a moderate increase compared to PCV-13 suggesting that PCV-15 will have a more limited impact in the UK.

Serotype 9N was one of several pneumococcal serotypes that unexpectedly emerged post 2013/14 as a rapidly increasing cause

of IPD in the UK [2] but is not included in PCV-15 or PCV-20 [5,6]. Recent UK data shows that serotype 9N IPD affects older individuals and those with underlying co-morbidities and is associated with a higher mortality compared to other serotypes [10]. Serotype 9N is therefore a candidate serotype to consider for inclusion in future higher valency PCVs in addition to other pneumococcal serotypes that may in future emerge as important causes of pneumococcal disease.

Despite compelling evidence that PCV-13 is efficacious in adults aged 65+ years it has been difficult to detect a measurable impact following the introduction of routine vaccination with PCV-13 for this age group in the US in 2014 when trends using US Active Bacterial Core Surveillance data for IPD are considered [11]. As with any impact assessments, these data need interpreting with some caution. Coverage of PCV-13 in US adults, for example, has been low until more recently and this may contribute to the lack of observed impact using these IPD surveillance data to 2017. It is also notable that IPD incidence due to PCV-13 serotypes in US adults aged 65+ years has remained stable since routine PCV-13 vaccination for older adults began in 2014. This contrasts with data from the UK where older adults are not routinely vaccinated with PCV-13, with a clear trend of increasing incidence post 2013/14 for PCV-13 serotype IPD in those aged 65+ years [2,3]. Furthermore, potential for vaccine impact may be optimally measured by incidence rate reductions measured in RCTs. In this context, PCV-13 vaccination of older adults in the CAPiTA trial resulted in rate reduction of 72 cases per 100,000 population for clinical CAP, equating to a vaccine efficacy of 8% [12]. Similar vaccine effectiveness estimates of 6–11% against all-cause CAP have also now been reported by a study undertaken by the US CDC for PCV-13 vaccinated adults aged 65+ years [13]. Given the importance of the broader public health impact of vaccines for public health decision making, the SmPC of PCV-13 has recently been updated to include the results from this analysis of CAPiTA [14].

In conclusion, directly vaccinating UK adults aged 65+ years with PCV-13, which is currently available and licensed for use in adults, could potentially address a significant proportion of the contemporary pneumococcal disease burden in this age group. However, the serotypes included in higher valency next generation PCVs (PCV-15 and PCV-20) reflect increasing proportions of the current adult pneumococcal disease burden in the UK, with ~65% of the burden attributed to those serotypes included in PCV-20. When available the higher valency next generation PCVs will therefore present an important opportunity to optimise protection for UK adults against pneumococcal disease.

Declaration of Competing Interest

AV, JC, CC and GE are employees of Pfizer, and MS works as a contractor for Pfizer. Pfizer has an interest in PCVs. It is the manufacturer of PCV-13 and is in the process of developing PCV-20.

References

[1] Immunisation against infectious disease. Pneumococcal: the Green Book. Available from: https://www.gov.uk/government/publications/pneumococcal-the-green-book-chapter-25.
[2] Ladhani SN et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. Lancet Infect Dis 2018;18(4):441–51.
[3] Djennad A et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine and changes in invasive pneumococcal disease incidence from 2000 to 2017 in those aged 65 and over in England and Wales. EClinicalMedicine 2019;6:42–50. https://doi.org/10.1016/j.eclinm.2018.12.007.
[4] Goldblatt D, Miller E. Pneumococcal pneumonia. Thorax 2020;75(1):6–7. https://doi.org/10.1136/thoraxjnl-2019-214135.
[5] Peterson JT et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine compared to 13-valent pneumococcal conjugate vaccine in adults ≥65 years of age previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Hum Vaccin Immunother 2019;15:540–8.
[6] Thompson A et al. Phase 1 trial of a 20-valent pneumococcal conjugate vaccine in healthy adults. Vaccine 2019;37:6201–7.
[7] Pick H et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. Thorax 2020;75(1):38–49. https://doi.org/10.1136/thoraxjnl-2019-213725.
[8] Adebanjo TA et al. Pneumococcal Conjugate Vaccine Breakthrough Infections: 2001–2016 e20190836. Pediatrics 2020;145(3). https://doi.org/10.1542/peds.2019-0836.
[9] Gessner BD et al. A post-hoc analysis of serotype-specific vaccine efficacy of 13-valent pneumococcal conjugate vaccine against clinical community acquired pneumonia from a randomized clinical trial in the Netherlands. Vaccine 2019;37:4147–54.
[10] Amin-Chowdhury Z, et al. Characteristics of invasive pneumococcal disease (IPD) caused by emerging serotypes after the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in England; prospective observational cohort study, 2014-2018. Clin Infect Dis 2020 Jan 19: ciaa043. doi: 10.1093/cid/ciaa043.
[11] Matanock A et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019 Nov 22;68(46):1069–75. https://doi.org/10.15585/mmwr.mm6846a5.
[12] Gessner BD et al. A public health evaluation of 13-valent pneumococcal conjugate vaccine impact on adult disease outcomes from a randomized clinical trial in the Netherlands. Vaccine 2019;37:5777–87.
[13] Lessa FC, Spiller M. Effectiveness of PCV13 in adults hospitalized with pneumonia using centers for Medicare and Medicaid data, 2014-2017. ACIP Meeting 2019.
[14] Pfizer. Prevenar 13 Summary of Product Characteristics (https://www.medicines.org.uk/emc/medicine/22689/SPC/Prevenar+13+suspension+for+injection/#PHARMACODYNAMIC_PROPS).

Epidemiology and Infection

cambridge.org/hyg

A novel approach to estimate the local population denominator to calculate disease incidence for hospital-based health events in England

James Campling[1], Elizabeth Begier[2], Andrew Vyse[1], Catherine Hyams[3,4,5], Dave Heaton[6], Jo Southern[2], Adam Finn[3], Harish Madhava[2], Bradford D. Gessner[2] and Gillian Ellsbury[1]

[1]Pfizer Limited, Walton Oaks, Dorking Road, Tadworth Surrey, KT20 7NS, UK; [2]Vaccines Medical Development, Scientific and Clinical Affairs, Pfizer Inc, Collegeville, PA, USA; [3]Bristol Vaccine Centre, Schools of Cellular and Molecular Medicine and of Population Health Sciences, University of Bristol, Bristol, BS2 8AE, UK; [4]Academic Respiratory Unit, Learning and Research Building, Southmead Hospital, Bristol, BS10 5NB, UK; [5]Acute Medical Unit, Southmead Hospital, Bristol, BS10 5NB, UK and [6]Harvey Walsh, Open Health Group, Marlow, Buckinghamshire, SL7 2FF, UK

Original Paper

Cite this article: Campling J *et al* (2022). A novel approach to estimate the local population denominator to calculate disease incidence for hospital-based health events in England. *Epidemiology and Infection* **150**, e150, 1–14. https://doi.org/10.1017/S0950268822000917

Received: 18 January 2022
Revised: 17 April 2022
Accepted: 9 May 2022

Key words:
Community-acquired pneumonia; epidemiology; incidence; pneumonia

Author for correspondence:
James Campling,
E-mail: james.campling@pfizer.com

Abstract

While incidence studies based on hospitalisation counts are commonly used for public health decision-making, no standard methodology to define hospitals' catchment population exists. We conducted a review of all published community-acquired pneumonia studies in England indexed in PubMed and assessed methods for determining denominators when calculating incidence in hospital-based surveillance studies. Denominators primarily were derived from census-based population estimates of local geographic boundaries and none attempted to determine denominators based on actual hospital access patterns in the community. We describe a new approach to accurately define population denominators based on historical patient healthcare utilisation data. This offers benefits over the more established methodologies which are dependent on assumptions regarding healthcare-seeking behaviour. Our new approach may be applicable to a wide range of health conditions and provides a framework to more accurately determine hospital catchment. This should increase the accuracy of disease incidence estimates based on hospitalised events, improving information available for public health decision making and service delivery planning.

Introduction

When considering the introduction of an immunisation programme, it is paramount that the incidence of the diseases of interest is estimated as accurately as possible. Calculating annual incidence rates (expressed as the number of cases per 100 000 population) depends on the accurate estimation of two parameters: (1) the number of people diagnosed with the disease during a specified time interval, (2) the size of the population from which the cases originated at the start of the time interval of interest. Measuring each parameter has its own challenges, but here we focus on challenges associated with estimating the size of local populations within England, hereafter referred to as the denominator. For national datasets where the catchment area is determined based on clear geographic boundaries, the denominator can be estimated using census data which are maintained through annually adjusted estimates. However, many surveillance studies use health centres such as clinics and hospitals, and in these cases, the denominator population usually is not clearly defined.

To estimate healthcare facility catchment populations, a few map-based approaches have previously been proposed (e.g. defined urban conurbation area, crow-fly distance, road distance and road time access) [1–5], all of which rely on census data to provide population estimates based on where the boundary is drawn on the map from the given approach. However, in England, and for several reasons, geographically defined denominators may provide a poor estimate of the population accessing care at a particular health centre. The National Health Service (NHS) provides healthcare free of charge for all residents in England and allows patients to choose where they receive medical care, which is an important principle of the English healthcare system. Although geography plays an important role in influencing this choice, other factors may be important including public transport, parking, waiting times, traffic considerations both for patients and visiting family members, experience with a particular hospital, GP recommendation, ambulance preference, hospital capacity, specialist services and hospital reputation [6]. Moreover, while it might be expected that those who live close to a

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

hospital would preferentially choose that location, many people live equidistant to more than one hospital (both in terms of distance and travel time). In summary, no standardised methodology exists to estimate incidence based on the person seeking healthcare at a given facility.

In this report, we describe a novel methodology to estimate local population denominators for the Bristol AvonCAP study – a study set up with the specific aim of measuring the burden of hospitalised respiratory disease in England, to provide evidence for informed decision making for public health interventions including vaccines, that have the potential to alleviate some of this burden. The study was designed to measure the incidence of hospitalised community-acquired pneumonia (CAP) and other acute lower respiratory tract diseases (aLRTD) in two large secondary care hospitals located in Bristol. We think this methodology could be replicated for other health outcomes and other regions in England (or elsewhere if a high level of formal primary care practice registration exists), which could substantially improve disease incidence estimates and thus accurate public health decision-making.

Methods

Methodology overview

The conceptual distinction between previously proposed approaches to determine population denominators and our methodology is that the former are based on assumptions about which hospitals patients are expected to use. Our new methodology attempts to minimise the use of assumptions by utilising multiple data sources to assess which hospitals these populations have used in the past.

The NHS in England allocates an annual budget to local geographically defined clinical commissioning groups (CCGs) broadly based on population numbers and utilisation in prior years. In April 2021, there were 106 CCGs across England and their boundaries were drawn to complement local healthcare resources [7]. See the Method step 1 section for an important organisational change for the NHS.

Robust systems are used by CCGs to reimburse hospital care, therefore we hypothesised that CCG geographical regions may be helpful in determining hospital catchment areas and local populations. To test our hypothesis, we utilised Hospital Episode Statistics (HES) data which were re-used with the permission of NHS Digital via Harvey Walsh Limited. aLRTD admissions at the study hospitals between April 2017–March 2020 were linked to aggregated general practitioner (GP) data to understand from which CCG the hospitals' patients came (Methods Part 1). Then, we estimated the proportion of patients hospitalised at the study hospitals among all patients hospitalised with LRTD for each practice and multiplied that by count of patients registered at that GP practice to calculate the Bristol hospital catchment population (Methods Part 2).

In England, all hospitalisations in NHS hospitals are captured in HES and all acute care is provided by NHS hospitals. HES contains information on bed days, length of admission, outpatient appointments, attendances at Accident and Emergency Departments at NHS hospitals in England, discharge diagnoses and hospital death [8]. The primary diagnosis and other clinical conditions are specified using the tenth revision of the International Classification of Diseases version 10 (ICD-10) [9]. Furthermore, in England a high proportion of the population are registered with General Practice where it is not possible to be registered at two practices concurrently [10, 11].

Method step 1 – defining GP practices associated with patients treated at study hospitals

To understand from where patients treated at the study hospitals originated (i.e. to which CCG the patients' GP practices belong), HES data were extracted for all adult patients coded for aLRTD between April 2017–March 2020 and filtered to include only patients treated at the study hospitals: North Bristol NHS Trust (NBT), and University Hospitals Bristol NHS Foundation Trust & Weston NHS Foundation Trust (UHBW). Finally, data were analysed to determine in which CCG area the patients lived based on their GP registration. There are 6 CCG regions in the South West of England within a 1-hour drive of the study hospitals, as illustrated in Figure 1.

Fig. 1 shows a map of the CCGs described in the results pie chart (Fig. 2) along with the location of relevant hospitals. In July 2022 NHS England establised 42 integrated care systems (ICS) and as a consequence CCGs were closed down and new statutory organisations called integrated care boards (ICB) were introduced. The remit of an ICB includes managing the NHS budget and arranging for the provision of health services in the ICS area. The boundaries of the new ICSs in the south-west of England remain unchanged from the previous CCG boundaries and therefore this change does not impact this analysis (https://www.england.nhs.uk/integratedcare/).

Method step 2 – defining the catchment population of study hospitals

As patients registered in the CCG might seek care at a different hospital for a variety of reasons, we could not assume every patient registered with a GP in the Bristol, North Somerset and South Gloucestershire (BNSSG) CCG used the study hospitals. Therefore, we estimated the proportion of patients from each GP practice treated at the study hospitals among all BNSSG CCG patients, stratified by age group. This proportion was used to calculate the study hospitals' catchment population. All aLRTD hospitalisations (based on ICD-10 codes; Appendix 1) occurring between April 2017 – March 2020 among patients registered in the BNSSG CCG were analysed by GP practice. For each GP practice, the per cent of hospitalisations occurring at study hospitals was calculated within each age-group (18–34, 35–49, 50–64, 65–74, 75–84 and ⩾85 years). The percentage of hospitalisations occurring at study hospitals was the number of patients at each GP practice who were admitted for aLRTD at study hospitals (study hospital aLRTD patients) divided by the total number of patients at that GP practice who were hospitalised for aLRTD at any English hospital in the time period (overall aLRTD inpatients). This proportion (i.e. per cent of aLRTD inpatients using study hospitals) was multiplied by the practice population for each GP practice by age strata to provide an expected Bristol hospital catchment population contribution for each GP practice (once all age groups summed). GP populations were obtained from NHS Digital 'Patients Registered at a GP Practice' data for October 2019. Finally, the catchment population contribution for each GP practice in the BNSSG CCG was combined to provide an expected total Bristol hospital catchment population. In summary, if:

- E = Calculated catchment population
- SHP = Number of patients at a GP practice hospitalised at a study hospital with aLRTD during 2017–2019
- OL = Overall number of patients at a GP practice hospitalised in England with aLRTD during 2017–2019
- POP = Local GP population
- i = Each individual practice

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

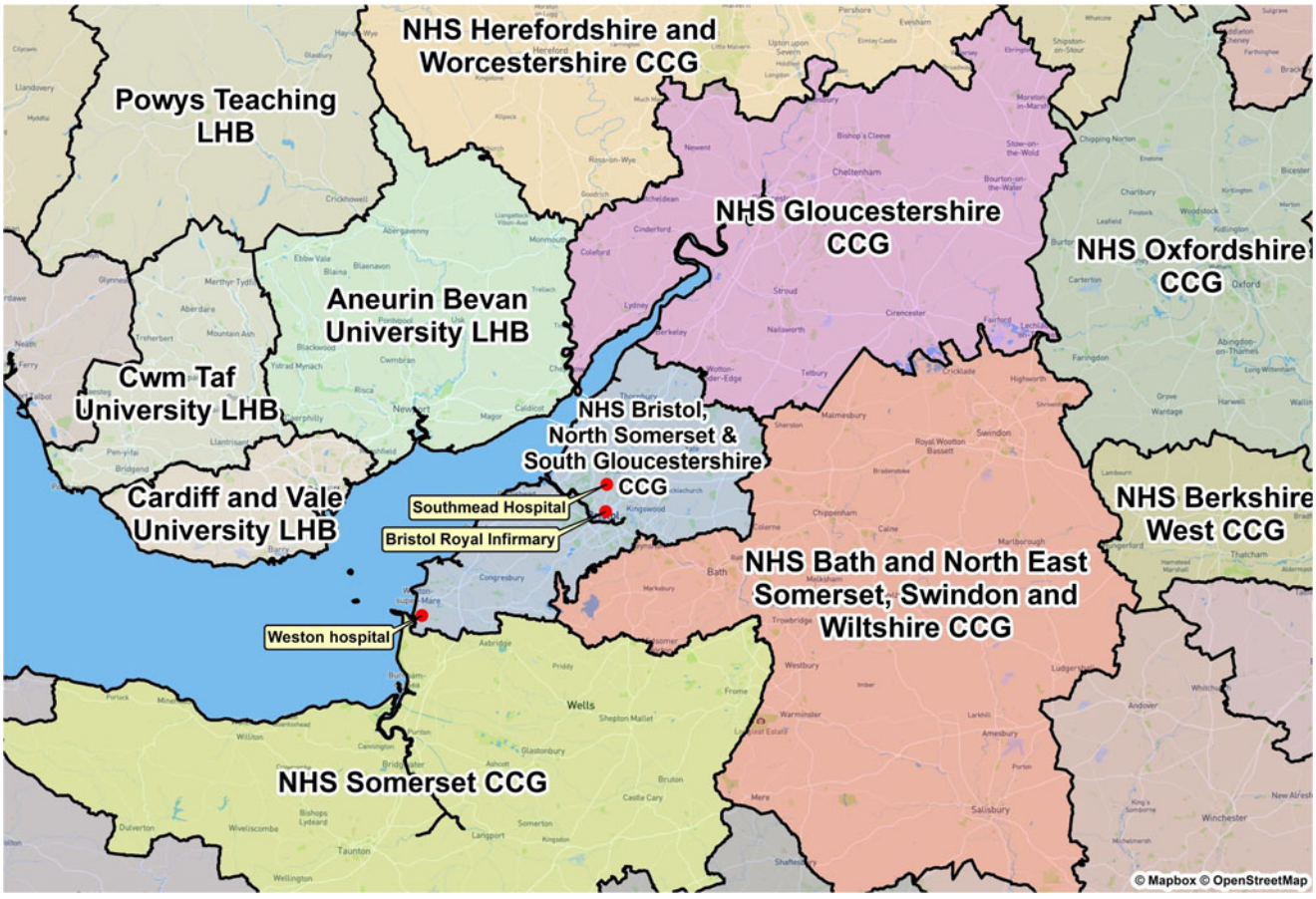


Fig. 1. South West England clinical commissioning groups map.

Then:

$$E = \sum \left(\left(\frac{\mathrm{SHP}_i}{\mathrm{OL}_i} \right) \mathrm{POP}_i \right)$$

Drive-time methodology

The BNSSG CCG used a 20-minute drive-time for their healthcare utilisation mapping purposes [12]. We have included this alternative methodological approach to allow comparison between our methodology and other methodologies in current use. We obtained data from the BNSSG CCG which divides the CCG region into small geographical areas used by the UK census known as lower layer super output areas (LSOA). LSOAs have a population of between 1000–3000 people or 400–1200 households [13]. Data were filtered according to estimated drive-time from each LSOA to the study hospitals according to the Automobile Association (AA) route planner, (AA, Hampshire, UK) [14]. UK population data by LSOA for all ages (0 – ⩾90 years) were downloaded from the UK Office of National Statistics census website. Population estimates were derived for the following drive-times from the study hospitals 20, 25, 30, 40 and 60 minutes by matching the LSOA population data with the drive-time data.

Results

In 2019, there were 82 GP practices in the BNSSG CCG. Figure 2 shows the proportion of patients that attended the study hospitals in 2019 that were registered at GP practices in both the BNSSG CCG as well as six other CCGs that, combined, represented where >99% of patients hospitalised at study hospitals were registered. The majority of hospitalised patients (96%) were registered at BNSSG CCG GP practices, with most of the remaining 4% based in the surrounding CCGs.

Substantial variability existed by GP practice in the per cent of all persons hospitalised for aLRTD who were hospitalised at a study hospital with much less variability by age (Fig. 3) (based on a representative sample of 10 anonymised GP practices within the BNSSG CCG). Lower proportions were reported for GP practices that were located either close to the CCG boundary or close to Weston hospital (a non-study hospital situated in the BNSSG CCG). Full tables reporting these data for all GP practices located in the BNSSG CCG for 2017, 2018, 2019 and the combined data can be found in Appendix 2.

The degree to which the estimates from our methodology compared to estimates produced by other methods varied, including within specific age groups (Table 1 and Fig. 4). The total CCG population (the sum of the population of all GP practices in the CCG) overestimated the catchment population compared to our estimates by 15% to 24%. By contrast, the population living within a 20 minute drive of the study hospitals underestimated the catchment population by 10% to 29%. As drive-time increased linearly, the estimated population increased non-linearly such that the population based on a 60 minute drive-time overestimated the catchment population by 276% to 428%. The degree of underestimation or overestimation from other methods did not vary substantially by age group.

The map in Fig. 5 shows the location of the study hospitals and Weston General Hospital. The BNSSG CCG boundary is shown in

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

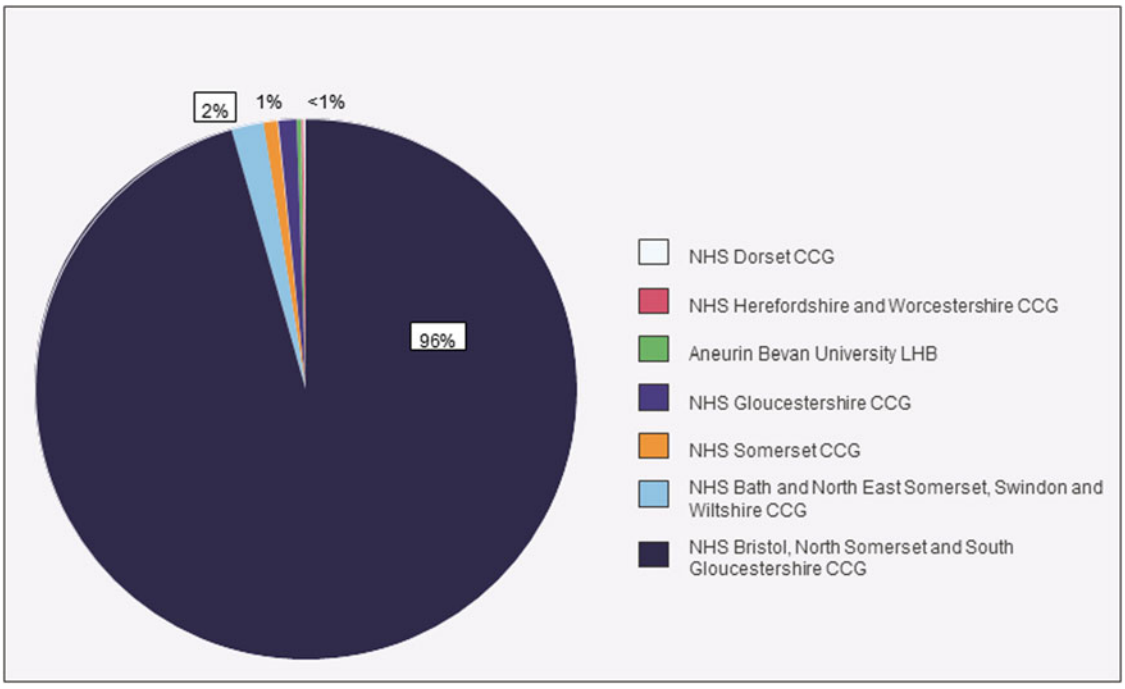


Fig. 2. 2017–2019 study hospital admissions by clinical commissioning group of the patients' GP practices.

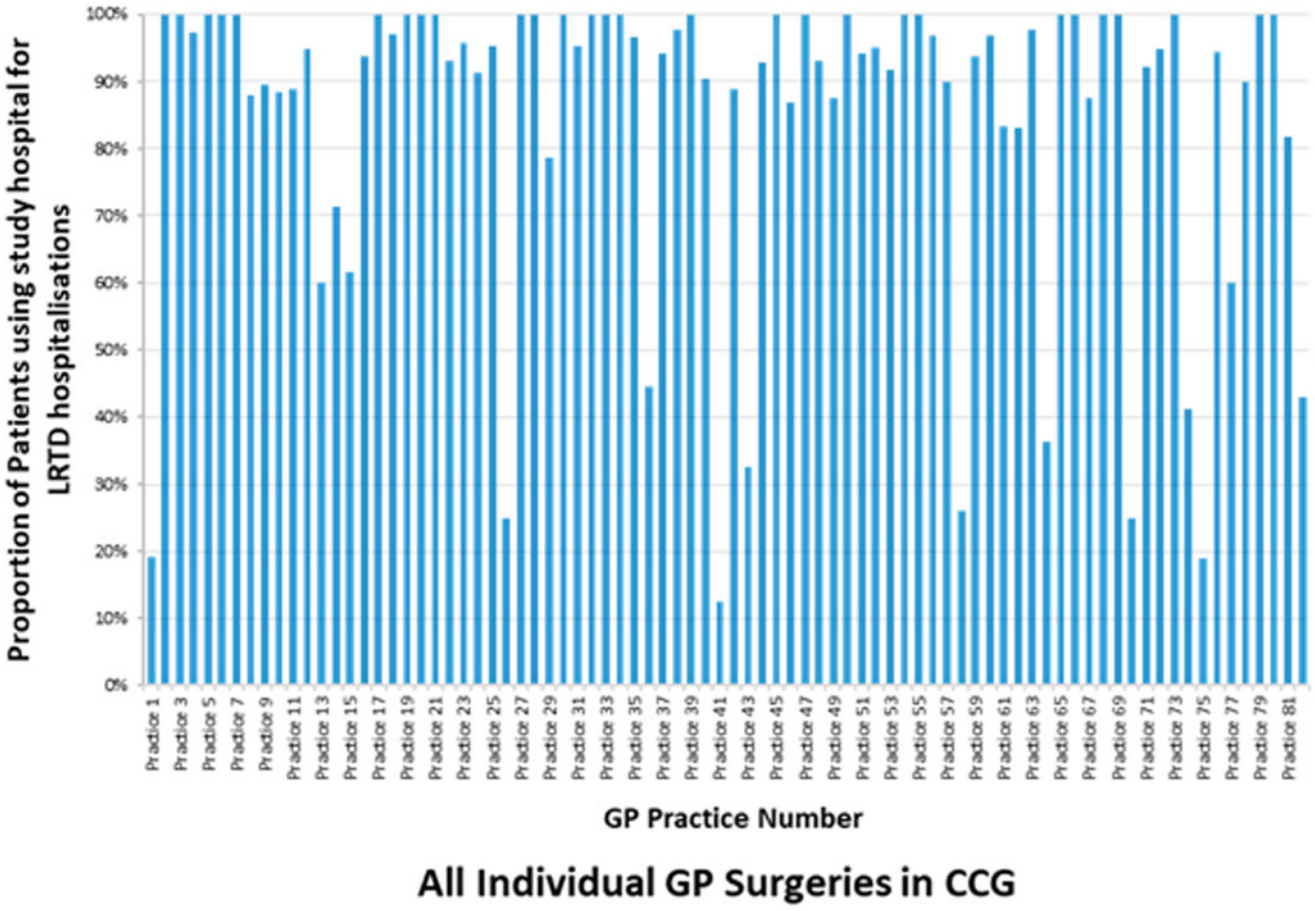


Fig. 3. A bar chart showing the proportion of persons hospitalised for acute lower respiratory tract disease who were hospitalised at a study hospital, stratified by individual anonymised general practice and patient age group.

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

Table 1. Comparison of study hospital catchment population estimates based on different approaches

Age group	Estimated catchment (Study method)	Total CCG catchment	Estimated based on ⩽20 min drive-time	Estimated based on ⩽25 min drive-time	Estimated based on ⩽30 min drive-time	Estimated based on <40 min drive-time	Estimated based on <60 min drive-time
Five adult age groupings							
18–34	231 342	268 093 (↑16%)	208 924 (↓10%)	238 301 (↑3%)	295 130 (↑28%)	442 590 (↑91%)	870 841 (↑276%)
35–49	184 269	211 568 (↑15%)	130 881 (↓29%)	162 469 (↓12%)	211 452 (↑15%)	337 781 (↑83%)	714 415 (↑288%)
50–64	152 380	178 970 (↑17%)	108 404 (↓29%)	143 508 (↓6%)	196 307 (↑29%)	331 795 (↑118%)	732 702 (↑381%)
65–74	74 245	89 015 (↑20%)	52 954 (↓29%)	73 368 (↓1%)	102 148 (↑38%)	175 757 (↑137%)	391 718 (↑428%)
75–84	45 989	55 720 (↑21%)	33 712 (↓27%)	46 919 (↑2%)	65 244 (↑42%)	111 109 (↑142%)	239 310 (↑420%)
85+	19 229	23 938 (↑24%)	15 280 (↓21%)	20 400 (↑6%)	28 261 (↑47%)	47 108 (↑145%)	99 865 (↑419%)
Two adult age groupings							
18–64	567 991	658 631 (↑16%)	448 209 (↓21%)	544 278 (↓4%)	702 889 (↑24%)	1 112 166 (↑96%)	2 317 958 (↑308%)
⩾65	139 463	168 673 (↑21%)	101 946 (↓27%)	140 687 (↑1%)	195 653 (↑40%)	333 974 (↑139%)	730 893 (↑424%)
Total	707 454	827 304 (↑17%)	550 155 (↓22%)	684 965 (↓3%)	898 542 (↑27%)	1 446 140 (↑104%)	3 048 851 (↑331%)

black and travel time boundaries are identified by colour to the study hospitals based on the shortest travel time to either study hospital.

Discussion

Incidence studies based on counts of hospitalisations from one or a few study hospitals are common, but there is no standard methodology to define a health centre's catchment population for the purpose of accurately estimating incidence denominators. Traditional geography-based approaches (such as defining a population with a certain drive-time to a study health centre) that rely on census data do not account for the nuanced ways in which populations access healthcare and therefore are prone to error. We devised a novel approach for establishing local population estimates in England to support disease incidence studies conducted at single or multiple hospital sites. This approach was made possible because nearly everyone in England is registered with a GP and because of the comprehensive healthcare data captured by NHS Digital [15]. Moreover, a strength of our approach is that it is uses healthcare utilisation data to calculate specific study hospital usage by GP centre and age group and makes no assumptions about which health centres are used by a population within a particular census area.

Depending on the precise method, the geography-based approaches assessed in our study would have overestimated or underestimated the true catchment population and thus either underestimated or overestimated aLRTD incidence. At the extreme, defining the catchment population as those people living within a 60 minute drive from a study hospital would have overestimated the catchment population by 4-fold to 5-fold and thus underestimated incidence to the same degree. At the other extreme, a drive-time of 20 minutes would have underestimated denominators by 20–25% and thus overestimated incidence. Alternatively, the use of the entire CCG population would have overestimated denominators by 15%. The differences between geographically estimated denominators and our method are likely to vary by location and thus, the specific results from our study are illustrative of the principle and cannot be used to make conclusions about the relative accuracy of using an entire CCG population or drive-time for other areas. For example, higher density areas with a larger number of hospitals would decrease the accuracy of drive-time or CCG for defining the catchment area of any particular hospital. This was illustrated in our study by demonstrating that for some practices and age groups, less than 20% of the practice population with an aLRTD hospitalisation presented to a study hospital. Since the only way to document the distortion in catchment population estimate for any particular health centres inherent in traditional estimates would be to first employ the methods described here, we suggest a better approach is simply to use our methods, or some similar approach, to define incidence denominators.

Other issues must be considered when using our approach. For example, the percentage of people with aLRTD hospitalisation who were hospitalised in a study hospital was relatively stable for older age groups and larger practices but varied substantially for younger populations and smaller practices, predominantly because of small absolute case counts for the latter groups. We largely overcame this issue by combining data for multiple years and creating larger age bands for younger populations. This issue will be more problematic for rarer diseases, which may require even larger age bands, greater numbers of study years, or aggregating individual ICD-10 codes into a common outcome.

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

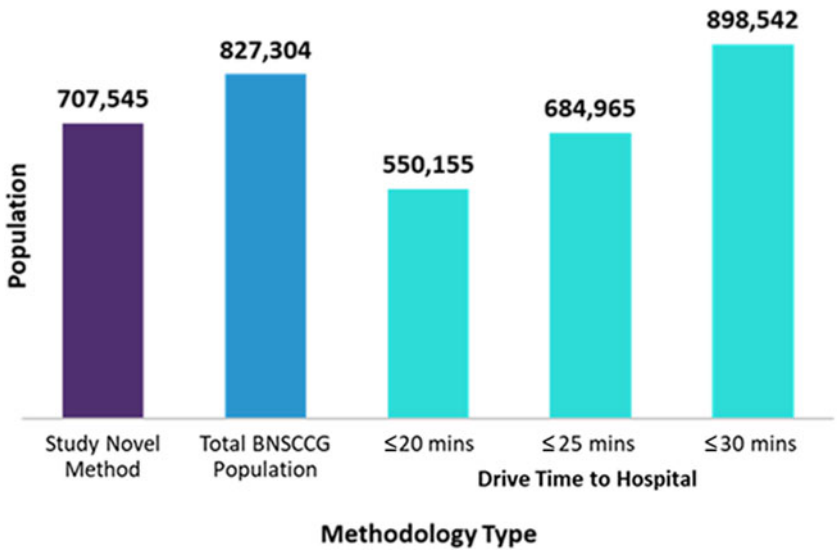


Fig. 4. Comparison of study hospital population size (⩾18yrs) by methodology.

The AvonCAP study was designed primarily to inform decisions on respiratory vaccine use among older adults, including vaccines to prevent the pneumococcal, respiratory syncytial virus, and SARS-CoV-2 infection. Policymakers, including vaccine technical committees, have consistently indicated that disease burden is the number one factor in setting priorities for vaccines [16, 17]. Disease incidence, and usually severe disease incidence using hospitalisation as a proxy, is the cornerstone of disease burden and usually is the key outcome driving cost-effectiveness models. Cost-effectiveness values in turn are often used for policy and pricing decisions. For example in England, a vaccine must be below a threshold of £ 30 000 per Quality Adjusted Life Year

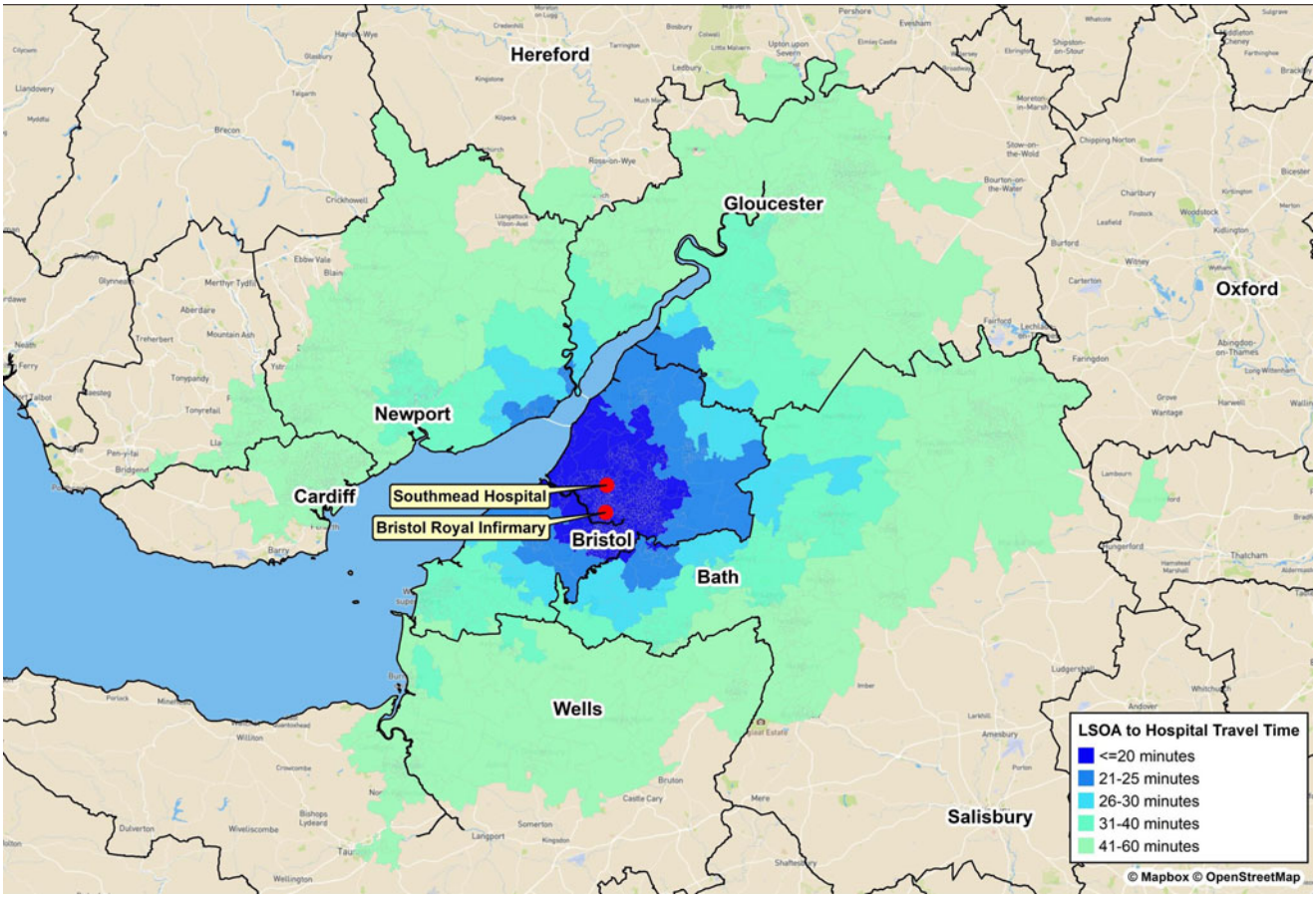


Fig. 5. Map showing travel time by car to study hospitals

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

(QALY) saved to meet the criteria to be recommended for a national immunisation programme [8]. Since disease incidence underlies all these downstream measures, its accurate determination is critical for policy decisions. This requires a focus not just on the accurate determination of case counts (that is, numerators) but also the catchment population for the surveillance system (that is, denominators).

Our approach has a few limitations. We could not account for people who were not registered with a GP; although, nearly all English residents are registered [10]. Our methodology also did not include the 4% of people that use the study hospitals but are registered with a GP practice outside of the CCG. However, this will be largely addressed in Avon-CAP by excluding from incidence calculations patients with a study outcome living outside the CCG. Our approach requires a new estimate to be calculated for each disease of interest because some conditions will be disproportionately observed in some hospitals due to therapy area specialism. As discussed above, our approach may not be suitable for rare diseases or surveillance systems with small populations. Lastly, our methodology is appropriate for the particular circumstances of England and remains so with the recent transition to the ICS structure. The extent to which this approach can be generalised to other countries will need to be evaluated on a case-by-case basis, but other areas where nearly all persons are formally registered with a primary care provider could consider its use.

We will use the described methodology to define denominators for incidence calculations within the AvonCAP study, which in turn should contribute to providing better data for informing decisions related to adult respiratory vaccine use. A similar approach could be used to refine previous estimates where these are being used to inform respiratory disease vaccine decision making. A historical study reporting disease incidence of hospitalised pneumonia in England was conducted in Hull and the East Riding of Yorkshire [5]. This study included 8 hospitals in the region and a geography-based approach was used to define the denominator. Whilst an effort was made to specifically exclude defined postcode areas reflecting a geographic region unlikely to use the study hospitals the accuracy of the denominator used in this study remains uncertain. A more recent study published hospitalised CAP incidence estimates from Nottingham, England and used a denominator based on the entire population of the Greater Nottingham area, but the market share of the two study hospitals used was not formally defined [3, 18]. Since the Greater Nottingham area is surrounded by other urban areas with hospitals that also treat CAP, it is unclear how well Greater Nottingham census data matches the hospital catchment population, and this could be formally evaluated by replicating our methodology. More generally, the method we describe may be used for other disease incidence calculations and for relatively common diseases could be extended to focus on specific groups such as those with underlying comorbidities. While the approach we describe takes considerably more human and financial resources than using census data (through commissioning a specialist vendor that holds an appropriate license to analyse the data), this cost is negligible compared to the inefficiencies introduced when inaccurate disease incidence estimates are used as a core basis for public health decision making.

Conclusion

Use of the entire CCG or drive-times does not account for the nuanced ways that populations access healthcare and may overestimate or underestimate denominators and distort incidence estimates. Our data-driven method provides more accurate incidence estimates and thus can improve public health decision-making. Denominators for hospital-based incidence studies should be based on healthcare usage rather than geographical boundaries.

Author contributions. JC, EB, AV, DH & GE contributed to the initial design of the methodology. All authors contributed to the analysis, interpretation, and discussion of the results. We would like to acknowledge the assistance of Qi Yan, PhD (Pfizer, Inc.) who provided indispensable medical writing and literature review support for this manuscript and Harvey Walsh, Open Health Group who performed the denominator calculation. HES Data were re-used with the permission of NHS Digital via Harvey Walsh, Open Health Group.

Conflict of interest. JC, EB, AV, JS, HM, BG & GE are employees of Pfizer Vaccines and hold stock or stock options. DH is an employee of Harvey Walsh Ltd. CH is the Principal Investigator of the Avon CAP study which is an investigator-led University of Bristol study funded by Pfizer and has previously received support from the NIHR in an Academic Clinical Fellowship. AF is a member of the Joint Committee on Vaccination and Immunization (JCVI) and chair of the World Health Organization European Technical Advisory Group of Experts on Immunization (ETAGE) committee. In addition to receiving funding from Pfizer as Chief Investigator of the Avon CAP study, he leads another project investigating the transmission of respiratory bacteria in families jointly funded by Pfizer and the Gates Foundation.

Data availability statement. The data that support the findings of this study are available from Harvey Walsh, Open Group. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from the authors with the permission of Harvey Walsh, Open Group.

Disclosure. This study was conducted as a collaboration between the University of Bristol, Pfizer and Open Health Group. Pfizer is the study sponsor.

References

1. **Schuurman N *et al.*** (2006) Defining rational hospital catchments for non-urban areas based on travel-time. *International Journal of Health Geographics* **5**, 43.
2. **Roderick P *et al.*** (1999) What determines geographical variation in rates of acceptance onto renal replacement therapy in England? *Journal of Health Services Research & Policy* **4**, 139–146.
3. **Pick H *et al.*** (2020) Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. *Thorax* **75**, 38–49.
4. **Clarke JM, Barahona M and Darzi AW** (2019) Defining hospital catchment areas using multiscale community detection: a case study for planned orthopaedic care in England. *bioRxiv*, 619692. https://doi.org/10.1101/619692.
5. **Elston JW *et al.*** (2012) Increasing incidence of invasive pneumococcal disease and pneumonia despite improved vaccination uptake: surveillance in Hull and East Yorkshire, UK, 2002–2009. *Epidemiology & Infection* **140**, 1252–1266.
6. **Dealey C** (2005) The factors that influence patients' choice of hospital and treatment. *British Journal of Nursing* **14**, 576–579.
7. **Anon** (2021) NHS Clinical Commissioning Group (CCG) reorganisation as of 1 April 2021. NHS Business Services Authority. In.
8. **Joint Committee on Vaccination and Immunisation** (2013) Code of practice June 2013. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/224864/JCVI_Code_of_Practice_revision_2013_-_final.pdf. In.
9. **World Health Organization** (2004) *ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision in*, 2nd Edn. Geneva: World Health Organization. https://apps.who.int/iris/handle/10665/42980 (Accessed September 2021).
10. **Baker C** (2016) Population estimates & GP registers: why the difference? https://commonslibrary.parliament.uk/population-estimates-gp-registers-why-the-difference/#_ftn1. In.

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

11. **UK Government** (2019) Petition; Allow students to register at two GPs. https://petition.parliament.uk/archived/petitions/229573#:~:text=It%20is%20not%20possible%20for,risks%20in%20maintaining%20duplicate%20records. In.
12. **Personal Communication with BNSSG CCG** (2020) Drive-time used for healthcare utilisation planning. In.
13. **The National Archives; Office for National Statistics** (2016) Home > Guidance and Methodology > Geography > A beginner's guide to UK geography > Census Geography > Super Output Area (SOA). https://webarchive.nationalarchives.gov.uk/ukgwa/20160106001702/http://www.ons.gov.uk/ons/guide-method/geography/beginner-s-guide/census/super-output-areas--soas-/index.html. In.
14. **The AA Route Planner**. https://www.theaa.com/route-planner/traffic-news/index.jsp. In.
15. **NHS Digital** (2021) https://digital.nhs.uk/data. In.
16. **Munira SL and Fritzen SA** (2007) What influences government adoption of vaccines in developing countries? A policy process analysis. *Social Science & Medicine* **65**, 1751–1764.
17. **Bryson M *et al.*** (2010) A global look at national immunization technical advisory groups. *Vaccine* **28**, A13–A17.
18. **Rodrigo C *et al.*** (2015) Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. *European Respiratory Journal* **45**, 1632–1641.

Appendix 1: ICD-10 codes used for the analysis

Appendix 1

ICD-10 Code	ICD-10 Description
I110	Hypertensive heart disease with (congestive) heart failure
I130	Hypertensive heart and renal disease with (congestive) heart failure
I132	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
I50	Heart failure
I500	Congestive heart failure
I501	Left ventricular failure
I509	Heart failure, unspecified
J09	Influenza due to identified avian influenza virus
J09X	Influenza due to identified zoonotic or pandemic influenza virus
J10	Influenza due to identified seasonal influenza virus
J100	Influenza with pneumonia, seasonal influenza virus identified
J101	Influenza with other respiratory manifestations, seasonal influenza virus identified
J108	Influenza with other manifestations, seasonal influenza virus identified
J11	Influenza, virus not identified
J110	Influenza with pneumonia, virus not identified
J111	Influenza with other respiratory manifestations, virus not identified
J118	Influenza with other manifestations, virus not identified
J12	Viral pneumonia, not elsewhere classified
J120	Adenoviral pneumonia
J121	Respiratory syncytial virus pneumonia
J122	Parainfluenza virus pneumonia
J123	Human metapneumovirus pneumonia
J128	Other viral pneumonia
J129	Viral pneumonia, unspecified
J13	Pneumonia due to Streptococcus pneumoniae
J13X	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J14X	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J150	Pneumonia due to Klebsiella pneumoniae
J151	Pneumonia due to Pseudomonas

(*Continued*)

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

Appendix 1 (*Continued.*)

ICD-10 Code	ICD-10 Description
J152	Pneumonia due to staphylococcus
J153	Pneumonia due to streptococcus, group B
J154	Pneumonia due to other streptococci
J155	Pneumonia due to *Escherichia coli*
J156	Pneumonia due to other Gram-negative bacteria
J157	Pneumonia due to Mycoplasma pneumoniae
J158	Other bacterial pneumonia
J159	Bacterial pneumonia, unspecified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J160	Chlamydial pneumonia
J168	Pneumonia due to other specified infectious organisms
J17	Pneumonia in diseases classified elsewhere
J170	Pneumonia in bacterial diseases classified elsewhere
J171	Pneumonia in viral diseases classified elsewhere
J172	Pneumonia in mycoses
J173	Pneumonia in parasitic diseases
J178	Pneumonia in other diseases classified elsewhere
J18	Pneumonia, organism unspecified
J180	Bronchopneumonia, unspecified
J181	Lobar pneumonia, unspecified
J182	Hypostatic pneumonia, unspecified
J188	Other pneumonia, organism unspecified
J189	Pneumonia, unspecified
J20	Acute bronchitis
J200	Acute bronchitis due to Mycoplasma pneumoniae
J201	Acute bronchitis due to Haemophilus influenzae
J202	Acute bronchitis due to streptococcus
J203	Acute bronchitis due to coxsackievirus
J204	Acute bronchitis due to parainfluenza virus
J205	Acute bronchitis due to respiratory syncytial virus
J206	Acute bronchitis due to rhinovirus
J207	Acute bronchitis due to echovirus
J208	Acute bronchitis due to other specified organisms
J209	Acute bronchitis, unspecified
J21	Acute bronchiolitis
J210	Acute bronchiolitis due to respiratory syncytial virus
J211	Acute bronchiolitis due to human metapneumovirus
J218	Acute bronchiolitis due to other specified organisms
J219	Acute bronchiolitis, unspecified
J22	Unspecified acute lower respiratory infection
J22X	Unspecified acute lower respiratory infection
J40	Bronchitis, not specified as acute or chronic
J40X	Bronchitis, not specified as acute or chronic

(*Continued*)

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

Appendix 1 (*Continued.*)

ICD-10 Code	ICD-10 Description
J41	Simple and mucopurulent chronic bronchitis
J410	Simple chronic bronchitis
J411	Mucopurulent chronic bronchitis
J418	Mixed simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
J42X	Unspecified chronic bronchitis
J43	Emphysema
J430	MacLeod syndrome
J431	Panlobular emphysema
J432	Centrilobular emphysema
J438	Other emphysema
J439	Emphysema, unspecified
J44	Other chronic obstructive pulmonary disease
J440	Chronic obstructive pulmonary disease with acute lower respiratory infection
J441	Chronic obstructive pulmonary disease with acute exacerbation, unspecified
J448	Other specified chronic obstructive pulmonary disease
J449	Chronic obstructive pulmonary disease, unspecified
J45	Asthma
J450	Predominantly allergic asthma
J451	Nonallergic asthma
J458	Mixed asthma
J459	Asthma, unspecified
J46	Status asthmaticus
J46X	Status asthmaticus
J47	Bronchiectasis
J47X	Bronchiectasis
J85	Abscess of lung and mediastinum
J850	Gangrene and necrosis of lung
J851	Abscess of lung with pneumonia
J852	Abscess of lung without pneumonia
J853	Abscess of mediastinum
J86	Pyothorax
J860	Pyothorax with fistula
J869	Pyothorax without fistula
J90	Pleural effusion, not elsewhere classified
J90X	Pleural effusion, not elsewhere classified
J91	Pleural effusion in conditions classified elsewhere
J91X	Pleural effusion in conditions classified elsewhere
J95	Postprocedural respiratory disorders, not elsewhere classified
J950	Tracheostomy malfunction
J951	Acute pulmonary insufficiency following thoracic surgery
J952	Acute pulmonary insufficiency following nonthoracic surgery
J953	Chronic pulmonary insufficiency following surgery

(*Continued*)

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

Appendix 1 (*Continued.*)

ICD-10 Code	ICD-10 Description
J954	Mendelson syndrome
J955	Postprocedural subglottic stenosis
J958	Other postprocedural respiratory disorders
J959	Postprocedural respiratory disorder, unspecified
J96	Respiratory failure, not elsewhere classified
J960	Acute respiratory failure
J9600	Acute respiratory failure, Type I [hypoxic]
J9601	Acute respiratory failure, Type II [hypercapnic]
J9609	Acute respiratory failure, Type unspecified
J961	Chronic respiratory failure
J9610	Chronic respiratory failure, Type I [hypoxic]
J9611	Chronic respiratory failure, Type II [hypercapnic]
J9619	Chronic respiratory failure, Type unspecified
J969	Respiratory failure, unspecified
J9690	Respiratory failure, unspecified, Type I [hypoxic]
J9691	Respiratory failure, unspecified, Type II [hypercapnic]
J9699	Respiratory failure, unspecified, Type unspecified
J98	Other respiratory disorders
J980	Diseases of bronchus, not elsewhere classified
J981	Pulmonary collapse
J982	Interstitial emphysema
J983	Compensatory emphysema
J984	Other disorders of lung
J985	Diseases of mediastinum, not elsewhere classified
J986	Disorders of diaphragm
J988	Other specified respiratory disorders
J989	Respiratory disorder, unspecified
J99	Respiratory disorders in diseases classified elsewhere
J990	Rheumatoid lung disease
J991	Respiratory disorders in other diffuse connective tissue disorders
J998	Respiratory disorders in other diseases classified elsewhere

https://doi.org/10.1017/S0950268822000917 Published online by Cambridge University Press

Appendix 2: Anonymised GP Practice Data

GP Practice names are anonymised and presented as Practice 1, Practice 2 etc…

Appendix 2

Total practice population by age							18 to 34		35–49		50–64		65–74		75–84		⩾85	
18–34	35–49	50–64	65–74	75–84	85+	Practice name	Proportion	Population	Proportion	Population	Proportion	Population	Proportion	Population	Proportion	Population	Proportion	Population
2638	2216	2498	1497	997	481	Practice 1	19%	507	10%	216	15%	375	18%	276	17%	169	9%	46
3254	3063	2342	1043	773	315	Practice 2	100%	3254	93%	2839	100%	2342	100%	1043	100%	773	100%	315
979	1176	1132	482	362	161	Practice 3	100%	979	100%	1176	100%	1132	100%	482	100%	362	100%	161
3899	2965	1874	728	377	134	Practice 4	97%	3796	98%	2891	97%	1825	98%	717	100%	377	100%	134
2714	2507	2030	894	469	234	Practice 5	100%	2714	94%	2364	100%	2030	100%	894	100%	469	99%	231
2383	1914	1262	558	302	133	Practice 6	100%	2383	100%	1914	100%	1262	100%	558	97%	294	100%	133
1488	743	267	38	8	5	Practice 7	100%	1488	89%	660	89%	239	100%	38	100%	8	100%	5
4487	4894	2750	721	348	109	Practice 8	88%	3949	97%	4750	100%	2750	100%	721	96%	335	100%	109
11 794	9416	5370	2301	1451	615	Practice 9	90%	10 565	100%	9416	100%	5370	100%	2301	98%	1429	100%	615
7402	2155	597	142	44	14	Practice 10	88%	6548	97%	2091	100%	597	100%	142	100%	44	100%	14
2731	2160	2474	1017	580	203	Practice 11	89%	2428	88%	1906	77%	1895	88%	894	80%	466	75%	152
4707	4042	2873	717	457	185	Practice 12	95%	4459	100%	4042	99%	2850	100%	717	100%	457	100%	185
767	716	945	452	307	199	Practice 13	60%	460	42%	298	28%	260	19%	87	11%	33	17%	33
2816	2960	3384	2044	1301	676	Practice 14	71%	2011	83%	2445	86%	2914	68%	1389	63%	826	59%	398
1459	1255	1682	833	428	142	Practice 15	62%	898	79%	986	83%	1395	67%	555	68%	292	62%	88
3400	3203	2811	1363	699	219	Practice 16	94%	3188	100%	3203	99%	2780	96%	1303	99%	692	98%	215
2462	2112	1838	774	609	244	Practice 17	100%	2462	100%	2112	100%	1838	100%	774	100%	609	99%	241
2967	2781	2872	1544	1024	371	Practice 18	97%	2882	100%	2781	99%	2832	99%	1528	99%	1018	100%	371
3148	2796	1415	395	253	96	Practice 19	100%	3148	97%	2718	100%	1415	100%	395	100%	253	100%	96
2578	2921	1939	666	356	139	Practice 20	100%	2578	87%	2532	91%	1768	100%	666	98%	349	98%	136
1611	2108	2100	1136	684	481	Practice 21	100%	1611	92%	1932	100%	2100	100%	1136	100%	684	100%	481
5815	5152	3864	1720	1009	372	Practice 22	93%	5409	100%	5152	95%	3682	100%	1720	99%	1002	100%	372
3097	2930	2396	1240	668	323	Practice 23	96%	2962	93%	2735	100%	2396	100%	1240	100%	668	100%	323
2522	2610	3103	1638	1323	497	Practice 24	91%	2303	100%	2610	99%	3070	98%	1604	100%	1323	99%	493
4476	4634	3087	1322	613	290	Practice 25	95%	4263	100%	4634	97%	3004	100%	1322	100%	613	99%	286
1887	1719	1796	973	615	368	Practice 26	25%	472	26%	442	18%	331	19%	188	15%	91	12%	45
2714	2193	1942	761	467	243	Practice 27	100%	2714	100%	2193	95%	1847	100%	761	100%	467	99%	240
2057	1907	1406	689	483	227	Practice 28	100%	2057	97%	1841	100%	1406	100%	689	100%	483	100%	227
4204	4278	4354	2423	1668	755	Practice 29	79%	3303	89%	3792	88%	3825	86%	2077	83%	1389	75%	564
1657	2538	1881	825	499	188	Practice 30	100%	1657	94%	2397	94%	1763	100%	825	103%	514	100%	188

1871	1348	1322	516	342	163	Practice 31	95%	1782	100%	1348	100%	1322	100%	516	99%	338	100%	163
838	1193	921	435	176	80	Practice 32	100%	838	100%	1193	100%	921	92%	402	100%	176	100%	80
1124	1212	1437	846	658	222	Practice 33	100%	1124	88%	1061	98%	1401	100%	846	100%	658	100%	222
1779	1156	1176	353	250	98	Practice 34	100%	1779	100%	1156	100%	1176	100%	353	100%	250	100%	98
5366	3798	2498	1175	667	249	Practice 35	97%	5187	100%	3798	100%	2498	100%	1175	99%	662	100%	249
1467	1112	854	354	172	41	Practice 36	44%	652	37%	412	26%	219	36%	126	22%	38	35%	14
2625	1978	2690	1164	602	200	Practice 37	94%	2475	94%	1868	96%	2590	100%	1164	95%	573	100%	200
3148	2360	2127	1150	790	413	Practice 38	98%	3075	91%	2145	100%	2127	100%	1150	100%	790	96%	397
2447	2243	1376	534	434	183	Practice 39	100%	2447	98%	2206	100%	1376	100%	534	100%	434	100%	183
1776	1927	1934	1163	795	374	Practice 40	90%	1607	100%	1927	100%	1934	100%	1163	99%	788	99%	371
1397	1527	1495	946	678	244	Practice 41	13%	175	17%	254	22%	332	21%	203	16%	106	13%	32
1516	1419	627	213	144	81	Practice 42	89%	1348	100%	1419	100%	627	100%	213	100%	144	100%	81
7943	8350	9129	5466	3173	1211	Practice 43	33%	2581	34%	2860	34%	3111	34%	1862	39%	1242	21%	259
2183	1527	1006	445	259	154	Practice 44	93%	2027	100%	1527	97%	974	100%	445	100%	259	100%	154
7909	5507	2884	848	329	110	Practice 45	100%	7909	94%	5163	99%	2852	100%	848	100%	329	100%	110
3642	3841	2733	1248	663	242	Practice 46	87%	3167	94%	3628	100%	2733	100%	1248	100%	663	100%	242
1116	490	171	23	7	4	Practice 47	100%	1116	94%	459	100%	171	100%	23	100%	7	100%	4
2591	2526	2253	1088	791	338	Practice 48	93%	2412	97%	2452	95%	2140	100%	1088	100%	791	100%	338
5580	3486	2631	1245	599	232	Practice 49	88%	4883	88%	3084	100%	2631	100%	1245	100%	599	100%	232
863	826	981	504	283	117	Practice 50	100%	863	88%	723	100%	981	100%	504	98%	277	100%	117
5097	4548	3372	1671	863	432	Practice 51	94%	4803	97%	4428	100%	3372	100%	1671	100%	863	99%	430
2945	3684	3650	2554	1681	661	Practice 52	95%	2798	100%	3684	90%	3285	99%	2537	97%	1636	98%	645
2287	2483	2120	1066	654	274	Practice 53	92%	2096	96%	2391	96%	2044	100%	1066	100%	654	100%	274
1396	1437	1239	750	518	311	Practice 54	100%	1396	100%	1437	100%	1239	96%	723	100%	518	100%	311
2637	2211	2004	1014	567	262	Practice 55	100%	2637	100%	2211	100%	2004	100%	1014	99%	562	100%	262
2719	2173	1740	892	583	303	Practice 56	97%	2634	98%	2126	99%	1719	100%	892	100%	583	98%	298
1453	1486	1608	871	724	298	Practice 57	90%	1308	92%	1362	82%	1319	100%	871	95%	690	100%	298
2425	2671	1992	905	473	181	Practice 58	26%	633	26%	683	22%	433	17%	156	13%	60	13%	24
2161	1848	1856	999	808	295	Practice 59	94%	2026	100%	1848	100%	1856	99%	986	100%	808	100%	295
3953	3462	2943	1224	772	387	Practice 60	97%	3829	98%	3393	100%	2943	100%	1224	100%	772	100%	387
1006	928	1086	675	396	182	Practice 61	83%	838	100%	928	100%	1086	100%	675	94%	374	100%	182
18 188	188	11	1	1	0	Practice 62	83%	15 099	100%	188	100%	11	0%	0	0%	0	0%	0
3551	3011	3333	1811	1129	459	Practice 63	98%	3468	100%	3011	100%	3333	99%	1798	100%	1129	99%	456
2837	2784	3126	1900	1241	552	Practice 64	36%	1032	19%	539	22%	687	21%	403	18%	222	10%	58
1642	1473	1051	397	204	69	Practice 65	100%	1642	100%	1473	100%	1051	100%	397	100%	204	100%	69
5289	5309	4780	2495	1795	915	Practice 66	100%	5289	98%	5225	99%	4739	100%	2495	100%	1795	100%	911

(*Continued*)

Appendix 2 (*Continued.*)

Total practice population by age							18 to 34		35–49		50–64		65–74		75–84		⩾85	
18–34	35–49	50–64	65–74	75–84	85+	Practice name	Proportion	Population	Proportion	Population	Proportion	Population	Proportion	Population	Proportion	Population	Proportion	Population
5525	3868	2392	1084	560	230	Practice 67	88%	4834	95%	3684	100%	2392	100%	1084	98%	549	100%	230
2016	1629	1585	775	515	271	Practice 68	100%	2016	95%	1548	93%	1482	100%	775	100%	515	100%	271
1626	1393	1124	424	243	83	Practice 69	100%	1626	98%	1359	100%	1124	100%	424	100%	243	100%	83
1580	1622	1934	1178	775	368	Practice 70	25%	395	17%	270	24%	470	24%	288	11%	85	11%	41
16 118	2141	1564	708	532	298	Practice 71	92%	14 846	100%	2141	97%	1513	100%	708	99%	527	100%	298
2859	2514	1149	423	245	93	Practice 72	95%	2709	100%	2514	100%	1149	100%	423	100%	245	100%	93
1346	1372	1749	1341	884	315	Practice 73	100%	1346	100%	1372	100%	1749	100%	1341	100%	884	99%	311
1650	1600	2227	1147	741	282	Practice 74	41%	679	29%	457	40%	901	27%	307	26%	195	32%	91
1927	1938	2202	1362	893	413	Practice 75	19%	367	4%	78	16%	351	22%	303	17%	153	16%	65
4840	6245	6856	4225	2815	1241	Practice 76	94%	4571	98%	6106	98%	6722	97%	4114	96%	2706	94%	1168
635	552	683	355	240	73	Practice 77	60%	381	100%	552	100%	683	100%	355	100%	240	100%	73
2522	2421	1404	533	308	105	Practice 78	90%	2270	93%	2254	97%	1360	98%	522	100%	308	100%	105
2697	2479	2657	1464	1251	352	Practice 79	100%	2697	100%	2479	100%	2657	100%	1464	100%	1251	99%	349
1579	2622	1866	1107	669	383	Practice 80	100%	1579	100%	2622	100%	1866	100%	1107	100%	669	99%	379
4892	3973	3126	1641	738	252	Practice 81	82%	4003	94%	3752	93%	2913	98%	1609	100%	738	100%	252
1401	1613	2012	1371	916	423	Practice 82	43%	600	25%	403	26%	519	26%	363	22%	200	18%	77
268 093	211 568	178 970	89 015	55 720	23 938		18–34	231 342	35–49	184 269	50–64	152 380	65–74	74 245	75–84	45 989	⩾85	19 229
																	⩾65	139 463

BMJ Open

Incidence of acute lower respiratory tract disease hospitalisations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective methodology

Catherine Hyams ,[1,2] Elizabeth Begier ,[3] Maria Garcia Gonzalez,[4,5] Jo Southern,[6] James Campling,[6] Sharon Gray,[3] Jennifer Oliver,[2,7] Bradford D Gessner ,[8] Adam Finn[2,4]

To cite: Hyams C, Begier E, Garcia Gonzalez M, *et al*. Incidence of acute lower respiratory tract disease hospitalisations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective methodology. *BMJ Open* 2022;**12**:e057464. doi:10.1136/bmjopen-2021-057464

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-057464).

Received 18 September 2021
Accepted 06 June 2022

For numbered affiliations see end of article.

Correspondence to
Dr Catherine Hyams;
catherine.hyams@bristol.ac.uk

ABSTRACT

Objectives To determine the disease burden of acute lower respiratory tract disease (aLRTD) and its subsets (pneumonia, lower respiratory tract infection (LRTI) and heart failure) in hospitalised adults in Bristol, UK.

Setting Single-centre, secondary care hospital, Bristol, UK.

Design We estimated aLRTD hospitalisations incidence in adults (≥18 years) in Bristol, UK, using two approaches. First, retrospective International Classification of Diseases 10th revision (ICD-10) code analysis (first five positions/hospitalisation) identified aLRTD events over a 12-month period (March 2018 to February 2019). Second, during a 21-day prospective review (19 August 2019 to 9 September 2019), aLRTD admissions were identified, categorised by diagnosis and subsequently annualised. Hospital catchment denominators were calculated using linked general practice and hospitalisation data, with each practice's denominator contribution calculated based on practice population and per cent of the practices' hospitalisations admitted to the study hospital.

Participants Prospective review: 1322 adults screened; 410 identified with aLRTD. Retrospective review: 7727 adult admissions.

Primary and secondary outcome measures The incidence of aLRTD and its subsets in the adult population of Southmead Hospital, Bristol UK.

Results Based on ICD-10 code analysis, annual incidences per 100 000 population were: aLRTD, 1901; pneumonia, 591; LRTI, 739; heart failure, 402. aLRTD incidence was highest among those ≥65 years: 65–74 (3684 per 100 000 adults), 75–84 (6962 per 100 000 adults) and ≥85 (11 430 per 100 000 adults). During the prospective review, 410/1322 (31%) hospitalised adults had aLRTD signs/symptoms and annualised incidences closely replicated retrospective analysis results.

Conclusions The aLRTD disease burden was high, increasing sharply with age. The aLRTD incidence is probably higher than estimated previously due to criteria specifying respiratory-specific symptoms or radiological change, usage of only the first diagnosis code and mismatch between case count sources and population denominators. This may have significant consequences for healthcare planning, including usage of current and future vaccinations against respiratory infection.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We used two analytical methods at the same site over a comparable period, to calculate incidence using both prospective and retrospective approaches.
⇒ The case burden of acute lower respiratory tract disease (aLRTD) and its subgroups was predefined and included patients with atypical presentations.
⇒ We calculated incidence using a denominator derived from general practitioner records, providing increased accuracy compared with population calculations based on census data.
⇒ This was a single-centre study, with a predominantly Caucasian cohort; therefore, the findings might not be generalisable to other populations.
⇒ The International Classification of Diseases 10th revision coding data analysis was limited to codes within the first five positions, and therefore may have excluded some cases where other diagnoses were placed higher in the diagnostic coding hierarchy.

INTRODUCTION

Acute lower respiratory tract disease (aLRTD) encompasses pneumonia, non-pneumonic lower respiratory tract infection (NP-LRTI), acute bronchitis, exacerbation of underlying respiratory diseases (including asthma and chronic obstructive pulmonary disease (COPD)) and acute heart failure (HF) events resulting in respiratory symptoms (eg, breathlessness). Before

the COVID-19 pandemic, European healthcare costs for pneumonia alone in adults were estimated at €10 billion annually, including €5.7 billion for inpatient care.[1] Pneumonia incidence in Europe varies by country and intracountry region, age, socioeconomic status and gender[2–4]; however, in all studies pneumonia incidence in adults increases sharply with age.[3] Pneumonia affects an estimated 0.5%–1% of UK adults each year.[5 6] Overall LRTI incidence is considerably higher with ~15% of UK adults aged ≥65 years experiencing an event each year.[7] While HF is not typically clinically included as an acute respiratory illness, HF with respiratory symptoms may be caused by respiratory viral infection, such as respiratory syncytial virus (RSV), either acutely or 3–4 weeks after the primary infection.[8 9]

However, aLRTD incidence may be considerably higher than previously reported, given that published literature has documented several reasons why previous estimates may have been erroneously low.[1] Estimates of aLRTD based on pneumonia defined as radiologically demonstrated alveolar infiltrates, may underestimate true disease burden as chest radiography (CXR) is an imperfect gold-standard.[10 11] Immunosuppressed, elderly or dehydrated patients are likely to be under-represented if respiratory infection is defined by radiologically demonstrated changes.[10 11] Microbiological investigations for pneumonia are undertaken variably and identify a causative pathogen in 50% of cases at most[12 13]; hence, the disease is probably under-reported when confirmed microbiological diagnosis is required. Furthermore, RSV infection has recently been recognised as an important respiratory pathogen later in life,[9] with severe disease occurring in patient groups in whom the diagnosis is likely to be under-recognised (eg, the elderly or those with underlying cardiac conditions).[8] Studies of clinical coding data are retrospective and subject to recognised limitations associated with this methodology.[14 15] Older patients with pneumonia often have atypical presenting signs and symptoms, which may lead to missed or incorrect admission diagnoses.[16] Pneumonia may occur secondary to, or be an underlying cause of, the main presenting report, particularly in patients with cerebrovascular accidents, HF, COPD exacerbations or altered consciousness levels.[17] In these scenarios, pneumonia may not be the primary hospitalisation diagnosis code and may not even be coded as an associated diagnosis.

There are many studies examining the incidence of acute respiratory illness in children; however, data on respiratory illness in adults in the UK is lacking. Given the paucity of data supporting accurate aLRTD incidence rates and its disease subsets in adults, we undertook to assess aLRTD incidence by two approaches (retrospective and prospective) in Bristol, UK, seeking to determine the disease burden of hospitalised aLRTD and its subgroups more accurately.

METHODS

Study design

This study was conducted at a large secondary care institution in UK (North Bristol NHS Trust) with specialist respiratory services (interstitial lung disease, pleural disease). Two approaches were undertaken to estimate aLRTD incidence: (1) 'retrospective analysis' of aLRTD International Classification of Diseases 10th revision (ICD-10) diagnostic codes for an entire year; and, (2) 21-day observational 'prospective review' of aLRTD hospital admissions.

Patient and public involvement

No patient involved.

Retrospective analysis

For the retrospective analysis, all adult inpatient admissions (≥18 years) obtained from Hospital Episode Statistic to the study hospital during March 2018 to February 2019 with aLRTD ICD-10 diagnostic codes (online supplemental data 1) in any of the first five positions were identified and categorised into aLRTD subgroups: pneumonia, NP-LRTI, other lower respiratory tract disease (LRTD) and HF (online supplemental data 2). A mutually exclusive hierarchy was used (pneumonia, NP-LRTI, then other LRTD) although HF diagnoses could co-occur with other categories. 'Other LRTD' included acute respiratory events that could not definitively be placed in another category. Only the first five ICD-10 codes were available for analysis.

Prospective review

Adult patients (≥18 years) resident within Bristol, North Somerset and South Gloucestershire Clinical Commissioning Group (CCG) referred to the acute medical unit (AMU) at North Bristol NHS Trust during 19 August 2019 to 9 September 2019 were included in an audit on acute respiratory illness. This time period was selected because it was felt to represent a period when there were an average number of adults hospitalised with aLRTD. A respiratory physician (CH) reviewed presenting features and investigation results for each admitted patient to determine whether aLRTD was present. Further medical record review was undertaken if patients had: new/worsening breathlessness, cough or sputum production; new or worsening peripheral oedema; pleurisy; clinical examination findings consistent with respiratory infection or HF; or, fever attributable to suspected respiratory infection. Patients with non-respiratory diagnoses were excluded. There were no patient refusals for either approach.

Prospective Review Outcome measures

aLRTD was considered confirmed in individuals with: new/worsening respiratory symptoms, with or without fever; sepsis, delirium or raised inflammatory markers attributable to likely respiratory infection in admitting clinical team's opinion; radiological change in keeping with infection (eg, consolidation); and/or final diagnosis of NP-LRTI, pneumonia or infective exacerbation of a chronic respiratory condition. A pneumonia diagnosis

was assigned if radiological changes likely due to infection were described by the reporting radiologist. An NP-LRTI diagnosis was assigned if aLRTD signs and symptoms likely to be due to infection were present without demonstrated radiological change. An HF diagnosis was assigned in presence of: new/worsening breathlessness and bi-basal crepitations, cardiac wheeze or new/worsening bilateral pitting oedema; elevated pro-NT BNP (N-terminal pro B-type natriuretic peptide) (≥450 pg/mL); radiologist-reported radiographic changes consistent with cardiac failure; or a final consultant physician diagnosis of HF, cardiac failure or left-ventricular failure. When present, ≥1 diagnosis was selected.

For both retrospective and prospective studies, pneumonia included both community and healthcare setting acquired cases; although, the prospective review only captured admitting diagnoses and pneumonias occurring later during hospitalisation were not included.

Incidence calculations

Annual incidence per 100 000 persons was calculated for both retrospective and prospective studies. Case counts from prospective review were annualised (ie, case counts by diagnosis and overall were divided by the percentage of annual admissions for these diagnosis groups that occurred in this 21-day period in the retrospective analysis).

Incidence denominators

To calculate appropriate population denominators for incidence calculations, aLRTD hospital admission event data were linked to aggregated general practitioner (GP) practice patient registration data within the NHS Bristol, North Somerset and South Gloucestershire CCG for 2017–2019. Only 4% of patients sought care at North Bristol NHS Trust hospital from outside these local CCGs, despite presence of specialist respiratory services. In the UK, GP registration is available free of charge for all, regardless of residential status. For GP practices within these same CCGs, the proportion of their aLRTD admissions occurring at North Bristol NHS Trust was multiplied by their patient registration count in 2019 by age group, to get each practice's contribution to the denominator (eg, if 50% aLRTD admissions were at North Bristol among persons 50–64 years, the practice would contribute half of their patients 50–64 years to the denominator). Further details of this methodology have been described previously.[18]

Statistical analysis

Patient characteristics were tabulated by aLRTD diagnosis. Categorical variables were presented as counts with percentages. Continuous data are presented with means and SD if normally distributed and medians and IQR if not normally distributed. Patient groups difference were evaluated using the Friedman test with Wilcoxon signed-rank test.

RESULTS

Retrospective analysis

Over a 12-month period, we identified 7727 hospital admissions for aLRTD: 3005 NP-LRTI admissions, 2402 pneumonia, 1633 HF and 1071 other LRTD (table 1). The aLRTD admissions were lowest in March and April and highest December through February (figure 1A), overall and for all aLRTD subgroups ($p<0.05$) (figure 1B–D). Overall, 28.1% (2244) cases were identified as being potentially hospital-acquired infection based on co-occurring ICD-10 code 'Y95 Nosocomial Infection'.

Table 1 Demographic characteristics of patients admitted with acute lower respiratory tract disease for 1-year International Classification of Diseases 10th revision code retrospective analysis and 21-day prospective review period—2018–2019

Characteristic	Pneumonia		NP-LRTI		Heart failure		Other LRTD	All LRTD	
Study	Prospective review	Retrospective analysis	Prospective review	Retrospective analysis	Prospective review	Retrospective analysis	Retrospective review only	Prospective review	Retrospective analysis
N	152	2402	188	3005	77	1633	1071	410	7727
Gender, females	61 (40)	1078 (45)	99 (53)	1482 (49)	39 (51)	731 (45)	489 (46)	194 (47)	3780 (49)
Age									
Median (IQR), years	80 (67–86)	81 (66–88)	70 (46–87)	69 (45–87)	87 (72–90)	87 (70–90)	74 (53–82)	80 (64–88)	81 (65–90)
18–24	4 (3)	72 (3)	9 (5)	151 (5)	0 (0)	0 (0)	26 (2)	13 (3)	249 (3)
25–34	2 (2)	48 (2)	12 (6)	183 (6)	0 (0)	3 (0)	33 (3)	14 (3)	267 (3)
35–44	6 (4)	97 (4)	14 (7)	209 (7)	2 (3)	10 (1)	59 (6)	22 (5)	375 (5)
45–54	8 (5)	118 (5)	11 (6)	183 (6)	0 (0)	22 (1)	112 (10)	19 (5)	435 (6)
55–64	18 (12)	293 (12)	19 (10)	305 (10)	8 (10)	158 (10)	210 (20)	45 (11)	966 (13)
65–74	34 (22)	501 (21)	32 (17)	549 (18)	10 (15)	199 (12)	223 (21)	75 (18)	1472 (19)
75–84	44 (28)	667 (28)	40 (21)	621 (21)	20 (30)	498 (31)	205 (19)	100 (24)	1991 (26)
≥85	38 (26)	606 (25)	51 (27)	704 (23)	37 (55)	742 (45)	203 (19)	123 (30)	2255 (29)

LRTD, lower respiratory tract disease ; NP-LRTI, non-pneumonic lower respiratory tract infection .

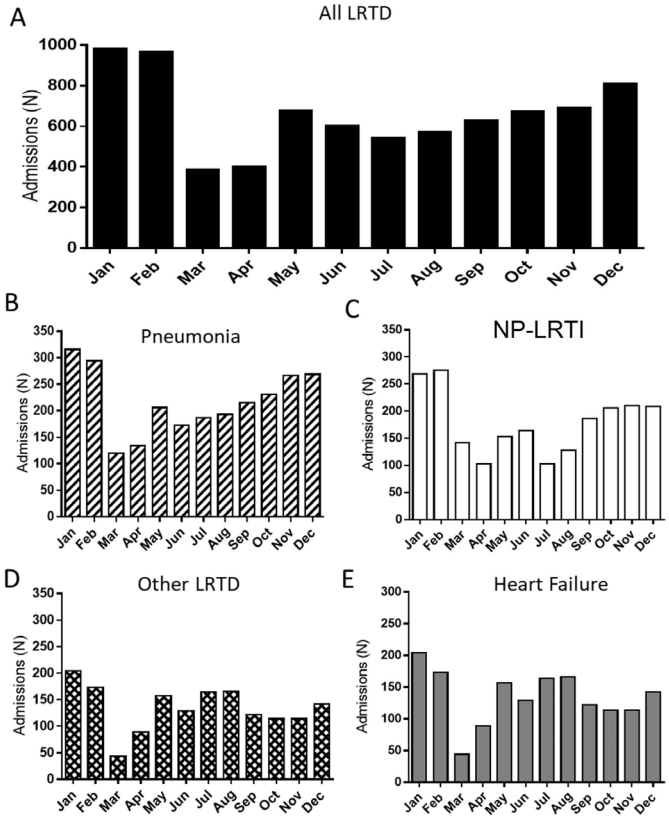


Figure 1 The aLRTD admissions identified by retrospective International Classification of Diseases 10th revision (ICD-10) diagnostic code analysis at North Bristol National Health Service Trust—UK 2018–2019. Monthly number of patients admitted, based on ICD-10 coding analysis, with (A) all acute lower respiratory tract disease (aLRTD) (black bars), (B) pneumonia (slashed bars), (C) non-pneumonic lower respiratory tract infection (NP-LRTI) (white bars), (D) other LRTD (cross-hash bars) and (E) heart failure (grey bars).

Prospective review

Among 1322 eligible adult patients referred to AMU over the 21-day review period (figure 2), 410 patients had signs or symptoms of aLRTD: 188 (46%) NP-LRTI, 152 (37%) pneumonia and 77 (19%) HF. Seven patients had both decompensated HF and a respiratory infection at hospital admission. On admission, >10% of patients with aLRTD did not have respiratory symptoms: 16 (11%) pneumonia, 25 (13%) NP-LRTI and 18 (14%) HF (table 2).

Almost all adults admitted with aLRTD underwent routine biochemistry, haematology and radiological investigation (99.9%, n=409). In contrast, only 150 (37%) patients with aLRTD had microbiological testing performed: blood cultures (n=149, 36%) and urine cultures (n=143, 35%). Pneumonia patients more commonly underwent microbiological investigation than patients with NP-LRTI ($p<0.05$) with highest disparity in rates of sputum culture, urinary antigens and respiratory viral PCR (table 2). All patients with cardiac failure who underwent microbiological investigation had concomitant respiratory infection (table 2). Overall, a microbiological diagnosis was found in 11 (3%) cases, highlighting

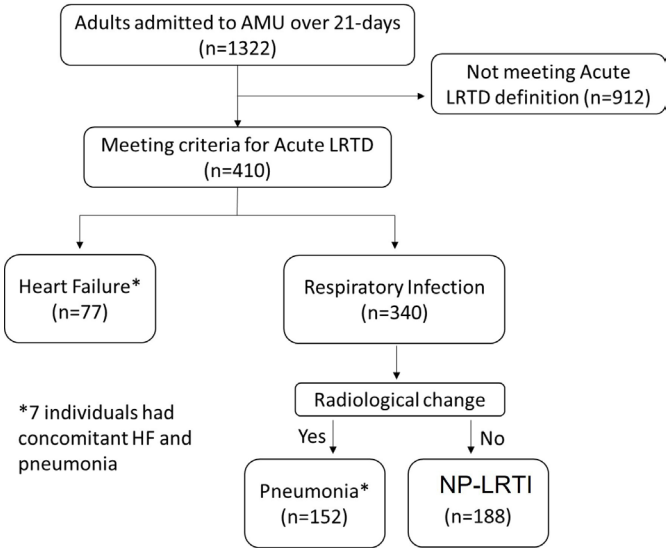


Figure 2 Flow diagram of the prospective review. AMU, acute medical unit; HF, heart failure; LRTD, lower respiratory tract disease; NP-LRTI, non-pneumonic lower respiratory tract infection.

the low frequency of definitive pathogen identification in aLRTD. Younger patients underwent microbiological testing more frequently than the elderly for all aLRTD categories (table 2).

Disease incidence

Retrospective analysis yielded an overall aLRTD incidence of 1901 per 100 000. Disease incidence rose with increasing age (table 3), both overall and for all disease subgroups; incidences per 100 000 among adults aged ≥85 years were: 11 430 (aLRTD), 6116 (NP-LRTI), 4215 (pneumonia) and 4005 (HF). Overall, 28.1% aLRTD hospitalisations also included an ICD-10 discharge code for 'nosocomial infection', suggesting the aLRTD event or other infection was hospital-acquired. For pneumonia 25.3% had the nosocomial infection code. If all of these were related to the pneumonia diagnosis, an estimated residual 1794 events would have been community-acquired pneumonia (CAP) (annual incidence 441/100 000 adults). Among older age categories, where the incidence of aLRTD was highest, NP-LRTI incidence was similar to pneumonia incidence, with an approximate 1:1 ratio of NP-LRTI to pneumonia cases. However, among adults under age 50 years, there were approximately twice as many NP-LRTI cases observed as pneumonia cases. Incidence calculations using annualised prospective review results were broadly comparable with retrospective analysis of ICD-10 data (table 3).

DISCUSSION

This is the first UK study to assess aLRTD incidence comprehensively. We conducted an analysis of 12 months of hospital admissions by ICD-10 diagnosis code data and a 21-day prospective review at a large academic hospital in South West England. With both approaches, we found

Table 2 Clinical characteristics and investigations of patients admitted with acute lower respiratory tract disease over 21-day prospective review period in August to September 2020

Characteristic	Pneumonia, n=152 (%)	NP-LRTI, n=188 (%)	Heart failure, n=77 (%)	All LRTD, n=410 (%)
GP	56 (37)	72 (39)	30 (39)	158 (39)
A&E department	93 (61)	100 (54)	45 (58)	238 (58)
Transfer from another unit	2 (1)	13 (7)	0 (0)	15 (4)
Other	1 (1)	1 (1)	2 (3)	4 (1)
Referral source				
Typical features*	136 (89)	163 (87)	63 (82)	355 (87)
Atypical features	16 (11)	25 (13)	14 (18)	55 (13)
Collapse/falls	11 (7)	12 (6)	0 (0)	23 (6)
Confusion	0 (0)	7 (4)	4 (5)	10 (2)
Drowsiness	1 (1)	1 (1)	2 (3)	4 (1)
Off legs/generally unwell	5 (3)	5 (3)	8 (10)	18 (4)
LRTD signs and symptoms on referral to AMU				
Biochemistry	152 (100)	185 (99)	77 (100)	419 (100)
Haematology	152 (100)	185 (99)	77 (100)	419 (100)
Radiology	152 (100)	185 (99)	77 (100)	419 (100)
Investigations performed				
Testing by age group				
All patients	79/152 (52)†	77/188 (41)	11/77 (14)	167 (41)
18–24	3/4 (75)	6/9 (66)	0/0 (0)	9/13 (69)
25–34	0/0 (0)	6/12 (50)	0/0 (0)	6/12 (50)
35–44	5/6 (83)	10/14 (71)	2/2 (100)	17/22 (77)
45–54	6/8 (75)	6/11 (55)	0/0 (0)	13/19 (68)
55–64	11/18 (61)	12/19 (63)	5/8 (63)	31/45 (69)
65–74	15/34 (44)	12/32 (38)	1/10 (10)	28/75 (37)
75–84	21/43 (49)	10/40 (25)	2/20 (10)	33/100 (33)
≥85	18/39 (46)	15/51 (19)	1/37 (3)	34/124 (27)
Test performed				
Blood culture	79 (52)	70 (37)	5 (6)	150 (37)
Urine culture	66 (43)	77 (41)	11 (14)	150 (37)
Sputum culture	27 (18)†	7 (4)	2 (3)	35 (9)
BinaxNOW Pn UAT	29 (19)†	6 (3)	0 (0)	35 (9)
Respiratory virus PCR	16 (11)†	11 (6)	1 (1)	28 (7)
Pleural fluid culture	3 (2)	0 (0)	1 (1)	4 (1)

*Typical symptoms included cough, breathlessness, increased or discoloured sputum production, wheeze, pleurisy, peripheral oedema, haemoptysis, reduced exercise tolerance and/or fever.
†P<0.05.
‡BinaxNOW Pn UAT was only performed in accordance with NICE/BTS guidelines.
A&E, accident and emergency department; AMU, acute medical unit; BTS, British Thoracic Society; GP, general practitioner; LRTD, lower respiratory tract disease; NICE, National Institute for Health and Care Excellence; NP-LRTI, non-pneumonic lower respiratory tract infection; Pn UAT, pneumococcal urinary antigen test.

a high annual incidence of aLRTD (>1700 per 100 000; 1.7%), pneumonia (~0.6%), NP-LRTI without pneumonia (>0.7%) and HF (>0.4%). Incidences increased sharply in a non-linear manner as age increased above 65 years for all aLRTD categories. These results suggest rates are probably significantly higher than previous disease estimates from the UK (table 4) but comparable with many results globally,[19 20] with important consequences for healthcare resources. For example, a recent review highlighted that pneumonia incidences ranged from 1000 to 2500 per 100 000 (1%–2.5%) among persons aged 65–74 years in Spain, Germany, France, Japan and the USA, which are comparable to the >1250 per 100 000 (1.3%) reported here. Some of the potential sources of

Table 3 Incidence of aLRTD resulting in hospital admission based on prospective and retrospective approaches by age group and condition, North Bristol National Health Service Trust—UK 2018–2019

	Age groups					
	All adults	18–49 years	50–64 years	65–74 years	75–84 years	≥85 years
Population in 2018	406 481	226 920	91 534	45 705	29 487	12 835
Retrospective analysis of a year's ICD-10 codes						
Annual cases—N (row %)						
All aLRTD	7727	1130 (14)	1103 (14)	1684 (22)	2053 (27)	1757 (23)
Pneumonia	2402	264 (11)	288 (12)	589 (25)	720 (30)	541 (22)
NP-LRTI	3005	576 (19)	410 (14)	572 (19)	662 (22)	785 (26)
Other LRTD	1071	246 (23)	268 (25)	226 (21)	200 (19)	131 (12)
Heart failure	1633	48 (3)	189 (12)	397 (24)	485 (30)	514 (31)
NP-LRTI/pneumonia ratio	1.3	2.2	1.4	1.0	0.9	1.5
Incidence (per 100 000)						
All aLRTD	1901	497	1205	3684	6962	13 689
Pneumonia	591	116	315	1289	2442	4215
NP-LRTI	739	254	448	1252	2245	6116
Other LRTD	263	108	293	494	678	1021
Heart failure	402	21	206	869	1645	4005
21-day prospective review (annualised)						
Annualised cases—N (row %)						
All aLRTD	7885	1038	962	1692	2231	1962
Pneumonia	2621	224	397	776	690	534
NP-LRTI	3857	796	531	653	1061	816
Heart failure	2000	51	205	308	641	795
NP-LRTI/pneumonia ratio	1.5	3.6	1.3	0.8	1.5	1.5
Incidence (per 100 000)						
All aLRTD	1940	458	1050	3703	7565	15 283
Pneumonia	645	99	433	1698	2339	4164
NP-LRTI	944	351	580	1429	3599	6360
Heart failure	492	23	224	673	2174	6193

Pneumonia category includes community and healthcare acquired. For retrospective ICD-10 based cohort, the following mutually exclusive hierarchy was used to define pneumonia, LRTI and other LRTD; heart failure event could overlap with other categories.
'Other LRTD' contains LRTD events that could not definitively be placed in one of the other respiratory disease categories.
aLRTD, acute lower respiratory tract disease ; HF, Heart Failure; ICD-10, International Classification of Diseases 10th revision; LRTD, lower respiratory tract disease; LRTI, lower respiratory tract infection; NP-LRTI, non-pneumonic lower respiratory tract infection ; pro-NT BNP, N-terminal pro B-type natriuretic peptide.

underestimation for other UK incidence studies (table 4) include: case source and denominator mismatch; use of first position in ICD-code analysis only; inclusion of enrolled subjects in consent-based prospective studies only; requiring specific symptoms and chest X-ray confirmation in order to be classified as pneumonia/aLRTD; and, lastly, the rising incidence of aLRTD.

Comparison with published literature

No studies have reported aLRTD incidence comprehensively in UK hospitalised patients within the last 20 years. However, eight publications report incidence of ≥1 aLRTD subgroup. Seven publications reported CAP incidence (three from Nottingham, UK). For pneumonia, our incidence estimates were three to fourfold higher than other UK inpatient incidence estimates (table 4) but comparable to estimates from other countries.[19 20] Only two UK studies from approximately 20 years ago reported NP-LRTI incidence (one with both CAP and NP-LRTIs; table 4), and only one provided an inpatient estimate.[21] NP-LRTI incidence was approximately twofold lower than that calculated here, taking into account inclusion of CAP and other NP-LRTI in their estimates.[21 22] The one UK study reporting HF incidence had methodological differences (ie, inclusion of outpatients and limiting to initial HF diagnosis) and estimates could not be compared.[23] Close examination of the existing literature methods yielded multiple sources for potential underestimation.

Table 4 Literature review of acute lower respiratory tract disease incidence in hospitalised adults, UK

Study	Study years	Location (facility)	Event setting	Age	Case definition*	Key inclusion	Denominator source	Overall incidence	Age breakdown (years)	Incidence per 100 000 by age†	Comments
Community-acquired pneumonia											
Current study	2018–2019	Bristol (Southmead Hospital)	Inpatients only	≥18 years	Clinical signs/ symptoms with radiological change in keeping with infection (prospective review portion). **AND** Retrospective ICD-10 code analysis (first five positions): J12–J18, J85 and J86.	Hospital-acquired pneumonia (HAP) included	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for per cent of admissions that came to Southmead.	648	18–49	116	Retrospective analysis includes first five positions.
									50–64	315	
									65–74	1289	
								591	75–84	2442	
									≥85	4215	
Elston 2012, Epidemiol Infect[26]	2002–2009	Hull and East Yorkshire Hospitals‡	Inpatients only	≥16 years	ICD-10 codes (first position only): J18.0, J18.9, J13X, J18.1 and J15X.	HAP included	Mid-year population estimates for Hull (city) and EroY (Surrounding County) from Office for National Statistics.	143 (2002) – 207 (2009)	15–64	48.8–84.1	Fewer ICD-10 codes included than other analyses; Y95 nosocomial infection included.
									≥65	543–781	
Millet 2013, J Clin Epidemiol[7]	1997–2011	UK	Both inpatients and outpatients	≥65 years	Read and ICD-10 codes; no specified codes provided. For ICD-10, used first diagnosis code for first episode of hospitalisation only.	HAP excluded	Mid-year UK population estimates from Office for National Statistics.	799	65–69	281	Incidence estimates converted to per 100 000 person-years.
									70–74	431	
									75–79	694	
									80–84 years	1205	
									85–89	2184	
									≥90	4194	
Pick 2020, Thorax§[25]	2013–2014	Nottingham (two large university hospitals)	Inpatients only	≥16 years	Inclusion criteria: one or more symptom suggestive of LRTI (defined as cough, increasing dyspnoea, sputum production and fever), with evidence of acute infiltrates consistent with respiratory infection on admission radiography, and treated for a diagnosis of CAP. Exclusion criteria: hospitalisation within 10 days of index admission, a diagnosis of tuberculosis or post-obstructive pneumonia.	HAP excluded	Mid-year estimates for the Greater Nottingham area from the Office for National Statistics, including local population data stratified by age group.	96.3	16–49	27.3	Only consented/ enrolled subjects included in estimates.
									50–64	80.2	
									65–74	181.3	Required CXR confirmation but not all LRTI patients had CXR.
									75–84	400.6	
									≥85	707.5	Census-derived denominator that may not have fully matched catchment area.
	2017–2018							158.4	16–49	29.9	
									50–64	146.9	
									65–74	310.4	Required specific symptoms and evidence of treatment and some CAP events may not have had this information documented.
									75–84	559.5	
									≥85	1522.6	
	2013–2018							120.4	--	--	

Continued

Table 4 Continued

Study	Study years	Location (facility)	Event setting	Age	Case definition*	Key inclusion	Denominator source	Overall incidence	Age breakdown (years)	Incidence per 100 000 by age†	Comments
Thorrington 2019, BMC Med	2004–2005	England	Inpatients only	≥65 years	ICD-10 codes (first position only): J18 (pneumonia of unspecified causative organism).	HAP included	Mid-year population estimates for England for 2004–2015 from Office for National Statistics.	NA	≥65	829	Incidence is per 100 000 person-years. Fewer ICD-10 codes included than other analyses.
	2014–2015								≥65	1787	
Trotter 2008, EID	1997–1998	England	Inpatients only	≥65 years	ICD-10 codes (first position only): J12–J18.	HAP included	Mid-year population estimates for England for 1997–2004 from the Office for National Statistics.	NA	65–74	263	Incidence estimates converted to 100 000 population.
									75–84	684	
									≥85	1599	
	2004–2005								65–74	355	
									75–84	877	
									≥85	2218	
Lower respiratory tract infection						**Pneumonia**					
Current study	2018–2019	Bristol (Southmead Hospital)	Inpatients only	≥18 years	Clinical signs/ symptoms of heart failure or elevated pro-NT BNP or radiological change. **AND** Retrospective ICD-10 code analysis: J09, J10, J11; J20, J21, J22, J40, J41, J42, J44, J45 and J46.	Excludes all pneumonia	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for per cent of admissions that came to Southmead.	802	18–49	254	
									50–64	448	
									65–74	1252	
								739	75–84	2442	
									≥85	6116	
Lovering 2001, Clinical Microbiol and Infection[21]	1994–1996	Bristol (Southmead Hospital)	Inpatients only	≥16 years	LRTI episodes from four groups by ICD 9/10 codes: (1) CAP; (2) chest infection or acute exacerbation in presence of asthma; (3) chest infection or acute exacerbation in presence of COPD; or (4) bronchitis with no radiological evidence of pneumonia or pre-existing respiratory disease, such as COPD or asthma. No specified codes provided.	Includes community-acquired pneumonia	No information on denominator provided.	623	16–39	151	Incidence converted to per 100 000 population.
									40–49	175	
									50–59	294	Study involved single hospital and no mention of source of denominator mentioned.
									60–69	1086	
									70–79	2135	
						HAP excluded			>79	3141	

Continued

Table 4 Continued

Study	Study years	Location (facility)	Event setting	Age	Case definition*	Key inclusion	Denominator source	Overall incidence	Age breakdown (years)	Incidence per 100 000 by age†	Comments
Millet 2013, J Clin Epidemiol[7]	1997–2011	UK	Both inpatients and outpatients	≥65 years	Read and ICD-10 codes; no specified codes provided. For ICD-10, used first diagnosis code for inpatient episode only.	Includes community-acquired pneumonia	Mid-year UK population estimates from Office for National Statistics. (Patients were not considered at risk for community-acquired LRTI during an LRTI illness-episode, during an HES hospitalisation, or for 14 days after any HES hospitalisation or CPRD hospital code. This person-time was excluded from denominator.)	12 293	65–69	9221	Incidence converted to per 100 000 person-years.
									70–74	10 740	
									75–79	12 607	
									80–84	15 137	
									85–89	18 791	
						HAP excluded			≥90	26 287	
Heart failure						**All or first episode**					
Current study	2018–2019	Bristol (Southmead Hospital)	Inpatients only	≥18 years	Clinical signs/ symptoms of heart failure or elevated pro-NT BNP or radiological change.	All	Based on number of persons ≥18 years registered in referring GP practices. For practices with split referral patterns, number adjusted for per cent of admissions that came to Southmead.	328	18–49	21	
									50–64	206	
									65–74	869	
					AND			402	75–84	1645	
					Retrospective ICD-10 code analysis: I110; I130; I132; I50.				≥85	4005	
Uijl 2019, Eur J Heart Fail[23]	2000–2010	UK	Both inpatients and outpatients	≥55 years	Four sources of EHR were linked: CPRD primary care records, HES secondary care hospital charges, Myocardial Ischaemia National Audit Project (MINAP) disease registry, and ONS national death registry. HES ICD-10 codes: Heart failure: I110, I130, I132, I260, I50 and I21. Individuals were excluded if they presented a history of HF before their index date in CPRD, HES or MINAP.	First episode at 55 years or older counted	Not reported.	Not Reported	55–64, M	360	Incidence converted to per 100 000 person-years.
									55–64, Female	190	
									65–74, Male	1360	Included first episode of HF (inpatient or outpatient) at age 55 and up, so repeat episodes not included.
									65–74, Female	920	
									>75, Male	3440	
									>75, Female	2800	

*Add text names for all listed ICD codes in this footnote or appendix.
†For the current study, only age-group estimates from the retrospective analysis were included in this table, but these were closely comparable to the annualised incidence estimates based on the prospective review. See table 3 for full results.
‡Included hospitals were Hull Royal Infirmary, Castle Hill Hospital, Princess Royal Hospital, Scarborough District General Hospital, Bridlington and District Hospital, York Teaching Hospital, Scunthorpe General Hospital, Goole and District Hospital.
§Only the most recent incidence estimates from the Nottingham CAP study were included.
CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease ; CPRD, Clinical Practice Research Datalink; CXR, chest radiography ; EHR, Electronic Health Record; GP, general practitioner; HES, Hospital Episode Statistic ; ICD-10, International Classification of Diseases 10th revision; LRTI, lower respiratory tract infection ; ONS, Office of National Statistics; pro-NT BNP, N-terminal pro B-type natriuretic peptide.

First, for incidence studies that were not countrywide, identifying an appropriate denominator is challenging. Like many other inpatient settings worldwide, UK hospitals' catchment areas for acute treatment are principally driven by geography, but the proportion of any area's residents expected to use the hospital becomes less clear as distance from the hospital increases because catchment areas and populations of different hospitals may overlap. Defining hospital catchment populations based solely on census data cannot account for this variability. Including all geographical areas using the hospital to any extent results in population denominator overestimation and underestimated incidence. Here, we addressed this by calculating population denominators based on hospital utilisation behaviour from referring general practices.

Second, other studies used fewer codes in their ICD code analysis: all limited their analyses to events where the diagnostic code was in the first position (table 4; case definition column), potentially excluding admissions in which pneumonia/NP-LRTI complicated other underlying respiratory diseases, including COPD and asthma. Limiting to first position has been shown to reduce sensitivity for pneumonia events by about 30% (66%–72% sensitive).[22 24] Conversely, the recent British Thoracic Society (BTS) audit on CAP found ~27% of pneumonia events identified by ICD code (J12–18) had no new CXR infiltrates.[6] Even accounting for this potential over coding practice, our estimates remain well above other published UK estimates.

Third, for other prospective studies, exclusion of events where patients did not consent to participation or were not identified by study surveillance processes (often conducted predominately during business hours) can introduce underestimation. Further, other prospective pneumonia studies specifically required documentation of specific symptoms, radiological findings and treatments,[25] potentially excluding those without these features documented in medical records. In our prospective review, approximately 11% did not display typical signs and symptoms of pneumonia and could have been excluded by that requirement. Requiring CXR confirmation has been shown to reduce incidence estimates for pneumonia,[20] although all pneumonia events in our prospective review were radiologically confirmed.

Fourth, trends over time may also contribute to our estimates being higher than previous reports. Our study's estimates are recent, and rising incidence of pneumonia has been documented in all studies that have reported such trends.[25–27]

Finally, this study included, in part, hospital-acquired pneumonias (HAP), which were excluded from estimates calculated in some other studies (table 4). The retrospective analysis may have included more nosocomial infection than the prospective review, as the latter was focused on evaluation of patients at admission for aLRTD and would not have reliably captured events that developed during hospitalisation. 25.3% pneumonia events included a nosocomial infection code, but this code could relate to any nosocomial infection during that hospitalisation. If all these cases were assumed to be HAP, our estimates CAP incidence would still be well above prior UK estimates: 441/100 000 (≥18 years).

While not impacting all-cause aLRTD incidence estimates discussed above, during the prospective review, we found low rates of microbial investigation which prevented us from generating pathogen-specific incidence estimates. Only 52% of patients with radiologically-confirmed pneumonia underwent microbiological testing during hospitalisation, with even lower rates in other aLRTD subgroups (41% NP-LRTI and 14% HF). Microbiological testing occurred less frequently as age increased, particularly in patients with NP-LRTI. It is possible that, because aLRTD hospitalisations are substantially more common among older persons, less aetiological investigation is performed. Furthermore, clinicians may elect to treat elderly patients with a more pragmatic and less invasive approach. Management guidelines do not require specific pathogen identification to inform treatment choice. Presence only of atypical features on presentation (in this series, 13% NP-LRTI and 11% pneumonia cases) may also reduce the likelihood of timely microbiological testing. Low rates of microbiological testing, and consequently of confirmed microbiological diagnosis, may represent a source of underestimation of pathogen-specific disease incidence in patient groups (ie, testing bias), particularly in elderly patient groups.

Strengths and limitations of this study

This study has many strengths. First, this study used two analytical methods at the same site over a comparable period, to calculate incidence using both prospective and retrospective approaches. Second, the case burden of aLRTD and its subgroups was pre-defined and included patients with atypical presentations but with clinical and/or radiological diagnoses, who may otherwise have been excluded from analysis. Additionally, we calculated incidence using a denominator derived from GP records, providing increased accuracy compared with population calculations based on census data.

However, the study also had some limitations. This was a single-centre study, with a predominantly Caucasian cohort; therefore, the findings might not be generalisable to other populations both within the UK and in other countries. Different healthcare systems may affect patient treatment preference, and as the National Health Service provides care which is free at the point of access, the hospitalisation rates seen in this study may be different than those in fee or insurance based healthcare systems. Similarly, physician treatment preferences may affect hospitalisation rates, and we have not explored these in this analysis. The ICD-10 coding data analysis was limited to codes within the first five positions, and therefore may have excluded some cases where other diagnoses were placed higher in the diagnostic coding hierarchy. Furthermore, we could not determine how many cases of the 28.1% ICD-10 cases also coded with

nosocomial infection had hospital-acquired respiratory infection rather than other nosocomial infections.

Although the denominator used to calculate incidence was derived from GP records, this was still an estimate as there is no precisely defined denominator hospital catchment. We were unable to exclude patients from outside the local CCGs in the retrospective analysis, due to the way ICD-10 data were obtained. However, these patients were excluded from the prospective review and the incidence calculated was comparable, suggesting any effect that patients attending North Bristol NHS Trust from outside the local CCGs have on incidence estimates is minimal. This may be because any effect of travelling or health-seeking behaviour is bi-directional: while some patients admitted to Southmead hospital were from outside the local area, it is also true that patients with aLRTD within the relevant CCGs would have been admitted to other hospitals. We also acknowledge the 21-day prospective review period was relatively short, not repeated, and may not be fully representative of clinical practice and cases throughout the year. This study was conducted before the emergence of COVID-19, and we think these data will be useful in one of two-ways in the context of COVID-19: (1) either COVID-19 will become endemic, and the data will reflect the first year before a new normal or (2) COVID-19 will abate and it will provide an anchor for understanding incidence during a respiratory viral pandemic.

In conclusion, we found similarly high estimates of LRTD incidence using two different approaches, and these estimates were higher than those obtained previously in the UK. Determining if there is a real increase in incidence, or if this estimate is larger due to more accurate methodology including a more accurate denominator will require ongoing comprehensive surveillance. Nonetheless, combining all types of LRTD highlights the high burden for this important and potentially life-threatening disease group. Incidence assessments require close assessments of potential areas of under ascertainment, including unidentified or unenrolled cases in prospective studies, reduced positions or number of ICD-10 codes included for retrospective studies, and population denominator mismatch for all study types. Our prospective review findings highlight the need to consider atypical clinical presentations for pneumonia and the lack of routine microbiological investigation in many patients with aLRTD required for pathogen-specific aLRTD incidence calculation. Future research should include a fully prospective assessment of aLRTD incidence with comprehensive diagnostic testing across multiple respiratory seasons, to ensure accurate capture of all aLRTD events, particularly in the elderly. Such research should be undertaken given the high and rising aLRTD burden to enable appropriate healthcare planning and identification of interventions which may reduce disease burden.

Author affiliations
[1]Academic Respiratory Unit, University of Bristol, Bristol, UK
[2]Bristol Vaccine Centre, University of Bristol, Bristol, UK
[3]Global Medical and Scientific Affairs, Pfizer Inc, New York City, New York, USA
[4]Population Health Sciences, University of Bristol, Bristol, UK
[5]Academic Respiratory Unit, Southmead Hospital, Bristol, UK
[6]Vaccines Medical Affairs, Pfizer Ltd, Tadworth, UK
[7]Schools of Cellular and Molecular Medicine and Population Health Sciences, University of Bristol, Bristol, UK
[8]Vaccines Medical Development, Scientific and Clinical Affairs, Pfizer Inc, Collegeville, Pennsylvania, USA

Acknowledgements We would like to acknowledge the assistance of Qi Yan, PhD (Pfizer) who provided indispensable medical writing and literature review support for this manuscript and Harvey Walsh Health who performed the hospital denominator calculation used here. For the denominator analysis, Hospital Episode Statistics (HES) data were re-used with the permission of NHS Digital via Harvey Walsh Limited.

Contributors CH, EB, MGG, JS, BDG and AF generated the research questions and analysis plan. CH, EB, MGG, JS, JC, SG and BDG undertook and contributed to the data analysis. AF oversaw the research and data collection which was undertaken by CH and MGG. All authors contributed to the preparation of the manuscript. CH is the guarantor for this study and accepts full responsibility for the study conduct, had access to the data, and controlled the decision to publish.

Funding CH was funded by the National Institute for Health Research (NIHR) (NIHR Academic Clinical Fellowship (ACF-2015-25-002)). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The remainder of the study funding was from Pfizer (WI255886-1).

Competing interests EB, JS, JC, SG and BDG are full-time employees of Pfizer Vaccines and hold stock or stock options. CH is the Principal Investigator of the Avon CAP study (ISRCTN:17354061) which is an investigator-led University of Bristol study funded by Pfizer and has previously received support from the NIHR in an Academic Clinical Fellowship. AF is a member of the Joint Committee on Vaccination and Immunization (JCVI) and chair of the WHO European Technical Advisory Group of Experts on Immunization (ETAGE) committee. In addition to receiving funding from Pfizer as Chief Investigator of this study, he leads another project investigating transmission of respiratory bacteria in families jointly funded by Pfizer and the Gates Foundation. The other authors have no relevant conflicts of interest to declare.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by North Bristol NHS Trust Research Audit Ethics Committee (CA52218). This work was conducted as part of an audit evaluating the patients admitted to Southmead Hospital with signs and symptoms of respiratory disease. Members of the clinical care team undertook the data collection, and only anonymised data was reviewed by research team members who were not part of the clinical care team.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. No additional data available due to the confidential and sensitive nature of the data in this study.

ORCID iDs
Catherine Hyams http://orcid.org/0000-0003-3923-1773
Elizabeth Begier http://orcid.org/0000-0002-1287-5416

Bradford D Gessner http://orcid.org/0000-0002-6216-7194

REFERENCES

1 Gibson GJ, Loddenkemper R, Lundbäck B, *et al*. Respiratory health and disease in Europe: the new European lung white book. *Eur Respir J* 2013;42:559–63.
2 Cillóniz C, Polverino E, Ewig S, *et al*. Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. *Chest* 2013;144:999–1007.
3 Torres A, Cillóniz C, Blasi F, *et al*. Burden of pneumococcal community-acquired pneumonia in adults across Europe: a literature review. *Respir Med* 2018;137:6–13.
4 European Lung White Book. Pneumonia. Available: https://www.erswhitebook.org/chapters/acute-lower-respiratory-infections/pneumonia/#:~:text=pneumonia%20(VAP).-,Incidence,000%20cases%20are%20expected%20annually [Accessed 25 Apr 2021].
5 British Lung Foundation. Pneumonia statistics. Available: https://statistics.blf.org.uk/pneumonia [Accessed 25 Apr 2021].
6 Lim W, Lawrence H. National audit report: adult community acquired pneumonia audit 2018-2019. National audit period: 1 December 2018 – 31 January 2019. *British Thoracic Society* 2019.
7 Millett ERC, Quint JK, Smeeth L, *et al*. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. *PLoS One* 2013;8:e75131.
8 Branche AR, Falsey AR. Respiratory syncytial virus infection in older adults: an under-recognized problem. *Drugs Aging* 2015;32:261–9.
9 Falsey AR, Walsh EE. Respiratory syncytial virus infection in elderly adults. *Drugs Aging* 2005;22:577–87.
10 Maughan BC, Asselin N, Carey JL, *et al*. False-Negative chest radiographs in emergency department diagnosis of pneumonia. *R I Med J* 2014;97:20–3.
11 Self WH, Courtney DM, McNaughton CD, *et al*. High discordance of chest X-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. *Am J Emerg Med* 2013;31:401–5.
12 Cillóniz C, Ewig S, Polverino E, *et al*. Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax* 2011;66:340–6.
13 Jain S, Self WH, Wunderink RG, *et al*. Community-Acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015;373:415–27.
14 Mainor AJ, Morden NE, Smith J, *et al*. Icd-10 coding will challenge researchers: caution and collaboration may reduce measurement error and improve comparability over time. *Med Care* 2019;57:e42–6.
15 Burns EM, Rigby E, Mamidanna R, *et al*. Systematic review of discharge coding accuracy. *J Public Health* 2012;34:138–48.
16 Henig O, Kaye KS. Bacterial pneumonia in older adults. *Infect Dis Clin North Am* 2017;31:689–713.
17 Fine MJ, Smith MA, Carson CA, *et al*. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *JAMA* 1996;275:134–41.
18 Campling J, Begier E, Vyse A, *et al*. A novel approach to calculate disease incidence for hospital-based health events in England. *The Lancet* 2021;398:S30.
19 Chalmers J, Campling J, Ellsbury G, *et al*. Community-Acquired pneumonia in the United Kingdom: a call to action. *Pneumonia* 2017;9:15.
20 Shi T, Denouel A, Tietjen AK, *et al*. Global and regional burden of hospital admissions for pneumonia in older adults: a systematic review and meta-analysis. *J Infect Dis* 2020;222:S570–6.
21 Lovering AM, MacGowan AP, Anderson P, *et al*. Epidemiology and resource utilization for patients hospitalized for lower respiratory tract infection. *Clin Microbiol Infect* 2001;7:666–70.
22 Yu O, Nelson JC, Bounds L, *et al*. Classification algorithms to improve the accuracy of identifying patients hospitalized with community-acquired pneumonia using administrative data. *Epidemiol Infect* 2011;139:1296–306.
23 Uijl A, Koudstaal S, Direk K, *et al*. Risk factors for incident heart failure in age- and sex-specific strata: a population-based cohort using linked electronic health records. *Eur J Heart Fail* 2019;21:1197–206.
24 van de Garde EMW, Oosterheert JJ, Bonten M, *et al*. International classification of diseases codes showed modest sensitivity for detecting community-acquired pneumonia. *J Clin Epidemiol* 2007;60:834–8.
25 Pick H, Daniel P, Rodrigo C, *et al*. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013-18. *Thorax* 2020;75:38–49.
26 Elston JWT, Santaniello-Newton A, Meigh JA, *et al*. Increasing incidence of invasive pneumococcal disease and pneumonia despite improved vaccination uptake: surveillance in Hull and East Yorkshire, UK, 2002-2009. *Epidemiol Infect* 2012;140:1252–66.
27 Thorrington D, Andrews N, Stowe J, *et al*. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. *BMC Med* 2018;16:13.

Incidence of community acquired lower respiratory tract disease in Bristol, UK during the COVID-19 pandemic: A prospective cohort study

Catherine Hyams,[a,b] Robert Challen,[c] Elizabeth Begier,[d] Jo Southern,[e] Jade King,[f] Anna Morley,[b] Zsuzsa Szasz-Benczur,[a] Maria Garcia Gonzalez,[a] Jane Kinney,[a] James Campling,[e] Sharon Gray,[g] Jennifer Oliver,[e] Robin Hubler,[g] Srinivas Valluri,[g] Andrew Vyse,[e] John M. McLaughlin,[g] Gillian Ellsbury,[e] Nick A. Maskell,[b] Bradford D. Gessner,[g] Leon Danon,[c] and Adam Finn [a], On behalf of the Avon CAP Research Group*

[a]Bristol Vaccine Centre, Population Health Sciences, University of Bristol, UK
[b]Academic Respiratory Unit, University of Bristol, UK
[c]Engineering Mathematics, University of Bristol, UK
[d]Global Medical Development Scientific and Clinical Affairs, Pfizer Vaccines, Ireland
[e]Vaccines Medical Affairs, Pfizer Ltd, Tadworth KT20 7NS, UK
[f]Clinical Research and Imaging Centre, UHBW NHS Trust, Bristol, UK
[g]Vaccines Medical Development, Scientific and Clinical Affairs, Pfizer Inc, Collegeville, PA, USA

The Lancet Regional Health - Europe 2022;21: 100473
Published online 8 August 2022
https://doi.org/10.1016/j.lanepe.2022.100473

Summary

Background The emergence of COVID-19 and public health measures implemented to reduce SARS-CoV-2 infections have both affected acute lower respiratory tract disease (aLRTD) epidemiology and incidence trends. The severity of COVID-19 and non-SARS-CoV-2 aLRTD during this period have not been compared in detail.

Methods We conducted a prospective cohort study of adults age ≥18 years admitted to either of two acute care hospitals in Bristol, UK, from August 2020 to November 2021. Patients were included if they presented with signs or symptoms of aLRTD (e.g., cough, pleurisy), or a clinical or radiological aLRTD diagnosis.

Findings 12,557 adult aLRTD hospitalisations occurred: 10,087 were associated with infection (pneumonia or non-pneumonic lower respiratory tract infection [NP-LRTI]), 2161 with no infective cause, with 306 providing a minimal surveillance dataset. Confirmed SARS-CoV-2 infection accounted for 32% (3178/10,087) of respiratory infections. Annual incidences of overall, COVID-19, and non- SARS-CoV-2 pneumonia were 714.1, 264.2, and 449.9, and NP-LRTI were 346.2, 43.8, and 302.4 per 100,000 adults, respectively. Weekly incidence trends in COVID-19 aLRTD showed large surges (median 6.5 [IQR 0.7–10.2] admissions per 100,000 adults per week), while other infective aLRTD events were more stable (median 14.3 [IQR 12.8–16.4] admissions per 100,000 adults per week) as were non-infective aLRTD events (median 4.4 [IQR 3.5–5.5] admissions per 100,000 adults per week).

Interpretation While COVID-19 disease was a large component of total aLRTD during this pandemic period, non-SARS-CoV-2 infection still caused the majority of respiratory infection hospitalisations. COVID-19 disease showed significant temporal fluctuations in frequency, which were less apparent in non-SARS-CoV-2 infection. Despite public health interventions to reduce respiratory infection, disease incidence remains high.

Funding AvonCAP is an investigator-led project funded under a collaborative agreement by Pfizer.

Keywords: Pneumonia; Lower respiratory tract infection; Cardiac failure; COVID-19; SARS-CoV-2

Abbreviations: aLRTD, acute lower respiratory tract disease; COVID-19, Coronavirus disease 2019; CAP, community acquired pneumonia; COPD, chronic obstructive pulmonary disease; NP-LRTI, non-pneumonic lower respiratory tract infection; HF, heart failure; CRDE, chronic respiratory disease exacerbation

*Corresponding author at: Bristol Vaccine Centre, University of Bristol, Level 6, UHB Education and Research Centre, Upper Maudlin Street, Bristol BS2 8AE, United Kingdom.
E-mail address: adam.finn@bristol.ac.uk (A. Finn).

Research in context

Evidence before this study

Acute respiratory infection remains a leading worldwide cause of morbidity and mortality, with estimates of disease varying by population. The most recent prospective data from the UK were obtained before the emergence of SARS-CoV-2, estimating annual incidences of hospitalised community acquired pneumonia (CAP) for persons aged 65–74, 75–84, and ≥85 years of 1.6–3.1, 3.9–5.16, 5.1–15.2 per 1000, respectively. SARS-CoV-2 has changed the epidemiology of respiratory infection and, whilst there are extensive epidemiological data detailing hospitalisations of patients with COVID-19, there are few data describing either the total burden of acute lower respiratory tract disease (aLRTD) or respiratory infection due to other pathogens during the pandemic period. Some data suggest non-pharmaceutical measures implemented to reduce SARS-CoV-2 infection may also have reduced the burden of non-SARS-CoV-2 respiratory disease.

Added value of this study

We provide the first prospectively obtained description of total aLRTD in hospitalised adults covering the end of the first wave of the Wuhan strain, through subsequent waves of the Alpha and Delta variants and pre-dates the Omicron variant emergence. COVID-19 accounted for 32% of respiratory infections and COVID-19 disease was more severe than non-SARS-CoV-2 respiratory infection in persons aged >65 years. Further, while COVID-19 disease formed a large component of aLRTD during the pandemic, non-SARS-CoV-2 accounted for the majority of aLRTD hospitalisations. We therefore demonstrate that the burden of non-SARS-CoV-2 infection remained substantial, greater than SARS-CoV-2 in hospitalised adults, and was significantly higher than that previously estimated in the UK, even before the emergence of SARS-CoV-2.

Implications of all the available evidence

These results, highlight the importance of non-SARS-CoV-2 infection in contributing to the burden of aLRTD throughout the pandemic. In the context of an aging population with increasing comorbid disease, demonstrate that aLRTD remains an important public health concern and accounts for significant healthcare resources. Despite implementation of public health measures, both vaccination and non-pharmaceutical interventions, aLRTD incidence remained high and the incidence of non-COVID-19 disease may yet increase further. It is therefore essential that appropriate healthcare planning and resource allocation is undertaken to care for patients with aLRTD, in addition to implementation of public health measures to reduce respiratory disease burden and improve patient outcomes.

Introduction

Respiratory infection is a leading cause of mortality and morbidity worldwide, with substantially higher disease in older and immunocompromised individuals. Data from the UK are relatively sparse. A population-based electronic database study conducted during 1997–2011 reported an average annual respiratory infection incidence of 123/1000 among UK adults aged ≥65 years, over half of whom were hospitalised, and a much lower incidence of pneumonia of 8.0/1000.[1] More recently, a prospective observational cohort study conducted in Nottingham from 2013 to 2018 reported annual incidences of hospitalised community-acquired pneumonia (CAP) for persons aged 65–74, 75–84, and ≥85 years of 1.6–3.1, 3.9–5.16, 5.1–15.2 per 1000, respectively. Previous studies have used either radiological or microbiological diagnosis to define disease[2,3] or retrospective collection of clinical-coding data[1,4,5] to estimate incidence: both methods may have resulted in under-ascertainment of disease and its burden. Studies relying on typical signs and symptoms of respiratory infection may exclude elderly patients, who often present atypically and yet have the highest disease incidence.[6] Furthermore, acute lower respiratory tract disease (aLRTD) also includes chronic respiratory disease exacerbation (CRDE) and heart failure (HF), which may co-exist with pneumonia and non-pneumonic lower respiratory tract infection (NP-LRTI). To provide appropriate healthcare resources and determine the effectiveness of public health interventions, including vaccinations against respiratory pathogens, it is essential that accurate data describing aLRTD disease phenotypes and incidences are generated and made available.

To address limitations of previous studies, the AvonCAP study prospectively and comprehensively captures data on all adults hospitalised with aLRTD within a defined geographical area. By ensuring all hospitalisations at study hospitals are screened for aLRTD using broad criteria, including patients presenting with atypical clinical features and those without a confirmed radiological or microbiological diagnosis, the study aims to capture aLRTD disease in its entirety. By conducting individual case assessment, hospital-acquired infection is excluded, and disease is accurately typed into subgroups including pneumonia, NP-LRTI, CRDE and HF.

As AvonCAP was preparing to start collecting data, the epidemiology of acute lower respiratory tract infection was changed in 2020–2021 by the COVID-19 pandemic, with large waves of admissions caused by the original strain of SARS-CoV-2 and successive variants, as well as changes in the incidence of many other respiratory infections resulting from the public health measures introduced to limit the pandemic. The emergence of COVID-19 resulted in unprecedented demand on

healthcare resources and the UK, like many countries, implemented social distancing measures and a series of national lockdowns to reduce infections and hospitalisations.[7] These measures probably also reduced transmission of other respiratory pathogens,[8,9] and consequently may have affected respiratory infection hospitalisation rates. Recent studies suggest that both asthma and chronic obstructive pulmonary disease (COPD) related hospitalisations decreased following the emergence of COVID-19.[10-12] Other factors may affect aLRTD admission rates among adults including clinician practice (including admission thresholds), and patient treatment preferences, which may have changed during the pandemic. The impact of these factors, in addition to the emergence of COVID-19, on total respiratory disease burden is unclear.

Our primary objective for the current analysis was to determine accurate incidences of aLRTD, aLRTI, and pneumonia, stratified by patient age during the pandemic period. We also stratified by SARS-CoV-2 status to determine the contribution of COVID-19 to disease incidence, to establish non- SARS-CoV-2 aLRTD incidences, and whether fluctuations were observed in the context of periods of mandatory non-pharmaceutical interventions. Lastly, we sought to assess disease severity for COVID-19 LRTI, non-COVID-19 LRTI, and non-infective LRTD.

Methods

Ethics and permission

This is a prospective observational cohort study of adults admitted to two large university hospitals in Bristol, UK. The study was approved by the Health Research Authority Research Ethics Committee East of England, Essex, reference 20/EE/0157, ISRCTN: 17354061.

Informed consent was obtained from cognisant patients, and declarations for participation from consultees for individuals lacking capacity. If it was not practicable to approach individuals for consent, data were included using approval from the Clinical Advisory Group under section 251 of the 2006 NHS Act.

Study design

All adults (≥18 years) admitted to both participating hospitals from 1st August 2020 to 15th November 2021, encompassing all acute secondary care in Bristol during this period, were screened for study inclusion. This time-period was selected as it encompassed the end of first wave of Wuhan, and subsequent Alpha and Delta waves in the UK, and pre-dates the emergence of the ongoing Omicron SARS-CoV-2 variant wave.[13] Patients were screened for signs and symptoms of respiratory disease, and those with ≥ signs or a confirmed clinical or radiological aLRTD diagnosis, and disease ≤28 days in duration were included. Signs and symptoms included: documented fever (≥38°C) or hypothermia (<35.5°C); cough; increased sputum volume or discolouration; pleurisy; dyspnoea; tachypnoea; examination findings (e.g. crepitations); or, radiological changes suggestive of aLRTD in the opinion of a consultant radiologist, such as consolidation or pulmonary oedema. Patients were excluded from the study if their symptoms developed within ≥48 h of admission or within 7 days of discharge from hospital. Additionally, patients whose signs/symptoms were not attributable to aLRTD were excluded (e.g. fever and tachypnoea attributable to urosepsis). Eligible cases of aLRTD disease were then classified in to the different aLRTD subgroups (pneumonia, NP-LRTI, heart failure, chronic respiratory disease exacerbation) following the case definitions provided below and in Supplementary Table 1.

Demographic and clinical data were collected from electronic and paper patient records and recorded on an electronic clinical record form using REDCap.[14] We collected data on co-morbidities at admission, determining Charlson co-morbidity index (CCI; with published estimates of 10-year survival)[15] and Rockwood clinical frailty score (with a score of 5–9 indicating frailty).[16] Vaccination records for each participant were obtained from linked general practitioner (GP) records.

Case definitions

SARS-CoV-2 infection was defined as PCR positive test, using the established assay (Hologic Panther TMA) conducted by UKHSA diagnostic laboratories (RCP Path 2021). Patients with no molecular SARS-CoV-2 test (3.3% eligible cases) were assigned to a non-SARS-CoV-2 group. Pneumonia was classified as acute respiratory illness with confirmed radiological changes compatible with infection or when the treating clinician confirmed the diagnosis. In keeping with NICE and BTS guidelines, patients assigned a diagnosis of pneumonia were counted as a pneumonia case even if a CXR was not taken or no infiltrate was seen, due to false-negative radiology occurring, for example when consolidation is behind thoracic structures or severe dehydration. NP-LRTI was defined as the presence of signs and symptoms of acute lower respiratory tract infection in the absence of infective radiological change and a clinical diagnosis of pneumonia. Under these case definitions, any patients with aLRTD signs or symptoms due to non-infectious aLRTD would have been assigned appropriately to CRDE or heart failure groups. Full case definitions can be found in Supplementary Data 1.

Outcomes

All-cause mortality for patients within 30-days of hospital admission was determined, in addition to hospital length of stay (days), requirement in intensive care or

high-dependency unit (ICU/HDU) and length of ICU/HDU admission (days). The population of Bristol was estimated as previously described, including full methodology.[17] Briefly, hospital admission data were linked to aggregated GP practice patient registration data within NHS Bristol, North Somerset and South Gloucestershire Clinical Commissioning Group for 2017–2019. The proportion of GP practices' aLRTD hospitalisations that occurred at a specific study hospital was multiplied by their patient registration count for six age groups to obtain the practices' contribution to that hospital's denominator (e.g., if 50% of GP practice admissions were at a specific study hospital among persons 50–64 years, the practice contributed half of their patients 50–64 years to the denominator). Incidence was calculated per 100,000 people from 1st August 2020 to 31st July 2021, using the case numbers (numerator) divided by population (denominator).

Statistical analysis

The primary goal of this analysis was to report incidence rates by disease categories and SARS-CoV-2 positivity as these data are critical to inform public health decision making. All data were descriptively summarised. Comparisons between ages and CCI of SARS-CoV-2 PCR positive and SARS-CoV-2 PCR negative cases were made using Kolmogorov–Smirnov tests. Non-parametric comparisons were used as age and CCI were shown to be not normally distributed by visual inspection and Shapiro tests. Categorical data are presented as counts and percentages, and continuous data as either means with standard deviations (SD) or medians with interquartile (IQR) ranges. Overlapping subsets of the data pertaining to the clinical presentation of SARS-CoV-2 PCR positive and SARS-CoV-2 PCR negative cases are described using a stratified UpSet diagram.[18] All persons aged ≥18 years contributed to the denominator for incidence estimate calculations and are reported per 100,000 persons for the aLRTD groups of the whole cohort. Analyses performed are stratified by SARS-CoV-2 PCR status, and by clinical presentation in various combinations of pneumonia, NP-LRTI, HF, and CRDE: pneumonia and NP-LRTI are mutually exclusive, but other groups could overlap. Patients that present with pneumonia or NP-LRTI are additionally grouped as having aLRTD of infectious origin (respiratory infection), whereas presentations involving only HF or CRDE are classified as having non-infectious aLRTD, comparisons of which are included in the supplementary material. Patients who were eligible for the study due to aLRTD but declined consent are analysed as undifferentiated aLRTD, also in the supplementary material. Estimates of admission incidence from weekly admission counts are made using maximum likelihood, assuming the observed case count is a Poisson distributed quantity with a time varying rate. The rate is estimated using a locally fitted order 2 polynomial using a logarithmic link function using the methods of Loader et al.[19] All analyses were conducted using R.[20]

Role of the funding source

The study funder had no role in data collection, but collaborated in study design, data interpretation and analysis and writing this manuscript. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 1,35,014 hospitalisations, 12,557 admissions were attributable to aLRTD, of which 12,248 (98%) consented to participate in the study. 3178 (26%) aLRTD admissions were SARS-CoV-2 infection-related, 6909 (55%) were due to infection with no evidence of SARS-CoV-2, and the remaining 2161 (17%) had no association with infection documented (Supplementary Figure 1). Overall, patients were elderly (median age 73y, IQR 25.7), with 8% residing in a care facility (Table 1). The cohort was broadly comorbid (59.8% patients had a Charlson Co-morbidity Index (CCI) ≥4) and frail (31.4%). 51.5% of patients were current or former smokers (Table 1, Supplementary Data 2).

The proportion of aLRTD hospitalisations due either to SARS-CoV-2 or other infections was high (10,087/12,557, 81%). SARS-CoV-2 infection usually presented as pneumonia alone (Figure 1C) and pneumonia was more frequent in patients with SARS-CoV-2 infection than those infection cases who had negative SARS-CoV-2 PCR results (Figure 1B). Similarly, SARS-CoV-2 infection more commonly presented as pneumonia than as NP-LRTI in patients who had associated HF, CRDE or both as a component of their aLRTD. The SARS-CoV-2 patients presenting with pneumonia alone were, on average, 11.3 years younger than SARS-CoV-2 PCR negative pneumonia patients ($P<0.001$) (Figure 1E, D), and had fewer comorbidities as indicated by an average CCI score lower by 1.42 ($P<0.001$) (Figure 1F, G). Similar significant, although smaller, differences were observed in patients with pneumonia combined with other factors such as HF and CRDE.

COVID-19 morbidity and mortality were considerable: median hospital length of stay was 5 days (IQR 9.0) and increased with patient age; 427/12,557 (3%) patients required ICU/HDU care with median ICU/HDU admission duration of 7 days (IQR 11.0), and 1146/12,557 (9%) patients died within 30 days of admission (Table 2, Supplementary Table 3). Mortality increased with patient age: hospitalised patients aged 18–34 years had a 30-day mortality rate <1.0% compared to 17.3% in those ≥85 years. Among all aLRTD subgroups, elderly patients with COVID-19 had a higher 30-day mortality than those with non-SARS-CoV-2 aLRTD (Table 2), e.g. 23.5% [20.2–27.1%] mortality for confirmed SARS-CoV-2 versus 11.8% [10.4

		All included aLRTD		Non-infective		Confirmed SARS-CoV-2				No evidence SARS-CoV-2			
		Total		Total		Pneumonia		NP-LRTI		Pneumonia		NP-LRTI	
Characteristic	**Group**	**N**	**value**	**N**	**value**	**N**	**value**	**N**	**value**	**N**	**value**	**N**	**value**
Age	(mean ± SD)	12248	68·4 ± 18·6	2161	72 ± 17·3	2633	62·1 ± 17·9	545	64 ± 20·9	4028	72·9 ± 16·7	2881	66·2 ± 20
Age category	18-34	845	6·9%	111	5·1%	207	7·9%	68	12·5%	156	3·9%	303	10·5%
	35-49	1312	10·7%	134	6·2%	483	18·3%	79	14·5%	280	7·0%	336	11·7%
	50-64	2345	19·1%	358	16·6%	742	28·2%	93	17·1%	655	16·3%	497	17·3%
	65-74	2376	19·4%	457	21·1%	476	18·1%	95	17·4%	777	19·3%	571	19·8%
	75-84	2933	23·9%	564	26·1%	448	17·0%	123	22·6%	1121	27·8%	677	23·5%
	85+	2437	19·9%	537	24·8%	277	10·5%	87	16·0%	1039	25·8%	497	17·3%
Age eligible for PneumoVax	18-64	4502	36·8%	603	27·9%	1432	54·4%	240	44·0%	1091	27·1%	1136	39·4%
	65+	7746	63·2%	1558	72·1%	1201	45·6%	305	56·0%	2937	72·9%	1745	60·6%
Gender	Male	6206	50·7%	1011	46·8%	1498	56·9%	250	45·9%	2127	52·8%	1320	45·8%
	Female	6042	49·3%	1150	53·2%	1135	43·1%	295	54·1%	1901	47·2%	1561	54·2%
Ethnicity	White British	9379	76·6%	1659	76·8%	1711	65·0%	390	71·6%	3276	81·3%	2343	81·3%
	White other	341	2·8%	51	2·4%	136	5·2%	20	3·7%	74	1·8%	60	2·1%
	Mixed origin	99	0·8%	15	0·7%	27	1·0%	4	0·7%	27	0·7%	26	0·9%
	Black	237	1·9%	28	1·3%	99	3·8%	14	2·6%	54	1·3%	42	1·5%
	Asian	339	2·8%	29	1·3%	175	6·6%	23	4·2%	59	1·5%	53	1·8%
	Other race	108	0·9%	19	0·9%	49	1·9%	6	1·1%	17	0·4%	17	0·6%
	Unknown	1735	14·2%	360	16·7%	433	16·4%	88	16·1%	516	12·8%	338	11·7%
	<missing>	10	0·1%	—	—	3	0·1%	—	—	5	0·1%	2	0·1%
Care home resident	no	9970	81·4%	1881	87·0%	2172	82·5%	398	73·0%	3243	80·5%	2276	79·0%
	yes	1032	8·4%	112	5·2%	163	6·2%	45	8·3%	472	11·7%	240	8·3%
	<missing>	1246	10·2%	168	7·8%	298	11·3%	102	18·7%	313	7·8%	365	12·7%
Smoker	Unknown	1311	10·7%	219	10·1%	295	11·2%	61	11·2%	442	11·0%	294	10·2%
	Non-smoker	4470	36·5%	690	31·9%	1227	46·6%	245	45·0%	1319	32·7%	989	34·3%
	Current	1217	9·9%	196	9·1%	127	4·8%	24	4·4%	442	11·0%	428	14·9%
	Ex-smoker	5247	42·8%	1055	48·8%	984	37·4%	215	39·4%	1823	45·3%	1170	40·6%
	<missing>	3	0·0%	1	0·0%	—	—	—	—	2	0·0%	—	—
Covid vaccination	Unknown	586	4·8%	91	4·2%	159	6·0%	36	6·6%	172	4·3%	128	4·4%
	Not received	6265	51·2%	893	41·3%	1817	69·0%	278	51·0%	1928	47·9%	1349	46·8%
	Received	5396	44·1%	1177	54·5%	657	25·0%	231	42·4%	1927	47·8%	1404	48·7%
	<missing>	1	0·0%	—	—	—	—	—	—	1	0·0%	—	—
CCI	(mean ± SD)	12237	3·97 ± 2·59	2161	4·53 ± 2·5	2628	3 ± 2·5	543	3·27 ± 2·5	4026	4·52 ± 2·48	2879	3·8 ± 2·61
CURB65 score	0-Very Low	3429	28·0%	456	21·1%	1077	40·9%	200	36·7%	784	19·5%	912	31·7%

Table 1 *(Continued)*

		All included aLRTD		Non-infective		Confirmed SARS-CoV-2				No evidence SARS-CoV-2			
		Total		Total		Pneumonia		NP-LRTI		Pneumonia		NP-LRTI	
Characteristic	**Group**	**N**	**value**	**N**	**value**	**N**	**value**	**N**	**value**	**N**	**value**	**N**	**value**
	1-Low	5534	45·2%	1096	50·7%	1043	39·6%	217	39·8%	1885	46·8%	1293	44·9%
	2-Moderate	2677	21·9%	502	23·2%	423	16·1%	108	19·8%	1081	26·8%	563	19·5%
	3-Severe	539	4·4%	97	4·5%	75	2·8%	17	3·1%	247	6·1%	103	3·6%
	4-Severe	58	0·5%	10	0·5%	10	0·4%	1	0·2%	29	0·7%	8	0·3%
	<missing>	11	0·1%	—	—	5	0·2%	2	0·4%	2	0·0%	2	0·1%
COPD	no	9121	74·5%	1574	72·8%	2314	87·9%	451	82·8%	2853	70·8%	1929	67·0%
	yes	3127	25·5%	587	27·2%	319	12·1%	94	17·2%	1175	29·2%	952	33·0%
Asthma	no	10283	84·0%	1816	84·0%	2209	83·9%	468	85·9%	3494	86·7%	2296	79·7%
	yes	1965	16·0%	345	16·0%	424	16·1%	77	14·1%	534	13·3%	585	20·3%
Bronchiectasis	no	11802	96·4%	2107	97·5%	2592	98·4%	534	98·0%	3829	95·1%	2740	95·1%
	yes	446	3·6%	54	2·5%	41	1·6%	11	2·0%	199	4·9%	141	4·9%
IHD	no	10570	86·3%	1780	82·4%	2358	89·6%	484	88·8%	3451	85·7%	2497	86·7%
	yes	1678	13·7%	381	17·6%	275	10·4%	61	11·2%	577	14·3%	384	13·3%
Hypertension	no	10484	85·6%	1829	84·6%	2324	88·3%	487	89·4%	3369	83·6%	2475	85·9%
	yes	1764	14·4%	332	15·4%	309	11·7%	58	10·6%	659	16·4%	406	14·1%
On immunosuppression	no	11159	91·1%	1948	90·1%	2489	94·5%	511	93·8%	3643	90·4%	2568	89·1%
	yes	1088	8·9%	213	9·9%	144	5·5%	34	6·2%	384	9·5%	313	10·9%
	<missing>	1	0·0%	—	—	—	—	—	—	1	0·0%	—	—
Diabetes type	None	9569	78·1%	1620	75·0%	2015	76·5%	441	80·9%	3197	79·4%	2296	79·7%
	Type 1	150	1·2%	24	1·1%	30	1·1%	10	1·8%	44	1·1%	42	1·5%
	Type 2	2528	20·6%	517	23·9%	588	22·3%	94	17·2%	786	19·5%	543	18·8%
	<missing>	1	0·0%	—	—	—	—	—	—	1	0·0%	—	—
CKD	None	9385	76·6%	1511	69·9%	2155	81·8%	447	82·0%	2993	74·3%	2279	79·1%
	Mild (CKD 1-3)	2384	19·5%	527	24·4%	405	15·4%	86	15·8%	867	21·5%	499	17·3%
	Moderate or Severe CKD (CKD 4+)	478	3·9%	123	5·7%	73	2·8%	12	2·2%	167	4·1%	103	3·6%
	<missing>	1	0·0%	—	—	—	—	—	—	1	0·0%	—	—

***Table 1*: Patient characteristics of adults hospitalised with aLRTD.**

Patient demographics are shown for total cohort, patients with non-infective aLRTD, confirmed SARS-CoV-2 infection (total, pneumonia, NP-LRTI) and infection without SARS-CoV-2 (total, pneumonia, NP-LRTI). Full demographics are presented in Supplementary Table 1.

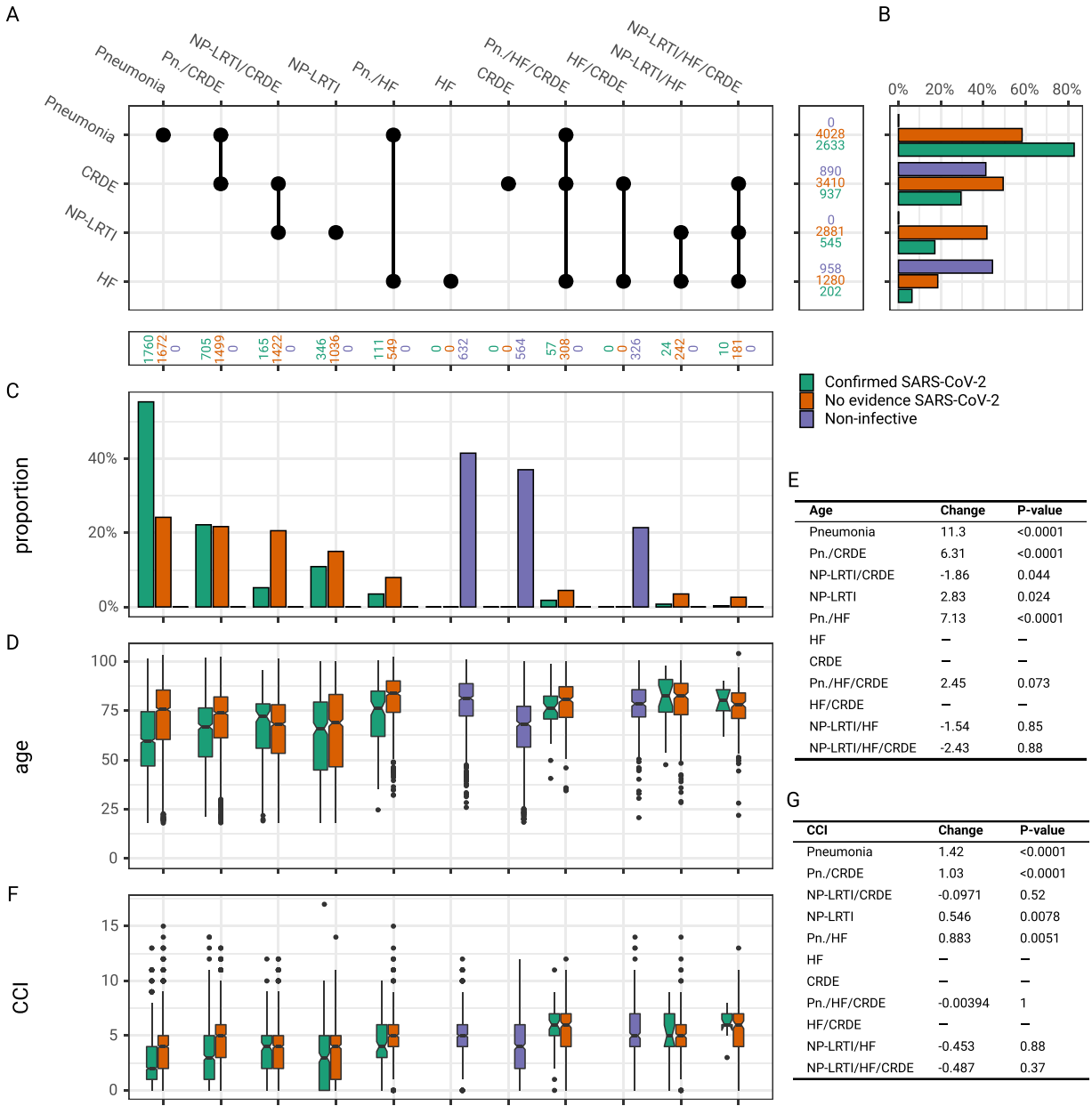
[a]LRTD, acute lower respiratory tract disease; CCI, Charlson comorbidity index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; NP-LRTI, non-pneumonic lower respiratory tract infection; PCR, polymerase chain reaction; SD, standard deviation.

[†]In the UK, patients aged ≥65 years are eligible for Pneumococcal vaccination (PneumoVax®, PPV23) once, and annual influenza vaccine.

*Hypertension was only included if causing other cardiac complications.

**Chronic kidney disease (CKD) was classified as mild if stage 1-3; moderate/severe if stage 4-5, end-stage renal failure or there was dialysis dependence.

Additional data are located in Supplementary Table 2.



E

Age	Change	P-value
Pneumonia	11.3	<0.0001
Pn./CRDE	6.31	<0.0001
NP-LRTI/CRDE	-1.86	0.044
NP-LRTI	2.83	0.024
Pn./HF	7.13	<0.0001
HF	–	–
CRDE	–	–
Pn./HF/CRDE	2.45	0.073
HF/CRDE	–	–
NP-LRTI/HF	-1.54	0.85
NP-LRTI/HF/CRDE	-2.43	0.88

G

CCI	Change	P-value
Pneumonia	1.42	<0.0001
Pn./CRDE	1.03	<0.0001
NP-LRTI/CRDE	-0.0971	0.52
NP-LRTI	0.546	0.0078
Pn./HF	0.883	0.0051
HF	–	–
CRDE	–	–
Pn./HF/CRDE	-0.00394	1
HF/CRDE	–	–
NP-LRTI/HF	-0.453	0.88
NP-LRTI/HF/CRDE	-0.487	0.37

Figure 1. Summary of aLRTD incidence between 1st August 2020 and 15th November 2021. Panel A shows categories with combinations of having a single aLRTD phenotype (e.g., pneumonia alone), two phenotypes (e.g., pneumonia and CRDE), or three phenotypes (e.g., pneumonia, CRDE and HF); the numbers along the axes show counts for each phenotype, both singly and in combination, stratified by SARS-CoV-2 PCR status. 640/6661 (9.6%) cases of pneumonia were not radiologically confirmed [423/6661 (6.4%) with no consolidation/infiltrate and 217/6661 (3.3%) with no radiology performed]. Panel B shows the proportion of cases with each single aLRTD phenotype out of the total number of cases in each strata. Where cases have multiple phenotypes they are counted once for each phenotype, hence proportions do not add up to 100%. Panel C shows the proportion of cases with every combination of aLRTD phenotypes, stratified by SARS-CoV-2 status. In this panel each case is counted only once and hence proportions do add up to 100%. Panels E and F show boxplot summaries of the distributions for key patient indicators in each phenotype combination category: E) age, and F) CCI score, stratified by SARS-CoV-2 PCR status. Panels D and G indicate differences in these key indicators between SARS-CoV-2 PCR positive and negative patients for D) age, and G) CCI score, in tabular form. *P*-values are the result of 2 sided Kolmogorov−Smirnov significance tests. CCI, Charlson Comorbidity Index; CRDE, chronic respiratory disease exacerbation; HF, heart failure; NP-LRTI, non-pneumonic lower respiratory tract infection; Pn, pneumonia.

	All included aLRTD	Non-infective	Confirmed SARS-CoV-2		No evidence SARS-CoV-2	
Length of stay	Total Median [IQR]	Total Median [IQR]	Pneumonia Median [IQR]	NP-LRTI Median [IQR]	Pneumonia Median [IQR]	NP-LRTI Median [IQR]
Overall	5 [2 – 11]	4 [1 – 10]	7 [3 – 13]	4 [1 – 9]	6 [2 – 12]	3 [1 – 7]
18-34	2 [0 – 4]	1 [0 – 3]	3 [1 – 6]	2 [1 – 4]	2 [1 – 5·2]	1 [0 – 3]
35-49	3 [1 – 7]	1 [0 – 4]	5 [3 – 9]	1 [0·5 – 5]	3 [1 – 7·2]	1 [0 – 4]
50-64	5 [2 – 9]	3 [1 – 8]	7 [4 – 12]	3 [1 – 7]	5 [2 – 10]	2 [1 – 5]
65-74	5 [2 – 11]	4 [2 – 9]	9 [4 – 16]	4 [2 – 8·8]	6 [2 – 12]	3 [1 – 8]
75-84	6 [2 – 13]	5 [2 – 12]	9 [4 – 15]	6 [3 – 14]	6 [3 – 14]	4 [1 – 9]
85+	7 [3 – 15]	6 [2 – 13]	10 [4 – 20]	10 [4 – 20]	7 [3 – 15]	5 [2 – 12]
18-64	3 [1 – 8]	2 [1 – 6]	6 [3 – 10]	2 [1 – 5]	4 [1 – 9]	2 [0 – 4]
65+	6 [2 – 13]	5 [2 – 11]	9 [4 – 17]	6 [2 – 14]	6 [3 – 14]	4 [2 – 9]
ICU admission	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Overall	427/12248 (3·5%)	27/2161 (1·2%)	251/2633 (9·5%)	7/545 (1·3%)	119/4028 (3·0%)	23/2881 (0·8%)
18-34	29/845 (3·4%)	1/111 (0·9%)	11/207 (5·3%)	1/68 (1·5%)	13/156 (8·3%)	3/303 (1·0%)
35-49	74/1312 (5·6%)	0/134 (0·0%)	57/483 (11·8%)	0/79 (0·0%)	14/280 (5·0%)	3/336 (0·9%)
50-64	151/2345 (6·4%)	7/358 (2·0%)	101/742 (13·6%)	3/93 (3·2%)	31/655 (4·7%)	9/497 (1·8%)
65-74	110/2376 (4·6%)	13/457 (2·8%)	60/476 (12·6%)	1/95 (1·1%)	34/777 (4·4%)	2/571 (0·4%)
75-84	57/2933 (1·9%)	5/564 (0·9%)	22/448 (4·9%)	2/123 (1·6%)	22/1121 (2·0%)	6/677 (0·9%)
85+	6/2437 (0·2%)	1/537 (0·2%)	0/277 (0·0%)	0/87 (0·0%)	5/1039 (0·5%)	0/497 (0·0%)
18-64	254/4502 (5·6%)	8/603 (1·3%)	169/1432 (11·8%)	4/240 (1·7%)	58/1091 (5·3%)	15/1136 (1·3%)
65+	173/7746 (2·2%)	19/1558 (1·2%)	82/1201 (6·8%)	3/305 (1·0%)	61/2937 (2·1%)	8/1745 (0·5%)
ICU length of stay	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]	Median [IQR]
Overall	7 [4 – 15]	5 [3 – 9]	9 [5 – 16]	6 [4·5 – 11]	6 [3 – 12]	3 [1·5 – 5]
18-34	3 [2 – 7]	6 [6 – 6]	4 [2·5 – 11]	1 [1 – 1]	3 [2 – 11]	3 [2 – 3·5]
35-49	7·5 [4 – 15]	–	7 [4 – 14]	–	9·5 [4·2 – 15]	3 [2·5 – 3]
50-64	8 [4 – 16]	3 [2 – 4]	9 [5 – 18]	15 [10 – 22]	7 [3·5 – 16]	3 [1 – 5]
65-74	8 [4 – 17]	7 [4 – 28]	10 [6 – 17]	4 [4 – 4]	6 [3 – 13]	7·5 [7·2 – 7·8]
75-84	7 [5 – 12]	5 [5 – 8]	11 [7·2 – 15]	6 [5·5 – 6·5]	6 [4 – 10]	3 [2 – 4·8]
85+	3 [2 – 4]	4 [4 – 4]	–	–	2 [2 – 4]	–
18-64	7 [4 – 15]	3·5 [2 – 4·5]	8 [4 – 16]	10 [4·8 – 18]	7 [3 – 15]	3 [1 – 4·5]
65+	8 [4 – 14]	6 [4 – 14]	10 [6 – 16]	5 [4·5 – 6]	6 [3 – 11]	4·5 [2 – 7·2]
All-cause mortality	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Overall	1146/12248 (9·4%)	124/2161 (5·7%)	339/2633 (12·9%)	32/545 (5·9%)	543/4028 (13·5%)	108/2881 (3·7%)
18-34	3/845 (0·4%)	0/111 (0·0%)	0/207 (0·0%)	0/68 (0·0%)	2/156 (1·3%)	1/303 (0·3%)
35-49	20/1312 (1·5%)	1/134 (0·7%)	11/483 (2·3%)	0/79 (0·0%)	8/280 (2·9%)	0/336 (0·0%)
50-64	93/2345 (4·0%)	11/358 (3·1%)	35/742 (4·7%)	2/93 (2·2%)	38/655 (5·8%)	7/497 (1·4%)
65-74	209/2376 (8·8%)	19/457 (4·2%)	79/476 (16·6%)	4/95 (4·2%)	82/777 (10·6%)	25/571 (4·4%)
75-84	390/2933 (13·3%)	44/564 (7·8%)	121/448 (27·0%)	13/123 (10·6%)	172/1121 (15·3%)	40/677 (5·9%)
85+	431/2437 (17·7%)	49/537 (9·1%)	93/277 (33·6%)	13/87 (14·9%)	241/1039 (23·2%)	35/497 (7·0%)
18-64	116/4502 (2·6%)	12/603 (2·0%)	46/1432 (3·2%)	2/240 (0·8%)	48/1091 (4·4%)	8/1136 (0·7%)
65+	1030/7746 (13·3%)	112/1558 (7·2%)	293/1201 (24·4%)	30/305 (9·8%)	495/2937 (16·9%)	100/1745 (5·7%)

***Table 2*: Outcomes of patients with non-infective aLRTD, proven SARS-CoV-2 aLRTD, and other infective aLRTD.**
*Number of ICU/HDU cases is numerator; patients (n) in corresponding age group is denominator.
**Cases with survival days ≤30 days following hospitalization is numerator; patients (n) in corresponding age group is denominator.
†In the UK, patients aged ≥65 years are eligible for Pneumococcal vaccination (PneumoVax®, PPV23) once and annual influenza vaccine.
aLRTD, acute lower respiratory tract disease; ICU, intensive care unit; IQR, interquartile range; NP-LRTI, non-pneumonic lower respiratory tract infection.
Additional data are located in Supplementary Table 3.

–13.4%] for non-SARS-CoV-2 infective aLRTD in 74–85 age category (Supplementary Table 5; $P<0.001$) . The interquartile ranges for length of hospital admission for non-SARS-CoV-2 infective aLRTD overlapped with those of SARS-CoV-2 infection across all patient age groups (Table 2), however a statistically significant difference in length of stay was observed over all age groups, with confirmed SARS-CoV-2 patients being in hospital longer than non-SARS-CoV-2 infective aLTRD patients. For example, the length of stay in 74–85-year-old patients increased from 5.5 [IQR 2 – 12] with non-SARS-CoV-2 aLRTD to 8 days [IQR 4 –

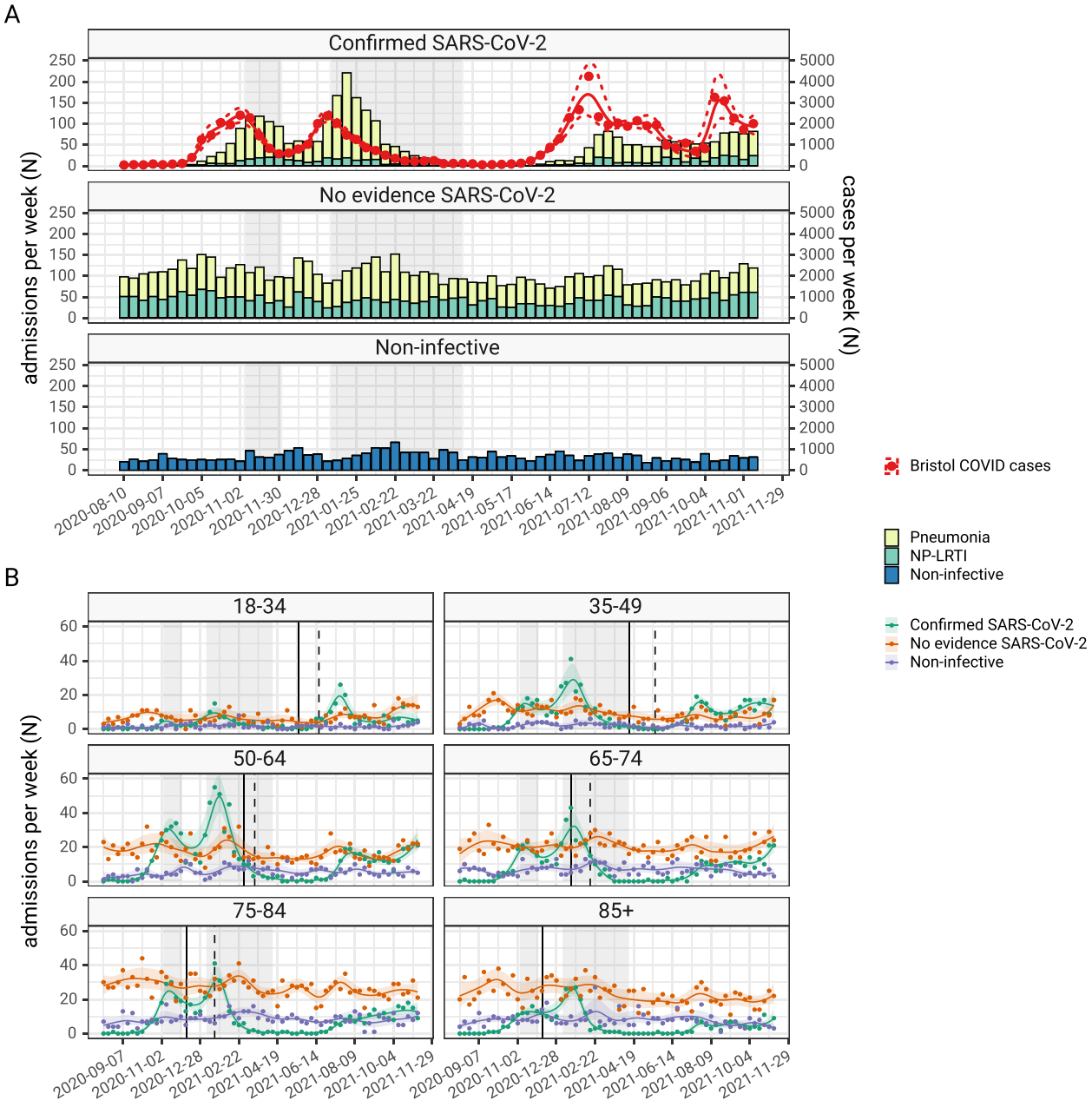
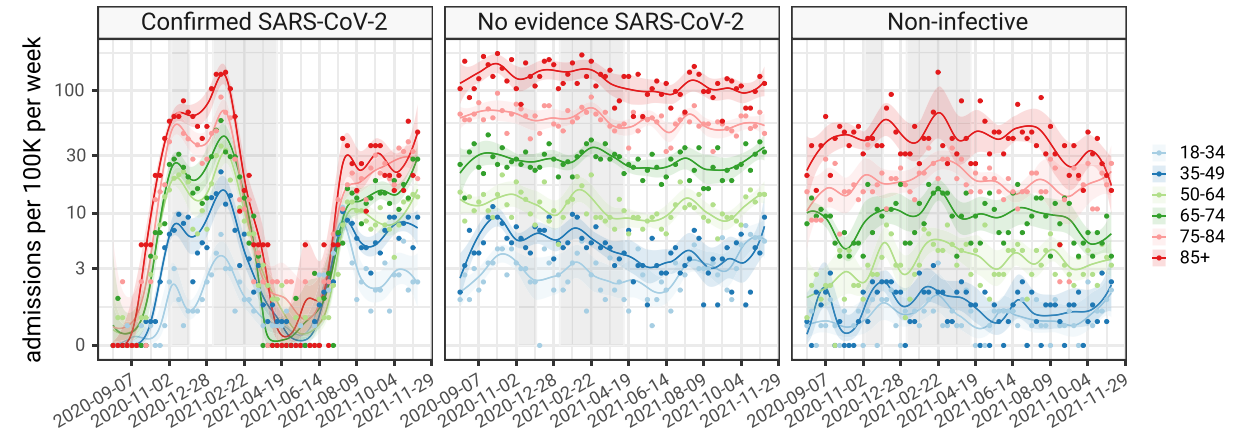


Figure 2. Hospitalisations with aLRTD, by primary clinical presentation (non-infective, SARS-CoV-2 infection and infection with no evidence of SARS-CoV-2) and age group. (A) The upper panel shows the weekly number of hospital admissions associated with positive SARS-CoV-2 PCR results taken at the time of admission, as a bar chart. For comparison the red line shows the weekly number of SARS-CoV-2 cases in the immediate locality of the study sites. In the second panel we show the remaining non-SARS-CoV-2 infection aLRTD admissions, stratified by primary clinical presentation, and in the 3rd panel non-infective aLRTD admissions (including primary presentations with heart failure and/or exacerbation of chronic respiratory disease). Pneumonia cases are shown in yellow, and NP-LRTI in green. (B) Points represent weekly counts of aLRTD admissions. Estimates of the underlying incidence rates are shown as continuous lines, assuming the admissions follow a Poisson distribution with a time varying rate, using a locally fitted polynomial in time, using a maximum likelihood method. The earliest date that the COVID-19 vaccination program opened to any people in each age group is marked on each panel with a solid vertical line, and the date by which all people in the age group were eligible for vaccination by a dashed vertical line (where different) (Supplementary Table 5). Grey bars in the background indicate periods when non-pharmaceutical interventions were in place to control the spread of SARS-CoV-2. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

A



B

Age	population	All included aLRTD Total per 100K	Non-infective Total per 100K	Confirmed SARS-CoV-2 Pneumonia per 100K	Confirmed SARS-CoV-2 NP-LRTI per 100K	No evidence SARS-CoV-2 Pneumonia per 100K	No evidence SARS-CoV-2 NP-LRTI per 100K
18-34	231342	239·9	36·3	57·9	16·9	45·0	83·9
35-49	184269	523·7	57·5	176·9	20·1	127·5	141·6
50-64	152380	1142·5	176·5	357·7	28·9	339·9	239·5
65-74	74245	2397·5	491·6	436·4	76·8	808·1	584·6
75-84	45989	4855·5	952·4	695·8	160·9	1930·9	1115·5
85+	19229	10016·1	2272·6	1144·1	306·8	4358·0	1934·6
18-64	567991	574·1	80·8	176·9	21·1	150·9	144·4
65+	139463	4258·5	889·1	619·5	136·2	1667·8	945·8
Overall	707454	1300·4	240·2	264·2	43·8	449·9	302·4

Figure 3. Incidence per 100,000 population per week by age group for non-infective aLRTD, PCR positive SARS-CoV-2 aLRTD, and infection with no evidence of SARS-CoV-2. (A) As in Figure 3 estimates of the underlying incidence rates are shown as continuous lines. Grey bars in the background indicate periods when non-pharmaceutical interventions were in place to control the spread of SARS-CoV-2. (B) aLRTD cumulative hospital cases (per 100,000 people) in adults in Bristol, UK over 12 months (August 2020–July 2021). Additional data are located in Supplementary Table 4. aLRTD, acute lower respiratory tract disease; NP-LRTI, non-pneumonic lower respiratory tract infection; PCR, polymerase chain reaction.

15] with confirmed SARS-CoV-2 (Supplementary Table 4; $P<0.01$).

There were considerable fluctuations in hospital admissions due to COVID-19 during the course of the study, which followed community COVID-19 disease incidence and aligned with different waves of lockdown in the UK (Figure 2A). The age distributions of patients admitted during the two waves of COVID-19 reported here were different. Admissions earlier in the study (Alpha wave) were predominantly older adults whereas later time periods (Delta wave) saw increasing numbers of younger adults hospitalised. Hospitalisations due to COVID-19 increased across all age groups during the COVID-19 waves until lockdown measures were introduced, following which they decreased (Figure 2B). Following the vaccine programme roll out in late 2020, COVID-19 hospitalisations in prioritised older age groups began to fall. The number of COVID-19 hospitalisations among younger adults fluctuated during the study period, with COVID-19 overall being the predominant cause of hospital treatment for respiratory disease among these patients (aged 18–35) (Figure 2B, 5).

In contrast, rates of admission with non-SARS-CoV-2 respiratory infection (pneumonia or NP-LRTI) showed much less variation during the study period (Figure 2A) and did not follow community COVID-19 incidence. Hospitalisation rates increased with patient age (Figure 2B), with disease predominantly affecting those over 65 years old. No clear associations between periods of implementation of lockdown measures and hospitalisation rates due to non-SARS-CoV-2 pneumonia and NP-LRTI were observed.

While COVID-19 contributed substantially to respiratory infection incidence during this pandemic period, non-COVID-19 cases contributed more to both pneumonia and NP-LRTI disease: annual incidences of the latter among adults aged ≥18 years were 450 and 302 per 100,000 population, respectively (Figure 3, Supplementary Table 4). Non-SARS-CoV-2 disease was the most

common cause of NP-LRTI in all age groups. Although non-SARS-CoV-2 pneumonia incidence was lower than COVID-19 among adults aged <65 years, among those aged 65–74, 75–84, and 85+ years it was 1.9, 2.8, and 3.8-fold higher, respectively. Weekly incidence per 100,000 population was higher for SARS-CoV-2 PCR negative aLRTD in hospitalised patients than for SARS-CoV-2 PCR positive disease across all age groups (Figure 3). Incidence rose with patient age and the incidence of SARS-CoV-2 infection in hospitalised patients increased as new variants emerged and fell, following non-pharmaceutical interventions.

Discussion

This two-site single-centre study conducted within a defined geographical area describes aLRTD during part of the COVID-19 pandemic, covering the end of the first wave of the Wuhan strain, through subsequent waves of the Alpha and Delta variants and pre-dates the emergence of the Omicron variant. By conducting comprehensive surveillance of all aLRTD, we determined the incidence and severity of both COVID-19 and non-SARS-CoV-2 disease in individuals needing hospital care in this population.

Notwithstanding the emergence of COVID-19, 56% (6909/12,248) of aLRTD was due to non-SARS-CoV-2 infection, despite public health interventions to reduce hospitalisations and NHS-burden whilst vaccination was rolled out, and the burden of hospitalised non-SARS-CoV-2 infection was greater than that of SARS-CoV-2 infection. Moreover, annual aLRTD, NP-LRTI, and pneumonia incidences were comparable to a pre-pandemic retrospective analysis undertaken at one of the study hospitals (pneumonia and NP-LRTI 591 and 739/100,000 versus 714 and 346/100,000 people found in this study, Supplementary Table 4).[21] Not only did non- SARS-CoV-2 pneumonia and NP-LRTI not substantially decline despite public health interventions to reduce hospitalisations and NHS burden, but compared to previous pre-pandemic UK studies[3-5,21,22] we report higher pneumonia incidences. For example, compared to a recent study from Nottingham reporting data from 2013 to 2018, non-COVID-19 pneumonia incidences from our study were 2.6 to 4.9-fold, 3.4 to 5.0-fold, and 2.9 to 8.6-fold higher for, respectively, persons age 65–74y, 75–84y, and ≥85y. The precise reasons for these discordant results is beyond the scope of our current evaluation but may relate to the methodology we employed to conduct comprehensive, prospective, population-based surveillance to identify every adult hospitalised with aLRTD. Further, the difference in estimated incidence may be explained in part by the inclusion criteria of this study, which allowed for patients with atypical symptoms and those with a clinical diagnosis of pneumonia.

Non-SARS-CoV-2 respiratory infection did not show much seasonal variation and did not follow trends in COVID-19-related admissions. Variation in the treatment preference, admission threshold,[23,24] or other confounders may have affected non-SARS-CoV-2 disease admissions more than COVID-19 admissions, and the incidence estimate calculated here may therefore be lower for non-SARS-CoV-2 aLRTD than if non-pharmaceutical interventions had not been implemented, as supported by previous studies showing that respiratory pathogen infections dramatically decreased during the pandemic.[9,25,26] Consequently, incidences for non-SARS-CoV-2 aLRTD disease may increase in the future as non-pharmaceutical interventions for reducing SARS-CoV-2 transmission are relaxed. Ongoing accurate and systematic surveillance will be needed to determine how disease incidences and risk groups change as the current pandemic evolves, and these data will be available in coming periods during this ongoing study. Even if incidence estimates calculated in this study change during future years, they provide valuable insight into the burden of acute respiratory infection and how effective public health measures, including increased use of vaccination in adults, might be used to reduce disease.

Overall, 26% (3178/12,248) of adults hospitalised with aLRTD had SARS-CoV-2 infection during this period of the pandemic, highlighting the significant impact of COVID-19 on total respiratory infection burden and healthcare resource usage. There was considerable variability in rates of hospital admission due to COVID-19 throughout the study and successive national lockdowns appear to have been effective in reducing these hospital admissions. Following the COVID-19 vaccination programme implementation, COVID-19 admissions declined, with no further surges observed as successive patient age groups were included (Figure 2). Although SARS-CoV-2 infection disproportionately affected older adults, a substantial number of younger patients required both hospitalisation and ICU treatment due to COVID-19, reinforcing the observation that this disease is not always mild in young individuals.[27]

Aligning with previous literature, aLRTD disease of all causes disproportionately affected older people, highlighting an incidence in people over 85 years old (10,016.1 cases per 100,000 per year) which was 42-times higher than that seen in people aged 18–34 (239.9 cases per 100,000 per year) (Figure 3). 20% of patients aged ≥65 years admitted with pneumonia died within 30 days (Supplementary Table 3), higher than that observed nationally for hip fracture (5.36%)[28] and myocardial infarction (15.6%),[29] and comparable to stroke (21.0% female, 19.8% males).[30] The non-SARS-CoV-2 pneumonia mortality of 13.5% in this study (Table 2) was comparable to that reported in a pre-pandemic national audit, which showed overall 30-day pneumonia mortality of 14.6%, but did not specify

mortality by age group and excluded NP-LRTI.[31] We found the 30-day mortality from non-SARS-CoV-2 NP-LRTI was lower in all patient age groups than that for patients with pneumonia, HF and CRDE. We also documented among persons age ≥65 years that disease severity was worse with SARS-CoV-2 versus non-SARS-CoV-2 respiratory infection. Whether the acute severity of SARS-CoV-2 infection translates into greater long-term morbidity, such as increased risk of subsequent aLRTD events, will be a subject for future evaluations from AvonCAP. Interestingly, 29.5% of patients admitted with pneumonia had a CURB-65 score of 0, also in line with findings from a pre-pandemic national audit, which was unable to elucidate reasons for the decrease in severity scores on admission.[31] Future evaluation from AvonCAP may provide some reason for the increasing rate of hospitalisation with low severity score respiratory infection.

This study has many strengths. Firstly, it was undertaken prospectively and by screening hospital admissions for signs/symptoms of aLRTD. Prospective, comprehensive case ascertainment within a defined geographical area remains the gold standard epidemiological methodology for estimating disease incidence. This study did not rely on ICD-10 coding or solely on national data-linkage and were able to assess each case individually and gather complete data. Secondly, we were able to include adults hospitalised with aLRTD through a consultee if patients lacked capacity and by using specific authorisation to collected data without consent, thus ensuring full ascertainment of cases. This ensured that patients lacking capacity, such as those severely ill or with advanced dementia or other frailty, were not under-represented in this study. This study was conducted at two hospitals which provide all acute secondary medical care for the same city and time-period to undertake comprehensive surveillance in a defined geographical area with a well-defined local population, and therefore provide an accurate estimate of disease incidence and severity. The study hospitals are within a few miles of each other, with overlapping patient catchments and clinicians rotate between the two healthcare facilities. Whilst there are some differences in the demographics of patients admitted to each hospital (Supplementary Data 5 and 6), we anticipate that any independent effect of hospital site on patient outcome (beyond differences associated with patient demographics) is likely to be small. The medical records were linked with community records to obtain detailed and accurate data for each study participant. Finally, we calculated incidence using a denominator derived from GP records and hospital utilization data, providing increased accuracy compared to population estimates based on assumptions using local geographic boundaries and their corresponding census data.[17]

There are also some limitations to this study, which was conducted over 15-months overall and 12-months for incidence determination, and is therefore only able to report incidence within this time period. The incidence calculations and disease severity determinations were measured during the COVID-19 pandemic and were undoubtedly affected by the emergence of this new respiratory pathogen, public health interventions such as social distancing and vaccination and other factors that may be difficult to quantify. It is difficult to determine whether access to healthcare changed during this period; for example, clinicians or patients may have preferred treatment at home, which may have affected severity assessment and admission rates, and therefore our observed incidence. However, the study hospitals reduced elective admissions and undertook measures to avoid exceeding maximum capacity; therefore, capacity is unlikely to have limited acute admissions and thus affected our incidence calculation. Whilst we assessed aLRTD at both acute care NHS hospitals in Bristol, we cannot be sure that it is generalisable to other cities and regions. Furthermore, this cohort is predominantly (75.9%) White-British and therefore aLRTD disease in cohorts with different ethnicity may vary from that reported here. 309 (2%) patients actively declined to participate in the study, so we can be certain they had aLRTD but could not ascertain any additional data. Previous exposure to SARS-CoV-2 could not be determined for study participants, and this may have impacted on our findings, although the magnitude of any such effect is unclear. Additionally, to prioritise SARS-CoV-2 testing, study hospitals undertook limited microbiological testing for other respiratory pathogens and, using standard-of-care results, we are unable to comment on the microbial aetiology of non-SARS-CoV-2 respiratory infection. Whilst we describe differences in patients admitted with COVID-19, non-SARS-CoV-2 infection and non-infective aLRTD, further analyses, including adjusting for potential confounders, is needed to fully explore the reasons for these differences.

These results, in the context of an ageing population with increasing comorbid disease, coupled with the emergence of COVID-19 and potentially future novel respiratory pathogens, demonstrate the significant burden of acute respiratory disease and infection, and demonstrate the importance of consideration of the impact of aLRTD on healthcare systems. Our findings demonstrate the significant contribution of non-SARS-CoV-2 respiratory infection to total aLRTD burden in hospitalisations, and highlight the importance of not overlooking the multiple causes of respiratory infection during the COVID-19 pandemic. Providing appropriate care for adults with aLRTD and its disease subsets will require appropriate healthcare planning and resource allocation. Appropriate public health measures to reduce respiratory disease burden as well as improve patient outcomes should be implemented. In the short-term social distancing and face masks, which are effective in reducing pathogen transmission and aLRTD incidence[8], should be considered.

Vaccination to prevent adult respiratory disease is likely to be one of the most effective available short-term and long-term strategy to reduce this substantial public health burden, alongside reductions in risk factors such as cigarette smoking and ambient air pollution.

Contributors

CH, RC, EB, JS, JO, AV, BG, LD and AF generated the research questions and analysis plans. The AvonCAP research team, CH, JK, AM, MGG, ZSB, and JK were involved in data collection. CH, MGG, ZSB and AF verified the data. CH, RC, EB, JS JC, AV, SV, SG, RH, JMM, GE, NM, LD and AF undertook data analysis. All authors contributed to preparation of the manuscript and its revisions before publication. BG and AF provided oversight of the research.

Data sharing statement

The data used in this study are sensitive and cannot be made publicly available without breaching patient confidentiality rules. Therefore, individual participant data and a data dictionary are not available to other researchers.

Declaration of interests

CH is Principal Investigator of the Avon CAP study which is an investigator-led University of Bristol study funded by Pfizer and has previously received support from the NIHR in an Academic Clinical Fellowship. JO is a Co-Investigator on the Avon CAP Study. LD is further supported by UKRI through the JUNIPER consortium (grant number MR/V038613/1), MRC (grant number MC/PC/19067), EPSRC (EP/V051555/1 and The Alan Turing Institute, grant EP/N510129/1). AF is a member of the Joint Committee on Vaccination and Immunization (JCVI) and chair of the World Health Organization European Technical Advisory Group of Experts on Immunization (ETAGE) committee. In addition to receiving funding from Pfizer as Chief Investigator of this study, he leads another project investigating transmission of respiratory bacteria in families jointly funded by Pfizer and the Gates Foundation and is an investigator in trials of COVID19 vaccines including ChAdOx1nCOV-19, Janssen and Valneva vaccines. EB, JS, JC, SG, RH, SV, AV, JM, GE, and BG are employees of Pfizer and own Pfizer stock. The other authors have no relevant conflicts of interest to declare. The AvonCAP study is a University of Bristol sponsored study which is investigator-led, and funded under a collaborative agreement by Pfizer Inc.

Acknowledgements

We thank colleagues at the University of Bristol for their support with this study, including Rachel Davies, Paul Savage, Emma Foose, Susan Christie, Mark Mummé, Alison Horne, Mai Baquedano, and Adam Taylor. We would like to thank Stewart Robinson, David Clint and Henry Stuart and their teams for the support provided during this study. We would also like to acknowledge the research teams at North Bristol and University Hospitals of Bristol and Weston NHS Trusts for making this study possible, including Helen Lewis-White, Rebecca Smith, Rajeka Lazarus, Jane Blazeby, Diana Benton, and David Wynick. Finally, we would like to thank Aman Kaur-Singh and Kevin Sweetland for their support with this study.

The Avon CAP Research Group

Amelia Langdon, Anabella Turner, Anya Mattocks, Bethany Osborne, Charli Grimes, Claire Mitchell, David Adegbite, Emma Bridgeman, Emma Scott, Fiona Perkins, Francesca Bayley, Gabriella Ruffino, Gabriella Valentine, Grace Tilzey, Johanna Kellett Wright, Julia Brzezinska, Julie Cloake, Katarina Milutinovic, Kate Helliker, Katie Maughan, Kazminder Fox, Konstantina Minou, Lana Ward, Leah Fleming, Leigh Morrison, Lily Smart, Louise Wright, Lucy Grimwood, Maddalena Bellavia, Madeleine Clout, Marianne Vasquez, Milo Jeenes-Flanagan, Natalie Chang, Niall Grace, Nicola Manning, Oliver Griffiths, Pip Croxford, Peter Sequenza, Rajeka Lazarus, Rhian Walters, Robin Marlow, Robyn Heath, Rupert Antico, Sandi Nammuni Arachchge, Seevakumar Suppiah, Taslima Mona, Tawassal Riaz, Vicki Mackay, Zandile Maseko, Zoe Taylor, Zsolt Friedrich.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2022.100473.

References

1 Millett ER, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. *PLoS One*. 2013;8(9):e75131.
2 Chalmers J, Campling J, Ellsbury G, Hawkey PM, Madhava H, Slack M. Community-acquired pneumonia in the United Kingdom: a call to action. *Pneumonia*. 2017;9(1):15.
3 Pick H, Daniel P, Rodrigo C, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. *Thorax*. 2020;75(1):38–49.
4 Elston JW, Santaniello-Newton A, Meigh JA, et al. Increasing incidence of invasive pneumococcal disease and pneumonia despite improved vaccination uptake: surveillance in Hull and East Yorkshire, UK, 2002–2009. *Epidemiol Infect*. 2012;140(7):1252–1266.
5 Thorrington D, Andrews N, Stowe J, Miller E, van Hoek AJ. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. *BMC Med*. 2018;16(1):13.
6 Henig O, Kaye KS. Bacterial pneumonia in older adults. *Infect Dis Clin N Am*. 2017;31(4):689–713.
7 Coronavirus: A history of 'Lockdown laws' in England. House of commons library briefing report, 22 December 2021. https://commonslibrary.parliament.uk/research-briefings/cbp-9068/ Brown J, Kirk-Wade, E.

8 Jefferson T, Del Mar CB, Dooley L, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database Syst Rev*. 2011;2011(7):CD006207. https://doi.org/10.1002/14651858.CD006207.pub4.

9 Choi YH, Miller E. Impact of COVID-19 social distancing measures on future incidence of invasive pneumococcal disease in England and Wales: a mathematical modelling study. *BMJ Open*. 2021;11(9):e045380.

10 Alqahtani JS, Oyelade T, Aldhahir AM, et al. Reduction in hospitalised COPD exacerbations during COVID-19: a systematic review and meta-analysis. *PLoS One*. 2021;16(8):e0255659.

11 Davies GA, Alsallakh MA, Sivakumaran S, et al. Impact of COVID-19 lockdown on emergency asthma admissions and deaths: national interrupted time series analyses for Scotland and Wales. *Thorax*. 2021;76(9):867–873.

12 Kyriakopoulos C, Gogali A, Exarchos K, et al. Reduction in hospitalizations for respiratory diseases during the first COVID-19 wave in Greece. *Respir; Int Rev Thoracic Dis*. 2021;100(7):588–593.

13 UKHSA. SARS-CoV-2 variants of concern and variants under investigation in England, Technical briefing 36. 2022.

14 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377–381.

15 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383.

16 Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *Can Med Assoc J*. 2005;173(5):489.

17 Campling J, Begier E, Vyse A, et al. A novel approach to calculate disease incidence for hospital-based health events in England. *Lancet*. 2021;398:S30.

18 Lex A, Gehlenborg N, Strobelt H, Vuillemot R. UpSet: visualization of intersecting sets. *IEEE Trans Vis Comput Graph (InfoVis)*. 2014;20:1983–1992.

19 Loader C. *Local Regression and Likelihood*. New York: Springer-Verlag; 1999.

20 R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2021.

21 Hyams C, Begier E, Gonzalez MG, et al. Incidence of acute lower respiratory tract disease hospitalisations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective methodology. *BMJ Open*. 2022;12(6):e057464. https://doi.org/10.1136/bmjopen-2021-057464.

22 Trotter CL, Stuart JM, George R, Miller E. Increasing hospital admissions for pneumonia, England. *Emerg Infect Dis*. 2008;14(5):727–733.

23 Sykes DL, Faruqi S, Holdsworth L, Crooks MG. Impact of COVID-19 on COPD and asthma admissions, and the pandemic from a patient's perspective. *ERJ Open Res*. 2021;7(1):00822–02020.

24 Taskforce for Lung Health BLF. Over a third of people with lung conditions felt pressure to avoid or delay seeking treatment during lockdown. 2021. https://www.blf.org.uk/taskforce/press-release/over-a-third-of-people-with-lung-conditions-felt-pressure-to-avoid-or-delay-seeking-treatment. Accessed 28 September 2020.

25 Public Health England. Six major respiratory viruses reported from PHE and NHS laboratories (SGSS) in England and Wales between week 1, 2011 and week 29, 2021. 9 August 2021 2021. https://www.gov.uk/government/publications/respiratory-virus-circulation-england-and-wales/six-major-respiratory-viruses-reported-from-phe-and-nhs-laboratories-sgss-in-england-and-wales-between-week-1-2009-and-week-23-2019. Accessed 16 February 2022.

26 Amin-Chowdhury Z, Aiano F, Mensah A, et al. Impact of the coronavirus disease 2019 (COVID-19) pandemic on invasive pneumococcal disease and risk of pneumococcal coinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): prospective national cohort study, England. *Clin Infect Dis*. 2020;72(5):e65–e75.

27 ICNARC. ICNARC report on COVID-19 in critical care: England, Wales and Northern Ireland: ICNARC, 2022.

28 Tsang C, Boulton C, Burgon V, Johansen A, Wakeman R, Cromwell DA. Predicting 30-day mortality after hip fracture surgery: evaluation of the national hip fracture database case-mix adjustment model. *Bone Joint Res*. 2017;6(9):550–556.

29 Information Services Devision Scotland. Scottish heart disease statistics year ending 31 March 2018. 2019.

30 Seminog OO, Scarborough P, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute stroke in England: linked national database study of 7,95,869 adults. *BMJ (Clin Res ed)*. 2019;365:l1778.

31 Lim WSLH. National audit report: adult community acquired pneumonia audit 2018—2019. 2019. https://www.brit-thoracic.org.uk/quality-improvement/clinical-audit/national-adult-community-acquired-pneumonia-audit-201819/. Accessed 21 July 2020.

Campling et al. Pneumonia (2019) 11:4
https://doi.org/10.1186/s41479-019-0063-z

Pneumonia

RESEARCH Open Access

The impact of certain underlying comorbidities on the risk of developing hospitalised pneumonia in England

J. Campling[1*], D. Jones[1], J. D. Chalmers[2], Q. Jiang[3], A. Vyse[1], H. Madhava[1], G. Ellsbury[1] and M. Slack[4]

Abstract

Background: UK specific data on the risk of developing hospitalised CAP for patients with underlying comorbidities is lacking. This study compared the likelihood of hospitalised all-cause community acquired pneumonia (CAP) in patients with certain high-risk comorbidities and a comparator group with no known risk factors for pneumococcal disease.

Methods: This retrospective cohort study interrogated data in the Hospital Episodes Statistics (HES) dataset between financial years 2012/13 and 2016/17. In total 3,078,623 patients in England (aged ≥18 years) were linked to their hospitalisation records. This included 2,950,910 individuals with defined risk groups and a comparator group of 127,713 people who had undergone tooth extraction with none of the risk group diagnoses. Risk groups studied were chronic respiratory disease (CRD), chronic heart disease (CHD), chronic liver disease (CLD), chronic kidney disease (CKD), diabetes (DM) and post bone marrow transplant (BMT). The patients were tracked forward from year 0 (2012/13) to Year 3 (2016/17) and all diagnoses of hospitalised CAP were recorded. A Logistic regression model compared odds of developing hospitalised CAP for patients in risk groups compared to healthy controls. The model was simultaneously adjusted for age, sex, strategic heath authority (SHA), index of multiple deprivation (IMD), ethnicity, and comorbidity. To account for differing comorbidity profiles between populations the Charlson Comorbidity Index (CCI) was applied. The model estimated odds ratios (OR) with 95% confidence intervals of developing hospitalised CAP for each specified clinical risk group.

Results: Patients within all the risk groups studied were more likely to develop hospitalised CAP than patients in the comparator group. The odds ratios varied between underlying conditions ranging from 1.18 (95% CI 1.13, 1.23) for those with DM to 5.48 (95% CI 5.28, 5.70) for those with CRD.

Conclusions: Individuals with any of 6 pre-defined underlying comorbidities are at significantly increased risk of developing hospitalised CAP compared to those with no underlying comorbid condition. Since the likelihood varies by risk group it should be possible to target patients with each of these underlying comorbidities with the most appropriate preventative measures, including immunisations.

Keywords: Pneumonia, Pneumococcus, Hospitalised community acquired pneumonia (CAP), Risk groups, Linkage, Hospital episodes statistics (HES) database, Big data, Prevention

* Correspondence: james.campling@pfizer.com
[1]Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS, UK
Full list of author information is available at the end of the article

Background

Community acquired pneumonia (CAP) remains a major cause of morbidity and mortality, resulting in a major impact on the UK and European healthcare systems. Across Europe, annual inpatient care for pneumonia accounts for approximately €5.7 billion of healthcare expenditure [1]. Pneumonia is responsible for more hospital admissions and bed days than any other respiratory disease in the UK [2]. Hospitalised CAP carries a mortality rate of 5–19% rising to more than 30% for those admitted to intensive care [3–5] and results in 29,000 deaths per annum. *Streptococcus pneumoniae* is the most commonly identified cause of CAP; however, the microbiological aetiology is not identified in approximately 50% of cases [6, 7].

There have been a number of studies that have shown patients with a range of underlying comorbidities are at an increased risk of developing IPD [8–12]. Van Hoek et al. used national surveillance data for IPD in England and Wales in combination with Hospital Episodes Statistics (HES) data to demonstrate an increased odds ratio (OR) for hospitalisation and death from IPD in patients with specific risk groups in the UK [12]. The risk varied by underlying comorbidity; with the most important risk factors predicting IPD being chronic liver disease, immunosuppression and chronic respiratory disease. There have to date been a limited number of studies that have examined the risk of developing CAP using healthcare utilisation database records [13, 14]. However, UK specific evidence on the risk of developing hospitalised CAP in key risk groups is lacking. This retrospective pilot study compared the likelihood of being hospitalised with all-cause community acquired pneumonia in patients with pre-specified high-risk comorbidities and a comparator group with no known risk factors for CAP.

Methods

This retrospective cohort study interrogated data contained within the Hospital Episodes Statistics (HES) dataset between financial years 2012/13 and 2015/16 [15]. 2012/13 will now be referred to as Year 0, 2013/14 as Year 1, 2014/15 as Year 2 and 2015/16 as Year 3. HES is a data warehouse containing clinical information of all admissions, bed days, length of admission, outpatient appointments, attendances at Accident and Emergency Departments at National Health Service (NHS) hospitals in England, discharge diagnoses and hospital death. It is a record-based system covering all NHS hospitals in England. These data are collected to allow hospitals to be paid for the care that they deliver. The primary diagnosis and other clinical conditions are specified using the tenth revision of the International Classification of Diseases version 10 (ICD-10) [16].

Data was extracted from the HES database for adults ≥18 yrs. based on the ICD-10 codes identified. Each patient had his or her own unique NHS identifier which ensured patients were not double counted within the analysis. NHS Digital applies a strict statistical disclosure control in accordance with the HES protocol, to all published HES data. This suppresses small numbers to prevent people identifying themselves and others, to ensure patient confidentiality is maintained.

Patients were grouped together according to their underlying comorbidity (i.e. clinical risk group) which was identified by the relevant ICD-10 codes (Table 3 in Appendix). We chose not to stratify by severity of underlying comorbidity in order to simplify the analysis. They were: Bone Marrow Transplant (BMT), Chronic Respiratory Disease, Diabetes Mellitus (DM), Chronic Kidney Disease (CKD), Chronic Heart Disease (CHD) and Chronic Liver Disease (CLD). These risk factors were selected because they are included in the conditions for which pneumococcal polysaccharide vaccine (PPV23) is recommended by the UK Department of Health [17].

The clinical risk group populations were defined by the following criteria:

Inclusion criteria for clinical risk group populations: 1) A risk group diagnosis (Table 3 in Appendix- ICD-10 CODE) in Year 0. 2) ≥ 18 years at point of risk group diagnosis. 3) No diagnosis of pneumonia (Table 3 in Appendix- ICD-10 CODE) in either the primary or secondary position in Year 0. 4) No evidence of in-patient death in Year 0. **Exclusion criteria for clinical risk group populations:** No pneumonia diagnosis in either the primary or secondary position in Year 0 or Year 1, but with pneumonia diagnosis in Year 2 and/or Year 3. **Identification of Pneumonia cases:** A pneumonia diagnosis (Table 3 in Appendix- ICD-10 CODE) in either the primary or secondary position in Year 1-Year 3. **Exclusion of Pneumonia cases:** Healthcare Acquired Pneumonia (HCAP) excluded if the pneumonia diagnosis was made within 48 h of the admission) [18].

Each risk cohort was determined independently; therefore, some patients may have been grouped into multiple risk groups. To ensure that all pneumonia presenting in secondary care was captured

we included records where the relevant ICD-10 codes were in either the primary or secondary position. The ICD-10 codes chosen to identify risk groups reflected the codes used by van Hoek et al. in their study of the impact of underlying comorbidities on invasive pneumococcal disease [12]. The comparator group consisted of healthy individuals admitted to hospital for a tooth extraction procedure in Year 0 (Table 3 in Appendix for list of ICD-10 codes). After careful consideration, we chose individuals admitted to hospital for a tooth extraction, who did not have any of the following underlying comorbidities (leukaemia, multiple myeloma, BMT, HIV, sickle cell, asplenic / splenic dysfunction, CHD, CKD, CLD, DM, malignant disease treatment on immunosuppressive chemotherapy or radiotherapy), as the comparator group. This elective procedure was selected as it was not believed to be directly associated with any underlying comorbidity associated with developing hospitalised CAP, but we excluded any individuals within the comparator group who had any comorbid condition associated with an increased risk of developing pneumococcal infection, as defined by the UK Department of Health, for the duration of the study (Year 0 – Year 3) [17].

Individuals were identified and tracked forward from Year 0 to Year 3 and all diagnoses of hospitalised CAP were recorded. All eligible individuals within the clinical risk groups and the comparator group were followed from Year 0 to Year 3. All episodes of hospitalised CAP that occurred from Year 1 to Year 3 in clinical risk group patients and the comparator group were identified. Information on the patients' age, gender, ethnicity, index of multiple deprivation (IMD) and strategic health authority (SHA) was also extracted.

The study design is shown in Fig. 1.

Statistical analysis

The outcome of interest was the diagnosis of hospitalised CAP. The odds ratio was calculated as odds of developing hospitalised CAP during Year 1 to Year 3 for patients within a risk group comparing to that for a "healthy" comparator cohort with no risk group diagnosis as defined by the UK Department of Health [17].

A logistic regression model was used to compare the odds of developing hospitalised CAP within a risk group vs within the 'healthy' comparator group. The model was simultaneously adjusted with the age, sex, strategic heath authority (SHA), index of multiple deprivation (IMD), ethnicity of patients, and comorbidity. To account for the fact that the comorbidity profile may have differed between the populations the Charlson Comorbidity Index (CCI) was used [19]. The model estimated odds ratios (OR) with 95% confidence intervals of developing hospitalised CAP for each specified clinical risk group.

Results

A total of 3,078,623 patient records were distributed into 6 risk groups and the comparator group. The number of patients within each group is shown in Table 1.

The observed number of cases of hospitalised CAP in each clinical risk group and the comparator group who developed hospitalised CAP between Years 0 to Year 3 is shown in Table 1. The largest clinical risk groups identified in the HES database were approximately 1.3 million patients with CHD; the smallest was approximately 6000 BMT patients.

The odds ratio of developing hospitalised CAP for patients in the clinical risk groups compared with hospitalised CAP cases in the patients with no

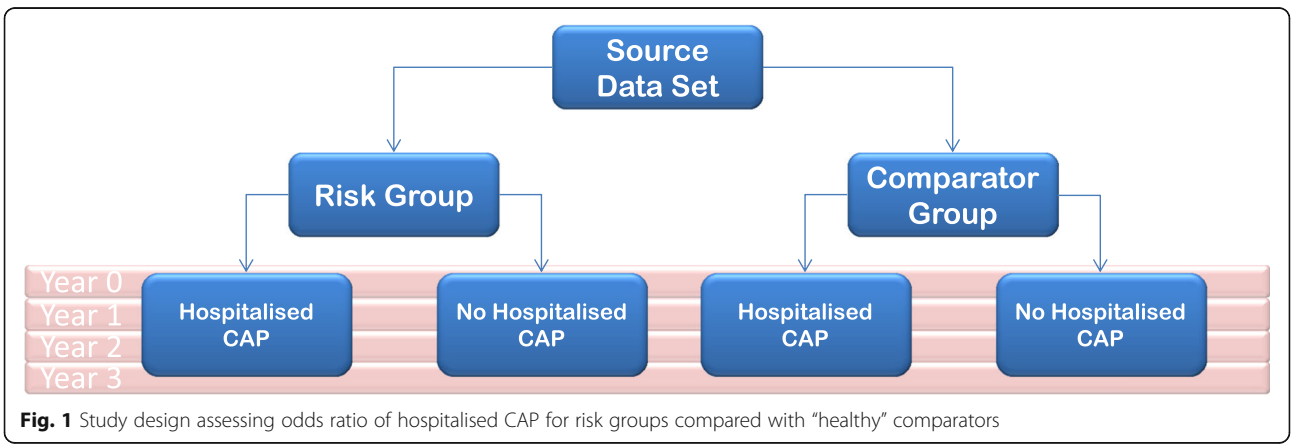


Fig. 1 Study design assessing odds ratio of hospitalised CAP for risk groups compared with "healthy" comparators

Table 1 Number of patients in risk groups and comparators who did or did not develop CAP

Group	Number of Patients Who Developed CAP (%)	Number of Patients Who Did Not Develop CAP (%)	Total Number of Patients
CHD	277,179 (21.5%)	1,104,335 (78.5%)	1,291,531
CKD	89,144 (26.3%)	249,384 (73.7%)	338,541
CLD	19,516 (19.9%)	78,798 (80.1%)	98,317
CRD	156,899 (33.7%)	309,071 (66.3%)	465,983
DM	12,072 (16.1%)	629,303 (83.7%)	750,379
BMT	1627 (26.4%)	4532 (73.6%)	6159
Comparator Group (tooth extraction)	3203 (2.5%)	124,510 (97.5%)	127,713
Total	–	–	3,078,623

underlying condition are shown in Table 2 and Fig. 2. These odds ratios (as approximations of relative risk) are reported as are unadjusted and adjusted for potential confounders. For example, the approximate unadjusted risk of CAP in the CHD risk group compared to the comparator group is more than 10-fold higher (OR = 10.62; 95% CI: 10.25–11.00). After adjusting for both gender and CCI the OR falls to 3.15. The final model included all factors simultaneously (age, gender, CCI, ethnicity, SHA and IMD), patients with CHD are about twice as likely to present with CAP compared to those without CHD (OR = 1.87; 95% CI = 1.80–1.94). For all risk groups studied the factor having the largest influence on the odds of developing CAP was the CCI.

Patients within all the risk groups studied were more likely to develop hospitalised CAP than patients in the comparator group. Patients with CRD had the highest likelihood, with an odds ratio of 5.48 (95% CI 5.28–5.70). The group studied with the second highest odds of developing CAP was post BMT (odds ratio 5.46 (95% CI 5.05–5.90). These two clinical risk groups had a five-fold increase of developing hospitalised CAP compared to the comparator group. Patients with DM had the lowest odds of developing hospitalised CAP (odds ratio 1.18 (95% CI 1.13–1.23).

Discussion

This is the first study utilising HES to quantify the increased likelihood of hospitalised CAP among adults with certain underlying comorbidities in England. HES is an administrative database that contains information on all episodes of hospital care in England. Patient notes are reviewed by coding clerks who assign the ICD-10 codes based on diagnoses recorded by the attending physician. Variabilit in both the quality and consistency of the coding is considered likely. HES also does not contain information on laboratory testing so aetiology of each case cannot be

Table 2 Odds Ratio of risk of hospitalised CAP compared to comparators for each potential confounder

Confounder	Comparison of CAP vs Non CAP (Odds Ratios)											
	CHD		CKD		CLD		CRD		DM		BMT	
	OR[a]	(95% CI)	OR[a]	(95% CI)	OR[a]	(95% CI)	OR[a]	(95% CI)	OR[a]	(95% CI)	OR[a]	(95% CI)
Overall (unadjusted)	10.62	(10.25, 11.00	13.90	(13.41, 14.40)	9.63	(9.27, 10.01)	19.73	(19.04, 20.45)	7.48	(7.22, 7.75)	13.96	(13.06, 14.92)
Gender: Male	13.57	(12.88, 14.28)	14.85	(14.09, 15.65)	10.98	(10.37, 11.61)	22.62	(21.47, 23.82)	8.38	(7.95, 8.82)	14.92	(13.43, 16.56)
Female	8.28	(7.89, 8.69)	12.81	(12.20, 13.46)	8.23	(7.81, 8.67)	16.92	(16.11, 17.77)	6.53	(6.22, 6.86)	12.35	(11.32, 13.47)
Adjusting for Gender	10.44	(10.08; 10.82)	13.74	(13.25, 14.24)	9.40	(9.05, 9.77)	19.39	(18.71, 20.09)	7.34	(7.08,7.61)	13.34	(12.47, 14.26)
Adjusting for Gender & CCI	3.15	(3.03, 3.27)	2.18	(2.09, 2.27)	2.71	(2.60, 2.82)	5.55	(5.34, 5.76)	1.02	(0.98, 1.07)	3.39	(3.16, 3.64)
Adjusting for Gender, Age & CCI	1.86	(1.79, 1.93)	2.20	(2.12, 2.30)	3.56	(3.41, 3.72)	5.61	(5.40, 5.83)	1.18	(1.14, 1.23)	5.37	(4.99, 5.79)
Adjusting for Gender, Age, CCI, Ethnicicty, STHA & IMD	1.87	(1.80, 1.94)	2.22	(2.13, 2.32)	3.43	(3.29, 3.59)	5.48	5.28, 5.70)	1.18	(1.13, 1.23)	5.46	(5.05, 5.90)

[a]Odds of CAP in the risk group compared to the comparator

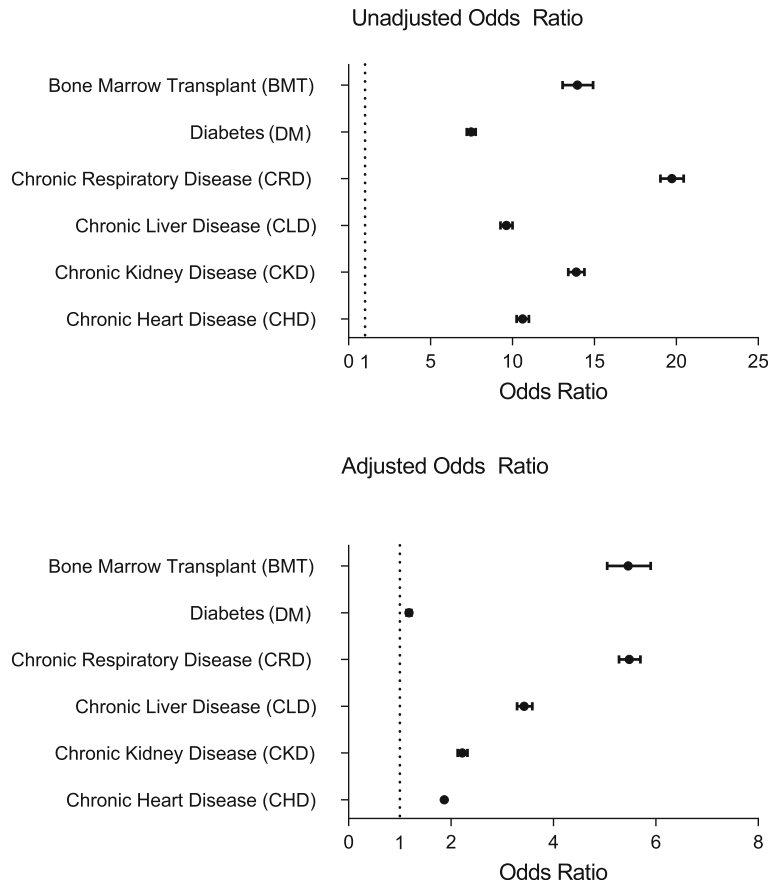


Fig. 2 Odds ratio of risk of developing hospitalised CAP for each clinical risk group

confirmed. Whilst a variety of ICD-10 codes can be used in conjunction with a diagnosis of pneumonia depending on the level of information available, code J18 is by far the most common of the pneumonia diagnoses and is used when the causative organism is either unknown or unspecified. The most commonly identified causative organism for hospital CAP is *S. pneumoniae* [20, 21]. Despite its limitations HES is frequently used for research in the UK due to its universal coverage, long period of data collection and ability to create nationally representative cohorts that can be followed over time. Whilst there are concerns regarding the accuracy of coding, epidemiological studies using HES are considered informative with HES recently used to study the impact of pneumococcal conjugate vaccine on pneumonia, sepsis and otitis media hospital admissions in England [22–24].

Selecting an appropriate comparator group requires careful consideration. We needed a group of healthy individuals but required them to have had a data entry in the HES database to analyse their health status. We considered people who had attended hospital with broken bones / elective hip & knee replacement but were concerned about the high level of associated comorbidities. We therefore chose individuals admitted to hospital for a tooth extraction who did not have any of the underlying comorbidities as the comparator group. We believed this procedure was unlikely to be associated with the risk groups under investigation. It has been suggested however that impaired oral hygiene is a risk factor for developing pneumonia therefore the choice of this comparator may have resulted in an underestimation of the impact of the comorbidities studied [25].

For all risk groups studied the factor having the largest influence on the odds of developing CAP was the CCI. Given that the CCI is strongly associated with the other confounding factors that we adjusted for this finding was unsurprising. However, even after adjusting for the CCI the effects of the underlying comorbidities studied remained significant. The impact of gender on the likelihood of developing CAP is well established and has been reported previously [26].

The presence of any of the defined underlying risk groups increases the likelihood of a hospital admission for CAP, with the risk varying by condition. The odds ratios varied between 1.18 (95% CI 1.13, 1.23) for DM to 5.48 (95% CI 5.28, 5.70) for those with CRD, indicating that not only do patients with a risk group diagnosis have an elevated risk of developing hospitalised CAP but also that the underlying diagnosis determines the magnitude of this risk.

Van Hoek and colleagues used the national surveillance programme which monitors IPD in England and linked it with the HES database to determine the odds of developing IPD in patients with specific clinical risk groups [12]. The most important risk factors that predicted IPD were chronic liver disease, immunosuppression and chronic respiratory disease. While van Hoek's results are not directly comparable to our study, the observed patterns in the odds ratios across the risk groups are similar.

Our results are comparable to previous studies within this area in Germany and the United States, which quantify the risk of developing pneumonia in individuals with underlying comorbidities [13, 14]. Shea et al. [14] utilising data from the United States found patients with chronic lung disease had a rate ratio of 6.6 (95% CI 6.6, 6.7) compared to a healthy population. Patients with chronic heart disease had a rate ratio of 3.8 (95% CI 3.8, 3.80). The lower rate ratios derived in our study may reflect a higher threshold for hospitalisation of cases of CAP in the UK, where many cases are treated in primary care.

As with any epidemiological study which relies on diagnostic coding it is possible that, due to the large amount of data within the HES database, some misclassification may have occurred. We therefore chose to interrogate HES from financial year 2012/13 because the reliability of data from this time point improved following changes to the NHS payment process [27].

While we accounted for several relevant confounders, we were unable to adjust for frailty. Frailty, an age-related decline in reserve and function, [28] often coexists with chronic diseases [29]. and will increase the likelihood of hospitalisation with CAP. Since frailty factors are not coded in HES we were unable to determine the contribution of the comorbidity or degree of frailty to hospitalised CAP.

Due to the nature of the coding system it was challenging to differentiate between hospitalised CAP and healthcare- acquired pneumonia (HCAP). We attempted to control for this by excluding cases of pneumonia that developed at least 48 h post admission (i.e. meeting the definition for HCAP) [30] however this was again dependant on the accuracy with which patients were coded. Patients with a risk group diagnosis may be at an increased risk of developing HCAP compared to those who have not been admitted with an underlying comorbidity. Therefore, it is possible that the presence of HCAP cases within the dataset may have slightly over-inflated the reported odds ratios.

We categorised patients based on ICD-10 codes into one of six risk groups. However, many patients will have more than one underlying comorbidity. The risk of developing CAP increases when patients have an increasing number of comorbidities, a phenomenon known as "risk stacking" [14, 31]. There is evidence that immunocompetent adults with two or more underlying risk groups (multimorbidity) have a higher risk of developing pneumococcal disease and patients with three or more at-risk conditions are at similar risk of developing pneumococcal infection as those with immunosuppressive conditions [32]. The role of severity or chronicity of the underlying comorbidity was outside the scope of this study but should be considered by subsequent relevant studies.

We have not accounted for losing patients from the study due to mortality. The HES data warehouse only includes records of patients' contacts with hospitals in England. Mortality data would therefore only reflect death in hospital during an admission, rather than 30-day mortality.

Conclusions

Individuals with any of 6 pre-defined underlying comorbidities are at significantly increased risk of developing hospitalised CAP compared to those with no underlying comorbid condition. The odds ratios varied between underlying conditions ranging from 1.18 (95% CI 1.13, 1.23) for those with DM to 5.48 (95% CI 5.28, 5.70) for those with CRD.

This work begins to address the data gap in terms of defining the burden of CAP in adults with risk factors and compliments work undertaken by van Hoek et al. on IPD. Our study highlights the importance of protecting 'at risk' patients against CAP and the need to consider the role of relevant vaccines in this context, including pneumococcal and influenza vaccine. Since the likelihood varies by risk group it should be possible to target each with the most appropriate preventative measures, including immunisations.

Appendix

Table 3 List of ICD-10 codes used to identify patients and associated activity

#	Cohort Name	ICD-10 Codes[a]
1.	Pneumonia	J12, J13, J14, J15, J16, J17, J18
2.	Chronic respiratory disease	J40, J41, J42, J43, J44, J47, J6, J7, J80, J81, J82, J83, J84, Q30, J31, Q32, Q33, Q34, Q35, Q36, Q37
3.	Chronic heart disease	I05, I06, I07, I08, I09, I11, I12, I13, I20, I21, I22, I25, I27, I28, I3, I40, I41, I42, I43, I44, I45, I47, I48, I49, I50, I51, I52, Q2
4.	Chronic kidney disease	N00, N01, N02, N03, N04, N05, N07, N08, N11, N12, N14, N15, N16, N18, N19, N25, Q60, Q61
5.	Chronic liver disease	K70, K71, K72, K73, K74, K75, K76, K77, P78.8, Q44
6.	Diabetes mellitus	E10, E11, E12, E13, E14, E24, G59.0, G63.2, G73.0, G99.0, N08.3, O24, P70.0, P70.1, P70.2
7.	Post BMT	Z94.8
8.	Tooth Procedure	F09: Surgical removal of tooth F10: Simple extraction of tooth

[a]ICD-10 codes taken from Rozenbaum et al. [11]

Abbreviations

BMT: Bone marrow transplant; CAP: Community acquired pneumonia; CCI: Charlson comorbidity index; CHD: Chronic heart disease; CI: 95% confidence interval; CKD: Chronic kidney disease; CLD: Chronic liver disease; CRD: Chronic respiratory disease; DM: Diabetes mellitus; HCAP: Healthcare acquired pneumonia; HES: Hospital episode statistics; ICD-10: International Statistical Classification of Diseases and Related Health Problems – 10th revision; NHS: National Health Service; OR: Odds ratio; PPV23: 23-valent plain polysaccharide pneumococcal vaccine

Acknowledgements

The authors gratefully acknowledge the input from A. P. J Rabe and K. Kishore of Health iQ Ltd. for help with the design of the study, provision of the data and ongoing support.

Authors' contributions

All authors were involved in draft content development, and in reading and approval of the final manuscript.

Funding

This research was sponsored by Pfizer. Pfizer provided funding for the following: Hospital Episode Statistics (HES) data processing and analysis by Health iQ Ltd. under an NHS digital re-use agreement and journal publication charges.

Availability of data and materials

The datasets used and/or analysed for the current article are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Prof. James Chalmers has received research grant support from AstraZeneca, Pfizer, GlaxoSmithKline, Boehringer-Ingelheim and Bayer Healthcare and has participated in advisory boards or lectures for Griffols, AstraZeneca, Pfizer, Napp, Boehringer-Ingelheim and Bayer Healthcare. He has also received remuneration from Pfizer for services as a member of the Steering Committee for this study. Prof. Mary Slack has received personal fees from GSK, Pfizer, AstraZeneca and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards (outside the scope of the submitted work). She has also worked as a contractor for Pfizer and received remuneration from Pfizer for services as a member of the Steering Committee for this study. James Campling, Dylan Jones, Qin Jiang, Andrew Vyse, Gillian Ellsbury and Harish Madhava are full-time employees and shareholders of Pfizer; no other conflicts of interest to declare.

Author details

[1]Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS, UK. [2]University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SQ, UK. [3]Pfizer Vaccines, Collegeville, PA, USA. [4]School of Medicine, Griffith University, Gold Coast Campus, Gold Coast, Queensland 4222, Australia.

Received: 30 April 2019 Accepted: 12 September 2019
Published online: 11 October 2019

References

1. Chalmers J, Campling J, Ellsbury G, Hawkey PM, Madhava H, Slack M. Community-acquired pneumonia in the United Kingdom: a call to action. Pneumonia. 2017;9(1):15.
2. Chalmers JD, Campling J, Dicker A, Woodhead M, Madhava H. A systematic review of the burden of vaccine preventable pneumococcal disease in UK adults. BMC Pulm Med. 2016;16(1):77.
3. Barlow G, Nathwani D, Davey P. The CURB65 pneumonia severity score outperforms generic sepsis and early warning scores in predicting mortality in community-acquired pneumonia. Thorax. 2007;62(3):253–9.
4. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009;64(Suppl 3):iii1–55.
5. Chalmers JD, Mandal P, Singanayagam A, Akram AR, Choudhury G, Short PM, et al. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. Intensive Care Med. 2011;37(9):1409–20.
6. Cilloniz C, Ewig S, Polverino E, Marcos MA, Esquinas C, Gabarrus A, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. Thorax. 2011;66(4):340–6.
7. Jain S, Self WH, Wunderink RG, Team CES. Community-acquired pneumonia requiring hospitalization. N Engl J Med. 2015;373(24):2382.
8. Wagenvoort GH, Knol MJ, de Melker HE, Vlaminckx BJ, van der Ende A, Rozenbaum MH, et al. Risk and outcomes of invasive pneumococcal disease in adults with underlying conditions in the post-PCV7 era, the Netherlands. Vaccine. 2016;34(3):334–40.
9. Baxter R, Yee A, Aukes L, Snow V, Fireman B, Atkinson B, et al. Risk of underlying chronic medical conditions for invasive pneumococcal disease in adults. Vaccine. 2016;34(36):4293–7.
10. Weycker D, Farkouh RA, Strutton DR, Edelsberg J, Shea KM, Pelton SI. Rates and costs of invasive pneumococcal disease and pneumonia in persons with underlying medical conditions. BMC Health Serv Res. 2016;16:182.
11. Rozenbaum MH, van Hoek AJ, Fleming D, Trotter CL, Miller E, Edmunds WJ. Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. BMJ (Clinical research ed). 2012;345:e6879.
12. van Hoek AJ, Andrews N, Waight PA, Stowe J, Gates P, George R, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Inf Secur. 2012;65(1):17–24.

13. Pelton SI, Shea KM, Farkouh RA, Strutton DR, Braun S, Jacob C, et al. Rates of pneumonia among children and adults with chronic medical conditions in Germany. BMC Infect Dis. 2015;15:470.
14. Shea KM, Edelsberg J, Weycker D, Farkouh RA, Strutton DR, Pelton SI. Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis. 2014;1(1):ofu024.
15. Kaplan V, Clermont G, Griffin MF, Kasal J, Watson RS, Linde-Zwirble WT, et al. Pneumonia: still the old man's friend? Arch Intern Med. 2003;163(3):317–23.
16. Organisation WH. International statistical classification of diseases and related health problems 10th revision 2010 [8 Nov 2018]. Available from: http://apps.who.int/classifications/icd10/browse/2010/en.
17. England PH. Immunisation against infectious diseases. Pneumococcal: the green book, chapter 25 2018 [8 Nov 2018]. Available from: https://www.gov.uk/government/publications/pneumococcal-the-green-book-chapter-25.
18. Masterton RG, Galloway A, French G, Street M, Armstrong J, Brown E, et al. Guidelines for the management of hospital-acquired pneumonia in the UK: report of the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother. 2008; 62(1):5–34.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
20. de Roux A, Schmole-Thoma B, Siber GR, Hackell JG, Kuhnke A, Ahlers N, et al. Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults: conjugate vaccine elicits improved antibacterial immune responses and immunological memory. Clin Infect Dis. 2008;46(7):1015–23.
21. Rodrigo C, Bewick T, Sheppard C, Greenwood S, McKeever TM, Trotter CL, et al. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. Eur Respir J. 2015;45(6):1632–41.
22. Trotter CL, Borrow R, Findlow J, Holland A, Frankland S, Andrews NJ, Miller E. Seroprevalence of antibodies against serogroup C meningococci in England in the postvaccination era. Clin Vaccine Immunol. 2008;15:1694–8.
23. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data resource profile: hospital episode statistics admitted patient care (HES APC). Int J Epidemiol. 2017;46(4):1093–i.
24. Thorrington D, Andrews N, Stowe J, Miller E, van Hoek AJ. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. BMC Med. 2018;16(1):13.
25. Azarpazhooh A, Leake JL. Systematic review of the association between respiratory diseases and Oral health. J Periodontol. 2006;77(9):1465–82.
26. Millett ER, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PLoS One. 2013;8(9):e75131.
27. Health and Social Care Act 2012 (c. 7) Accessed at http://www.legislation.gov.uk/ukpga/2012/7/pdfs/ukpga_20120007_en.pdf.
28. Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunananthan S, et al. Frailty: an emerging research and clinical paradigm--issues and controversies. J Gerontol A Biol Sci Med Sci. 2007;62(7):731–7.
29. Vaughan L, Corbin AL, Goveas JS. Depression and frailty in later life: a systematic review. Clin Interv Aging. 2015;10:1947–58.
30. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171(4):388–416.
31. Pelton SI, Shea KM, Weycker D, Farkouh RA, Strutton DR, Edelsberg J. Rethinking risk for pneumococcal disease in adults: the role of risk stacking. Open Forum Infect Dis. 2015;2(1):ofv020.
32. Muhammad RD, Oza-Frank R, Zell E, Link-Gelles R, Narayan KM, Schaffner W, et al. Epidemiology of invasive pneumococcal disease among high-risk adults since the introduction of pneumococcal conjugate vaccine for children. Clin Infect Dis. 2013;56(5):e59–67.

Publisher's Note

BMJ Open Respiratory Research

Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England

James Campling,[1] Dylan Jones,[2] James Chalmers,[3] Qin Jiang,[4] Andrew Vyse,[1] Harish Madhava,[1] Gillian Ellsbury,[1] Adrian Rabe,[5] Mary Slack[6]

To cite: Campling J, Jones D, Chalmers J, *et al*. Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England. *BMJ Open Resp Res* 2020;**7**:e000703. doi:10.1136/bmjresp-2020-000703

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2020-000703).

Received 30 June 2020
Revised 19 August 2020
Accepted 21 August 2020

[1]Vaccines Medical Affairs, Pfizer Ltd, Tadworth, UK
[2]Vaccines Health Economics and Outcomes Research, Pfizer Ltd, Tadworth, UK
[3]University of Dundee School of Medicine, Dundee, UK
[4]Pfizer Vaccines, Collegeville, PA, USA
[5]Epidemiology and Data Science, Health iQ Ltd, London, UK
[6]School of Medicine, Griffith University Faculty of Health, Gold Coast, Queensland, Australia

Correspondence to
James Campling;
james.campling@pfizer.com

ABSTRACT

Background Hospitalised pneumonia may have long-term clinical and financial impact in adult patients with underlying comorbidities.

Methods We conducted a retrospective cohort study using the Hospital Episode Statistics (HES) database to determine the clinical and financial burden over 3 years of hospitalised community-acquired pneumonia (CAP) to England's National Health Service (NHS). Subjects were adults with six underlying comorbidities (chronic heart disease (CHD); chronic kidney disease (CKD); chronic liver disease (CLD); chronic respiratory disease (CRD); diabetes mellitus (DM) and post bone marrow transplant (post-BMT)) with an inpatient admission in 2012/2013. Patients with CAP in 2013/2014 were followed for 3 years and compared with similarly aged, propensity score-matched adults with the same comorbidity without CAP.

Findings The RR of hospital admissions increased after CAP, ranging from 1.08 (95% CI 1.04 to 1.12) for CKD to 1.38 (95% CI 1.35 to 1.40) for CRD. This increase was maintained for at least 2 years. Mean difference in hospital healthcare costs (£) was higher for CAP patients in 2013/2014; ranging from £1115 for DM to £8444 for BMT, and remained higher for 4/6 groups for 2 more years, ranging from £1907 (95% CI £1573 to £2240) for DM to £11 167 (95% CI £10 847 to £11 486) for CRD.) The OR for mortality was significantly higher for at least 3 years after CAP, ranging from 4.76 (95% CI 4.12 to 5.51, p<0.0001) for CLD to 7.50 (95%CI 4.71 to 11.92, p<0.0001) for BMT.

Interpretation For patients with selected underlying comorbidities, healthcare utilisation, costs and mortality increase for at least 3 years after being hospitalised CAP.

Key messages

What is the key question?

- What is the clinical and financial burden to National Health Service (NHS) England for an episode of hospitalised community-acquired pneumonia (CAP) in patients with certain comorbidities?

What is the bottom line?

- In patients with certain comorbidities, an episode of hospitalised CAP results in an increase in the clinical and financial burden to NHS England for at least 3 years.
- Furthermore, the risk of death is significantly increased for at least 3 years.

Why read on?

- This study demonstrates the long-term impact of hospitalised CAP, both for individual patients with certain comorbidities and for the health service.

INTRODUCTION

Community acquired pneumonia (CAP) is a major cause of morbidity and mortality.[1] Pneumonia has a considerable impact on the healthcare systems of the UK, being responsible for more hospital admissions and bed days than any other lung disease in the UK.[1] Across Europe, annual inpatient care for pneumonia accounts for €5.7 billion of healthcare expenditure.[1] *Streptococcus pneumoniae* remains the most commonly identified cause of CAP; however, the microbiological aetiology is not identified in approximately 50% of cases.[2 3] Hospitalised CAP carries a mortality rate of 5% to 15%, rising to more than 30% for those admitted to intensive care,[2 3] and results in 29 000 deaths per annum in the UK.[1] Traditionally, the clinical and economic costs of an episode of hospitalised CAP have been assumed to be short-lived, with patients subsequently returning to their previous health state.[4] However, recent data challenge this assumption, with studies suggesting a long-term reduction in quality of life[5 6] and decreased long-term survival in those with an underlying comorbidity who experience an episode of hospitalised pneumonia. Recognition of the long-term health consequences of CAP is important to inform secondary prevention strategies. It is well established that a myocardial infarction, while being a serious acute event, also carries a significant long-term morbidity in

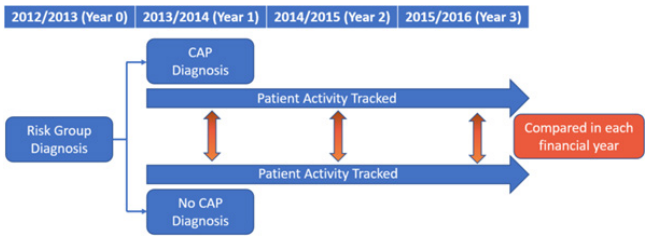


Figure 1 Study design. CAP, community-acquired pneumonia.

terms of direct and indirect health consequences, and increased mortality.[7] Patients with myocardial infarction are therefore offered secondary prevention and rehabilitation, interventions that are proven to reduce long-term morbidity and mortality. Such interventions are not available for CAP, in part because the long-term health consequences of CAP, particularly in multimorbid patients, are less well described. We hypothesised that a diagnosis of hospitalised CAP in an individual with a specific comorbidity would have clinical and economic implications beyond the initial diagnosis.

Aims of the study

Between 2013/2014 and 2015/2016, this study investigated the extent of any additional healthcare resource utilisation, patient costs and in-hospital mortality for patients with comorbidities who had CAP as a complicating condition in 2013/2014.

METHODS

Study design

This was a retrospective cohort study using data from the Hospital Episode Statistics (HES) database (online supplemental box 1) between the financial years 2012/2013 and 2015/2016. Eligible patients were identified in 2012/2013 and those who met the study criteria were then followed for three subsequent years (2013/2014, 2014/2015 and 2015/2016) (figure 1).

Participants were aged 18+ years in 2012/2013 and consisted exclusively of patients with one or more of six comorbidities as denoted by the relevant International Statistical Classification of Diseases and Related Health Problems, Tenth revision (ICD-10) codes (online supplemental table 1) in either the primary or secondary position.[8 9] The six comorbidities selected were: bone marrow transplant (BMT), chronic respiratory disease (CRD), diabetes, chronic kidney disease (CKD), chronic heart disease (CHD) and chronic liver disease (CLD). These were chosen because adults with these comorbidities are considered to be at an increased risk of pneumococcal disease.[10]

None of the participants selected had evidence of a diagnosis of pneumonia (online supplemental table 1) in 2012/2013 and none had died during 2012/2013. The study group were those participants who were subsequently hospitalised with a diagnosis of CAP (based on the relevant ICD-10 codes) in 2013/2014. The comparison group were those participants with no diagnosis of hospitalised CAP in 2013/2014 and who were not hospitalised with CAP at any subsequent point during the study period.

It was possible for patients to have more than one of the selected comorbidities. The risk of developing CAP increases when patients have an increasing number of risk factors, a phenomenon known as 'risk stacking'.[11] In order to correct for this confounder, we used the propensity scoring method[12] to match each participant in the study group with a participant in the comparator group (1:1 ratio). It was also not possible to account for severity of the underlying comorbidity, due to limitations of the HES database. To counterbalance this, we incorporated healthcare utilisation within the base year (2012/2013) in the propensity score matching (PSM). PSM is a statistical technique in which the group of interest is matched for similarity with one or more controls. For each individual comorbidity, the propensity score was estimated utilising: age, sex, ethnicity, index of multiple deprivation, other comorbidities from the six comorbidities selected and healthcare utilisation within the baseline year (2012/2013). A study participant with a diagnosis of hospitalised CAP was matched with a comparator participant with the same comorbidity but with no diagnosis of hospitalised CAP in 2013/2014 (and was not hospitalised with CAP at any subsequent point during the study period).

Once matched, the study group and comparison group were followed over a 3-year period from 2013/2014 to 2015/2016 and assessed for differences in healthcare resource utilisation (overall hospital admissions, outpatient attendance and accident and emergency department (A&E) visits), the associated hospital healthcare costs and mortality during each of the three study years. The objective was to investigate if, and to what extent, these outcome measurements differed in participants with comorbidities who were hospitalised with CAP in 2013/2014 compared with those with the same comorbidities who were not hospitalised with CAP (either in 2013/2014 or the subsequent two study years).

Inclusion/exclusion criteria

Participants had to be aged 18+ years in 2012/2013 and for inclusion needed to have at least one of the defined comorbidities. Patients with a diagnosis of CAP (online supplemental table 1, ICD-10) or evidence of inpatient death during 2012/2013 were excluded. Those patients with a secondary pneumonia diagnosis after 48 hours of the primary admission were also excluded as this as was considered to reflect hospital-acquired pneumonia (HAP) rather than CAP. Patients with missing data (approximately 0.5% of all data in HES), where the admission/visit/attendance did not have a corresponding Healthcare Resource Groups (HRG) code were excluded because it was not possible to cost the

associated admission/visit/attendance in the absence of an HRG code. HRGs are standard groupings of clinically similar treatments which use comparable levels of healthcare resource, including groups of ICD-10 diagnoses that have similar resource implications. Outpatient follow-up visits included regular and programmatic visits among all groups.

Categorisation of CAP and non-CAP

Within each individual risk population, subjects were categorised into two groups based on the presence or absence of a primary or secondary diagnosis code for CAP (online supplemental table 1, ICD-10) in 2013/2014. However, if any secondary pneumonia diagnosis occurred after 48 hours of the primary admission, this subject was excluded as it was considered to be a HAP.[13] Subjects were included in the non-CAP comparison group if there was no diagnosis of pneumonia (online supplemental table 1: ICD-10) during the three study years (2013/14 to 2015/16).

Outcome

The three key outcomes examined during the period 2013/2014 to 2015/2016 were healthcare resource utilisation (total number of hospital admissions, total number of outpatient attendances and total number of A&E visits), the costs associated with these activities and in-hospital mortality.

For each patient, the number of hospital admissions, outpatient attendances and A&E visits were retrieved from the database according to the corresponding HRG.[14] Hospitalised mortality was defined when hospital discharge status was 'death'.

The associated costs for each activity were then determined using the appropriate National Health Service (NHS) tariffs and reported in 2016 UK pounds sterling (£). Costs from earlier years were adjusted using the Hospital and Community Health Services (HCHS) index from the Personal Social Services Research Unit (PSSRU).[15]

Statistical analysis

Demographic characteristics were measured and summarised using means, medians, SD, and p values where appropriate.

Healthcare resource utilisation reported as activity was analysed using a negative binomial model. Negative binomial modelling corrects for overdispersion of the data, which is useful for studies utilising large data sets, such as this one. The model was run for patients from each comorbidity category and the rate ratio (RR) for each category was compared with their propensity score-matched pairs, in each of the three study years, using CAP diagnosis as the dependent variable and each type of healthcare resource use (admissions, outpatient appointments or A&E visits) as the outcome variable. The model was adjusted based on the recruitment of propensity-score matched patients for potential explanatory variables (age, gender, ethnicity, elective and non-elective admissions, conditions in the Charlson Comorbidity Index[16] and the presence of diagnoses used to identify the other comorbidities at the point of participant selection in 2012/2013). These variables were selected based on likelihood ratios calculated from univariate logistic regression performed on each of them.

To determine the costs for each type of healthcare resource use as calculated through HRG tariffs, a generalised linear model was used. In this model, CAP diagnosis was the dependent variable, while costs were the outcome variable. Adjustments were made with the same factors based on likelihood ratios from univariate logistic regression performed on each of them. Mean differences for costs were then calculated (with 95% CIs generated using the least squares method) between the study group and comparison group for each comorbidity, for each of the three study years individually and for all three study years collectively.

In both models statistical significance was considered achieved if the 95% CIs around the point estimate did not include 1 ($p<0.05$).

To investigate the effect of hospitalised CAP on subsequent in-hospital mortality, a conditional logistic regression model was used to reduce bias given that matched data were being used. In-hospital mortality was the dependent variable, while other variables (hospitalised CAP, age, gender, ethnicity, elective and non-elective admissions in at the point of selection in 2012/2013, conditions in the Charlson comorbidity index and presence of diagnoses used to identify the other comorbidities) were explanatory variables. ORs for mortality comparing the study group with the comparison group within each of the selected comorbidities were estimated with 95% CIs.

As the HES database includes all the data entered from the NHS in England, it is possible for implausible extreme values to be recorded in the database. For example, one individual was admitted to hospital, on average, every 1.5 days. To ensure this data did not skew the results to favour our hypothesis, the top 1 percentile of results were excluded from the analysis.

For quality control purposes, each query was validated by re-running the queries.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

A total of 2 205 850 candidate patients with one or more of the six comorbidities were identified in HES in 2012/2013. The total number of patients in each of the six comorbidities were as follows CHD n=981 397; CKD n=232 488; CLD n=71 261; CRD n=294 283; diabetes

n=6 21 887; and post-BMT n=4534. After selecting only those who had a diagnosis of hospitalised CAP in 2013/2014 and a 1:1 propensity score-matched control, the number of patients in each group was: CHD n=36 386; CKD n=12 190; CLD n=2222; CRD n=20 764; diabetes n=16 382; and post-BMT n=271. (table 1)

These formed the cohort that was investigated for healthcare resource utilisation, hospital admission costs and in-hospital mortality over the period 2013/2014 to 2015/2016.

Healthcare resource utilisation

For each of the three study years (2013/2014, 2014/2015 and 2015/2016), subsequent healthcare resource utilisation (overall hospital admissions, outpatient attendance and A&E visits) for patients with each category of comorbidity who were hospitalised with CAP in 2013/2014 were compared with those for patients with the same category of comorbidity but who were not hospitalised with CAP in 2013/2014 (or any of the subsequent two study years). Results are presented as RRs for each category of comorbidity and each category of healthcare resource utilisation during each of the three individual study years (table 2) (figure 2).

A statistically significant increase in the rate of healthcare resource utilisation was observed for patients with CHD, CKD, CLD, CRD and diabetes who were hospitalised with an episode of CAP in 2013/2014 compared with those with CHD, CKD, CLD, CRD and diabetes who did not develop hospitalised CAP. This was observed for each of the three categories of healthcare resource utilisation during each of the three study years with RRs ranging from 1.08 (95% CI 1.04 to 1.12) for overall hospital admissions for CKD patients during 2013/2014 to 1.42 (95% CI 1.37 to 1.46) for overall hospital admissions for CRD patients during 2015/2016. For BMT patients who had an episode of CAP in 2013/2014, there was evidence of an increase in healthcare resource utilisation for outpatient attendance only during 2013/2014 (RR 1.16; 95% CI 1.02 to 1.32). There was no evidence of a difference in any of the three categories of healthcare resource utilisation when comparing other BMT patients with a diagnosis of CAP in 2013/2014 to those without during any of the three study years (RRs ranged from 0.93 (95%CI 0.71 to 1.13) for A&E visits during 2013/2014 to 1.28 (95%CI 0.96 to 1.71) for overall hospital admissions during 2015/2016).

Hospital admission costs

Table 3 shows the mean difference in hospital healthcare costs (£) during the 3-year study period for patients with each comorbidity who developed hospitalised CAP in 2013/2014 compared with those who did not. Results are presented for each category of comorbidity, for each individual study year and overall for the combined 3-year duration of the study. During 2013/2014 and overall for the three study years collectively, the mean hospital healthcare costs were higher for patients with each of the six comorbidities who were hospitalised with CAP than for those with the same comorbidities who did not develop hospitalised CAP. During 2013/2014 the mean difference in cost ranged from an increase of £1115 for patients with diabetes to £8444 for patients with BMT who developed CAP in 2013/2014, while overall for the full 3-year study period, the mean difference in hospital healthcare costs ranged from an increase of £1907 for patients with diabetes who developed CAP in 2013/2014 to £11 167 for those with CRD who developed CAP in 2013/2014. During 2014/2015 and 2015/2016, mean higher costs were also incurred for four of the six comorbidity categories who developed CAP in 2013/2014. Exceptions were CKD and diabetic patients where a hospitalisation with CAP in 2013/2014 resulted in lower mean hospital healthcare costs during 2014/2015 and 2015/2016, respectively.

In-hospital mortality

Patients with comorbidities who developed hospitalised CAP in 2013/2014 had substantially higher ORs for in-hospital mortality when compared with those with comorbidities who did not develop CAP. This extended to each category of comorbidity for each of the three study years. Results are presented in figure 3. The OR was particularly high for BMT patients (OR 7.50, 95% CI 4.71 to 11.92, p<0.0001). For the remaining categories of comorbidity, ORs ranged from 4.76 (95%CI 4.12 to 5.51, p<0.0001) for CLD patients to 5.94 (95%CI 5.65 to 6.24, p<0.0001) for CRD patients.

DISCUSSION

This is a large study using a national data set reflecting the adult hospital population (~75 000 participants) in England with six comorbidities. This provided sufficient data to closely match participants in the study group with those in the comparator group. While there are shortcomings using HES epidemiologic studies, using HES can be informative.[17–19]

Principal findings

We previously reported the variation in the likelihood of hospitalisation for CAP among adults with six comorbidities in England.[20] The current analysis used the same data set to quantify the clinical and financial burden of hospitalised CAP in these patients over the same time period.

This study illustrates for the first time the increase in the rate of hospital admissions in patients with the six clinical comorbidities included following an episode of hospitalised CAP. This increase was statistically significant in all comorbidity categories apart from post-BMT and was maintained across all three study years. However, there is a lack of precision around point estimates for healthcare resource utilisation for post-BMT patients specifically due to the small number of these participants (n=271). As expected, there was variation between the different

Table 1 Demographics of matched participants in CAP/non-CAP groups for each of the six comorbidities

	CHD		CKD		CLD		CRD		Diabetes		Post-BMT	
Demographics	CAP	non-CAP	CAP	non-CAP	CAP	non-CAP	CAP	non-CAP	CAP	non-CAP	CAP	non-CAP
Participant												
All candidate participants	44215	937182	14428	218060	2604	68657	25500	268783	21222	600665	369	4165
1:1 Matched	36386	36386	12190	12190	2222	2222	20764	20764	16382	16382	271	271
Age												
Mean	79.1	79.5	78.8	79.2	62.1	61.8	75.0	75.3	74.9	75.3	53.9	54.6
Median	81.0	81.0	81.0	82.0	63.0	62.0	77.0	77.0	77.0	77.0	56.0	56.0
Gender												
Male	17432 (47.9%)	17524 (48.2%)	5791 (47.5%)	5892 (48.3%)	909 (40.9%)	975 (43.9%)	9944 (47.9%)	10040 (48.4%)	7600 (46.4%)	7930 (48.4%)	102 (37.6%)	117 (43.2%)
Ethnicity												
White	33128 (91.0%)	33210 (91.3%)	10773 (88.4%)	10795 (88.6%)	1936 (87.1%)	1933 (87.0%)	19327 (93.1%)	19479 (93.8%)	14007 (85.5%)	13960 (85.2%)	231 (85.2%)	239 (88.2%)
Mixed	68 (0.2%)	79 (0.2%)	29 (0.2%)	28 (0.2%)	11 (0.5%)	5 (0.2%)	34 (0.2%)	33 (0.2%)	54 (0.3%)	65 (0.4%)		
Asian/Indian	1167 (3.2%)	969 (2.7%)	558 (4.6%)	502 (4.1%)	108 (4.9%)	96 (4.3%)	462 (2.2%)	377 (1.8%)	1095 (6.7%)	1011 (6.2%)	13 (4.8%)	6 (2.2%)
Black/African origin	444 (1.2%)	456 (1.3%)	293 (2.4%)	260 (2.1%)	42 (1.9%)	45 (2.0%)	147 (0.7%)	153 (0.7%)	435 (2.7%)	454 (2.8%)	5 (1.8%)	7 (2.6%)
Chinese	31 (0.1%)	22 (0.1%)	11 (0.1%)	19 (0.2%)	3 (0.1%)	7 (0.3%)	12 (0.1%)	12 (0.1%)	23 (0.1%)	24 (0.1%)	0	1 (0.4%)
Other/not collected	1548 (4.2%)	1650 (4.5%)	526 (4.3%)	586 (4.8%)	122 (5.5%)	136 (6.1%)	782 (3.7%)	710 (3.5%)	768 (4.7%)	868 (5.3%)	22 (8.1%)	18 (6.6%)
Index of multiple deprivation (least to most)												
0 to 20	5693 (15.6%)	6238 (17.2%)	1864 (15.3%)	1970 (16.1%)	256 (11.6%)	289 (13%)	2472 (11.9%)	2768 (13.4%)	2147 (13.1%)	2283 (14.0%)	60 (22.1%)	67 (24.7%)
20 to 40	6579 (18.0%)	7039 (19.3%)	2156 (17.7%)	2288 (17.9%)	347 (15.7%)	331 (14.9%)	3290 (15.9%	3613 (17.4%)	2662 (16.3%)	2961 (18.1%)	63 (23.2%)	58 (21.4%)
40 to 60	8354 (22.9%)	7715 (21.2%)	2848 (23.4%)	2708 (22.3%)	611 (27.5%)	575 (25.9%)	5486 (26.4%)	4913 (23.7%)	4097 (25.0%)	3857 (23.6%)	45 (16.6%)	65 (24.0%)
60 to 80	8065 (22.2%)	7491 (20.5%)	2784 (22.8%)	2577 (21.2%)	584 (26.3%)	562 (25.3%)	5137 (24.7%)	4973 (23.9%)	3963 (24.2%)	3829 (23.4%)	47 (17.4%)	29 (10.7%)
80 to 100	7533 (20.7%)	7589 (20.8%)	2483 (20.3%)	2559 (21.0%)	411 (18.5%)	440 (19.8%)	4281 (20.7%)	4345 (20.9%)	3433 (21.0%)	3342 (20.4%)	56 (20.7%)	31 (18.8%)
Not collected	162 (0.4%)	314 (0.9%)	55 (0.5%	88 (0.7%)	13 (0.6%)	25 (1.1%)	98 (0.5%)	152 (0.7%)	80 (0.5%)	110 (0.7%)	0 (0.0%)	1 (0.4%)
CHD												
Yes	N/A	N/A	10473 (85.9%)	10509 (86.2%)	1322 (59.5%)	1326 (59.7%)	16053 (77.3%)	16114 (77.6%)	13213 (80.7%)	13293 (81.1%)	113 (41.7%)	112 (41.3%)
CKD												
Yes	14978 (41.2%)	14929 (41.0%)	N/A	N/A	661 (29.7%)	658 (29.6%)	6429 (31.0%)	6357 (30.6%)	7771 (47.4%)	7824 (47.8%)	90 (33.2%)	86 (31.7%)
CLD												
Yes	2348 (6.5%)	2207 (6.1%)	853 (7.0%)	795 (6.5%)	N/A	N/A	1487 (7.2%)	1351 (6.5%)	1538 (9.4%)	1442 (8.8%)	25 (9.2%)	20 (7.4%)
CRD												
Yes	18363 (50.5%)	18351 (50.4%)	5762 (47.3%)	5761 (47.3%)	1042 (46.9%)	1049 (47.2%)	N/A	N/A	7833 (47.8%)	7788 (47.5%)	97 (35.8%)	101 (37.3%)
Diabetes												
Yes	11849 (32.6%)	11779 (32.4%)	5094 (41.8%)	5159 (42.3%)	813 (36.6%)	817 (36.8%)	5791 (27.9%)	5528 (26.6%)	N/A	N/A	62 (22.9%)	81 (29.9%)

Continued

Table 1 Continued

Demographics	CHD		CKD		CLD		CRD		Diabetes		Post-BMT	
	CAP	non-CAP	CAP	non-CAP	CAP	non-CAP	CAP	non-CAP	CAP	non-CAP	CAP	non-CAP
post-BMT												
Yes	86 (0.2%)	51 (0.1%)	85 (0.7%)	76 (0.6%)	15 (0.7%)	7 (0.3%)	61 (0.3%)	35 (0.2%)	88 (0.5%)	64 (0.4%)	N/A	N/A
Mean admissions 2012/2013												
Elective (mean)	4.2	3.6	9.3	7.6	4.5	3.9	2.9	2.5	5	3.6	18.3	16.3
Non-elective (mean)	2.2	2.1	2.5	2.4	3.1	3.1	2.3	2.2	2.2	2.2	3.2	3.0
Total (mean)	3.7	3.4	6.3	5.5	5.3	5	3.3	3.1	4.2	3.5	20.0	17.3

BMT, bone marrow transplant ; CAP, community-acquired pneumonia ; CHD, chronic heart disease ; CKD, chronic kidney disease ; CLD, chronic liver disease ; CRD, chronic respiratory disease ; N/A, Not Applicable.

comorbidities included, which is consistent with previous findings on the impact of underlying comorbidities and the risk of invasive pneumococcal disease (IPD).[19]

Our study also shows that patients with these comorbidities who are diagnosed with hospitalised CAP subsequently cost more money to treat over the 3-year period following the initial episode of CAP compared with matched controls who did not have an episode of pneumonia. The costs varied substantially by comorbidity, with the mean difference ranging between £6000 over 3 years for CHD patients to over £11 000 for CRD patients. However, for CKD patients, this trend was inconsistent in 2014/2015, when those with hospitalised CAP cost less than their matched controls. A similar but not significant observation was also made for diabetic patients in 2015/2016. One possible explanation is that hospitalisation with CAP provides an opportunity to review the treatment for an individual's underlying condition. This review subsequently leads to an improvement in treatment of the underlying condition, thereby averting future related hospital costs and admissions related to their underlying condition. This might be specific to CKD and diabetes and the way in which they are managed. We chose to calculate the difference in cost using HRGs which provides insight to the cost that hospitals would have received for treating these patients, but it does not reflect the full picture of costs and notably is not able to capture costs in the community following discharge. A separate specific cost analysis of hospitalised pneumonia would be needed to more accurately determine a more accurate cost.

Our study found that patients with certain underlying comorbidities have a significantly higher likelihood of in-hospital mortality following an episode of hospitalised CAP. The ORs were >4 for all six comorbidities which underlines the importance of measures to prevent episodes of hospitalised pneumonia in patients with comorbidities.

The key findings of this study suggest that following an episode of CAP, adults with underlying comorbidities are subsequently associated with increased healthcare resource utilisation and are at increased risk of mortality for an extended period. An episode of hospitalised CAP is therefore likely to have a prolonged adverse effect on the subsequent health of adults with underlying comorbidities, which supports considering pneumonia as a chronic rather than an acute condition.[21] An episode of CAP in adults with underlying comorbidities appears likely to leave them particularly prone to long-term adverse health consequences.[22] While this is the first time insights in this context have been obtained using a population of UK adults with underlying comorbidities specifically, similar research undertaken outside the UK has previously highlighted that adults may be left with a compromised health status following an episode of hospitalised CAP. A recent systematic review and meta-analysis reported an increased risk of myocardial infarction, heart failure, dysrhythmias and stroke after CAP, which is maximal in the acute phase but persists long-term after resolution of the pneumonia .[23] The finding that there is an increased likelihood of mortality following an episode of hospitalised CAP is reflected by a study in Dutch adults which suggested long-term mortality was higher in those with an underlying comorbidity following an episode of IPD or pneumonia.[24] A possible explanation for this is that an episode of hospitalised CAP can compromise the long-term health status of patients with underlying comorbidities.

This study suggests it is not appropriate to continue to consider an episode of hospitalised CAP as a discreet event for patients with comorbidities. Rather, the impact of hospitalised CAP should be considered over a longer period accounting for the impact on both the patient and the healthcare system. Furthermore, it is important to consider the personal impact on quality of life for these patients and their families along with some of the often unreported consequences of CAP, including wider societal implications such as time off work.[25]

The increasing numbers of patients with comorbidities and elderly patients hospitalised with CAP will consume a

Table 2 Comparison of rate of hospital admissions, outpatient attendances and A&E visits for patients with a diagnosis of hospitalised CAP and those without a diagnosis of hospitalised CAP, stratified by underlying comorbidity and year, 2013 to 2015

Risk group	Total hospital admissions RR (95% CI)			Outpatient attendance RR (95% CI)			A&E visits RR (95% CI)		
	2013	2014	2015	2013	2014	2015	2013	2014	2015
CHD	1.21 (1.19 to 1.23)	1.25 (1.23 to 1.29)	1.22 (1.19 to 1.25)	1.16 (1.14 to 1.18)	1.12 (1.10 to 1.14)	1.13 (1.11 to 1.18)	1.30 (1.28 to 1.32)	1.30 (1.27 to 1.32)	1.25 (1.23 to 1.28)
CKD	1.08 (1.04 to 1.12)	1.32 (1.25 to 1.39)	1.38 (1.29 to 1.47)	1.15 (1.12 to 1.18)	1.16 (1.12 to 1.20)	1.18 (1.13 to 1.22)	1.29 (1.22 to 1.30)	1.26 (1.22 to 1.30)	1.26 (1.21 to 1.31)
CLD	1.19 (1.12 to 1.27)	1.16 (1.06 to 1.27)	1.30 (1.18 to 1.44)	1.22 (1.15 to 1.29)	1.20 (1.11 to 1.28)	1.12 (1.03 to 1.21)	1.18 (1.10 to 1.26)	1.20 (1.10 to 1.31) p=0.1227	1.05 (0.95 to 1.16)
CRD	1.38 (1.35 to 1.40)	1.39 (1.36 to 1.43)	1.42 (1.37 to 1.46)	1.15 (1.13 to 1.17)	1.09 (1.06 to 1.11)	1.11 (1.08 to 1.14)	1.30 (1.28 to 1.33)	1.33 (1.30 to 1.37)	1.35 (1.32 to 1.39)
Diabetes	1.24 (1.21 to 1.27)	1.28 (1.23 to 1.33)	1.24 (1.19 to 1.29)	1.21 (1.18 to 1.24)	1.14 (1.11 to 1.17)	1.13 (1.10 to 1.17)	1.28 (1.25 to 1.30)	1.24 (1.21 to 1.28)	1.23 (1.19 to 1.27)
Post-BMT	1.16 (0.96 to 1.39)*	1.25 (0.97 to 1.59)*	1.28 (0.96 to 1.71)*	1.16 (1.02 to 1.32)*	1.11 (0.94 to 1.37)*	1.00 (0.84 to 1.70)*	0.93 (0.77 to 1.13)*	0.94 (0.71 to 1.24)*	1.13 (0.87 to 1.48)*

*Not significant; where not indicated, p value is <0.001.
A&E, accident and emergency department; BMT, bone marrow transplant ; CAP, community-acquired pneumonia ; CHD, chronic heart disease; CKD, chronic kidney disease; CLD, chronic liver disease; CRD, chronic respiratory disease ; RR, rate ratio.

Figure 2 Comparison of rate of hospital admissions, outpatient attendances and A&E visits for patients with a diagnosis of hospitalised CAP and those without a diagnosis of hospitalised CAP, stratified by underlying co-morbidity and year. A&E, accident and emergency department; BMT, bone marrow transplant; CAP, community-acquired pneumonia; CHD, chronic heart disease; CKD, chronic kidney disease; CLD, chronic liver disease; CRD, chronic respiratory disease.

large percentage of health resources in the future.[26] Our data suggest that those with underlying conditions continue to be at an increased risk of hospitalised CAP and its associated consequences. Since the risk varies by comorbidity, it should be possible to target these comorbidity groups with appropriate preventative measures including influenza and pneumococcal immunisations.

This study reflects the UK healthcare system, the NHS, and its findings are therefore mainly of relevance for the UK, but may nevertheless be of interest for other healthcare systems.

CAP is a significant contributor to winter pressures that the NHS faces each year. Strategies to prevent pneumonia, including smoking cessation, pneumococcal vaccination and seasonal influenza vaccination, are important. Clinicians are advised to provide patients with written advice on pneumonia recovery when they are discharged from hospital. It is therefore disappointing that the most recent British Thoracic Society audit of adult CAP found that only 5.8% of participating hospitals routinely provided written advice to pneumonia patients when discharged from hospital.[27]

Strengths and weaknesses of the study

This study used HES data which has acknowledged limitations, particularly regarding quality and consistency of

Table 3 Mean difference in hospital healthcare costs for patients in each comorbidity who developed hospitalised CAP versus those who did not throughout the 3-year study

Hospital healthcare resource costs (£): mean difference (95% CI)						
	CHD	CKD	CLD	CRD	Diabetes	Post-BMT
Total admissions 2013/2014	4666 (4542; 4790)	4958 (4725; 5192)	5693 (5082; 6305)	5264 (5098; 5431)	1115 (869; 1361)	8444 (6026; 10 862)
Total admissions 2014/2015	2679 (2533; 2824)	−1,916 (−2295; −1537)	10 774 (9633; 11 915)	10 947 (10 611; 11 283)	2675 (2451; 2899)	8030 (3961; 12 099)
Total admissions 2015/2016	2056 (1907; 2206)	2181 (1894; 2468)	1664 (992; 2337)	2815 (2616; 3015)	−1,692 (−2020; 1364)	2010 (−319; 4341)
Total admissions 2013/2014 to 2015/2016	6103 (5930; 6275)	3800 (3436; 4164)	10 858 (9712; 12 004)	11 167 (10 847; 11 486)	1907 (1573; 2240)	9274 (4968; 13 580)

BMT, bone marrow transplant; CAP, community-acquired pneumonia ; CHD, chronic heart disease ; CKD, chronic kidney disease; CLD, chronic liver disease; CRD, chronic respiratory disease.

coding for pneumonia[28 29] and potential errors of omission and commission of underlying comorbidities. The most recent national audit of hospitalised cases of CAP, conducted on behalf of the British Thoracic Society,[27] compared prospectively identified pneumonia cases with HES data. The accuracy of a diagnosis of CAP at the national level varied widely between 124 participating hospitals. The median accuracy across all participating institutions was 65.6% (IQR 52.8% to 79.3%.[27] The most common reason for exclusion of the diagnosis of CAP was the absence of new radiographic changes on chest X-ray. It is therefore possible that some admissions for 'pneumonia' may in fact have been as a result of other conditions, including heart failure or decompensated underlying comorbidity. However, coding accuracy in HES has improved ever since the roll-out of financial incentives that are based on diagnosis and procedure codes.[30] Additionally, because of further reporting requirements in the NHS, coding completeness has increased substantially.[17 20] HES continues to be used in multiple studies for studying disease epidemiology and healthcare resource use in the NHS.[17 20] We chose to interrogate HES from financial year 2012/2013 when data reliability improved, following the introduction of payment by results.[30]

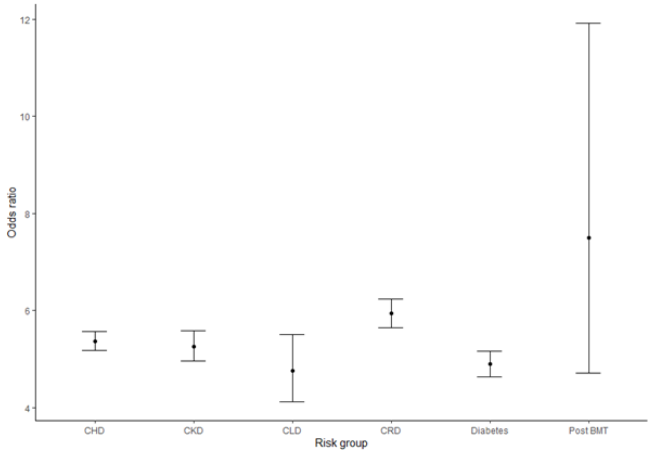


Figure 3 Adjusted ORs for mortality in each clinical risk group for those who developed hospitalised CAP compared with those who did not (online supplemental table 2). BMT, bone marrow transplant; CAP, community-acquired pneumonia; CHD, chronic heart disease; CKD, chronic kidney disease; CLD, chronic liver disease; CRD, chronic respiratory disease.

Due to the nature of coding in HES, it was not possible to fully differentiate between hospitalised CAP and HAP, although we did exclude all cases of pneumonia with onset occurring over 48 hours after admission. Patients admitted with a comorbidity diagnosis might be at an increased risk of developing HAP compared with those who have not been admitted with an underlying illness. Therefore, it is possible that presence of HAP within the data set may have resulted in overascertainment for all the outcomes measured.

Since we included patients whose comorbidity was coded in either the primary or secondary position, it is probable that a large proportion of patients will have multiple comorbidities.[26] The risk of developing CAP increases when patients have several risk factors, a phenomenon known as 'risk stacking'.[11 31] In order to correct for these confounders, we used PSM to compare the outcome variables between the two categories.[32] The propensity scoring method has been used in other HES and CAP studies.[8 33] We have not assessed the effect of multiple comorbidities in this study, but it is likely that the healthcare costs incurred, and in-hospital mortality would be elevated in patients with multiple risk factors. In a study of the impact of risk stacking on mortality from pneumococcal infections in adults, each additional risk factor increased the risk of mortality by 55%.[34] HES data does not include data on other known risk factors for CAP, for example, smoking, alcohol abuse and use of proton pump inhibitors. It is therefore unclear whether these additional risk factors or a worsening clinical condition rather than an episode of hospitalised CAP are predictors of a worse outcome. A prospective study would be needed to establish the relative importance of these factors.

Frailty increases the likelihood of hospitalisation with CAP.[35] For example, in one study using the FRAIL index[36] (FRAIL is a five-item scale of fatigue, resistance, ambulation, illnesses and weight loss) a score >3 was associated with an increase in duration of stay in hospital and an increase in in-hospital mortality.[37] Since prevalidated frailty scores such as the FRAIL index are not recorded in the HES database, we were unable to adjust for frailty. Another potential confounder is chronic disease severity. Based on the data extracted as part of this study, it was not possible to determine the contribution of the chronic disease severity or the degree of frailty to the clinical and financial burden consequent on an episode of hospitalised CAP.[38] It is unclear whether an episode of CAP requiring hospitalisation per se alters the course of a chronic disease, or is in fact a marker of worsening disease severity or increasing frailty resulting in a worse outcome. Millett *et al*[18] investigated the factors associated with hospitalisation for CAP among adults aged ≥65 years in England, using linked primary and secondary care data sets; the Clinical Practice Research Datalink[39] and HES. After adjusting for age, sex and year, they found frailty factors (inability to self-care, mobility problems, tiredness and a history of falling) did not increase the risk of hospitalisation for CAP. The authors did note that frailty factors and smoking were suboptimally recorded by general practitioners, preventing a full assessment of the role of these factors and highlighting the need for better data on these parameters.

Finally, it was not possible to account for loss of patients from the study due to mortality outside of the hospital setting. The HES data warehouse only includes records of patients' contacts with hospitals in England. The available data would therefore only reflect death in hospital during an admission, rather than longer-term mortality. The increased likelihood of dying for patients who have had an episode of hospitalised CAP presented in this analysis may therefore be an underestimate. By linking the HES database to Office for National Statistics central mortality data, it would be possible to estimate mortality without restricting the analysis to those patients who died in hospital.

Meaning of the study: implications for clinicians and policymakers

This study suggests the adverse effect of an episode of hospitalised CAP for those with underlying comorbidities, both for the individual patient and for the NHS. Quantification of these effects in patients with underlying comorbidities could be useful for policy makers when deciding about preventative measures.

Unanswered questions and future research

This study examined the impact of an episode of hospitalised CAP on patients with at least one of six selected underlying comorbidities over a period of 3 years. The longer-term duration of the impact of an episode of hospitalised CAP on healthcare utilisation and mortality for patients with the six comorbidities studied has not been determined. The study did not include patients with other comorbidities, including immunosuppression and functional asplenia. Future research could address these unanswered questions.

CONCLUSION

Following an admission to hospital for CAP, the impact on the patient and the healthcare system is significant and can continue for at least 3 years following the initial diagnosis. While there is variation by comorbidity, the risk of admission to hospital is significantly increased for at least 3 years after the episode of CAP, with increased pressure on hospital beds and also increased hospital costs. Furthermore, the likelihood of mortality was considerably raised in all comorbidities studied. This highlights the importance of prevention of CAP in these patient populations.

Acknowledgements The authors gratefully acknowledge the input from K Kishore of Health iQ Ltd for help with the design of the study, provision of the data and ongoing support.

Contributors JC, DJ, JDC, QJ, AV, HM and MS for study conception and design; APJR for data acquisition; QJ, AJPR and AV for statistical analysis; JC, MS, DJ and AV drafted the initial versions of article; all authors contributed to data interpretation, and read, commented on and approved the final version.

Funding This research was sponsored by Pfizer UK Ltd. Pfizer provided funding for the following: Hospital Episode Statistics (HES) data processing and analysis by Health iQ Ltd under an National Health Service digital re-use agreement and journal publication charges.

Competing interests All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following: JDC has received research grant support from AstraZeneca, Pfizer, GlaxoSmithKline, Boehringer Ingelheim and Bayer Healthcare and has participated in advisory boards or lectures for Griffols, AstraZeneca, Pfizer, Napp, Boehringer Ingelheim and Bayer Healthcare. He also received remuneration from Pfizer for services as a member of the Steering Committee for this study. MS has received personal fees from GSK, Pfizer, AstraZeneca and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards (outside the scope of the submitted work). She has also worked as a contractor for Pfizer and received remuneration from Pfizer for services as a member of the Steering Committee for this study. JC, DJ, QJ, AV, GE and HM are full-time employees and shareholders of Pfizer; no other relationships or activities that could appear to have influenced the submitted work. APJR reports other from Health iQ and grants from Pfizer, outside the submitted work; and at the present time, I am providing consultancy work to Health iQ Ltd (UK), which works with clients across the life sciences industry.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer-reviewed.

Data availability statement Data are available upon reasonable request from corresponding author.

REFERENCES

1 Chalmers J, Campling J, Ellsbury G, *et al*. Community-Acquired pneumonia in the United Kingdom: a call to action. *Pneumonia* 2017;9:15.

2 Lim WS, Baudouin SV, George RC, *et al*. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009;64 Suppl 3:iii1–55.
3 Chalmers JD, Mandal P, Singanayagam A, *et al*. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. *Intensive Care Med* 2011;37:1409–20.
4 van Hoek AJ, Miller E. Cost-Effectiveness of vaccinating immunocompetent ≥65 year olds with the 13-Valent pneumococcal conjugate vaccine in England. *PLoS One* 2016;11:e0149540.
5 Mangen M-JJ, Huijts SM, Bonten MJM, *et al*. The impact of community-acquired pneumonia on the health-related quality-of-life in elderly. *BMC Infect Dis* 2017;17:208.
6 Andrade LF, Saba G, Ricard J-D, *et al*. Health related quality of life in patients with community-acquired pneumococcal pneumonia in France. *Health Qual Life Outcomes* 2018;16:28.
7 Rae N, Finch S, Chalmers JD. Cardiovascular disease as a complication of community-acquired pneumonia. *Curr Opin Pulm Med* 2016;22:212–8.
8 Rozenbaum MH, van Hoek AJ, Fleming D, *et al*. Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. *BMJ* 2012;345:e6879.
9 van Hoek AJ, Andrews N, Waight PA, *et al*. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. *J Infect* 2012;65:17–24.
10 GOV.UK. Immunisation Against Infectious Diseases. In: *Pneumococcal: the green book, chapter 25*, 2018. https://www.gov.uk/government/publications/pneumococcal-the-green-book-chapter-25
11 Shea KM, Edelsberg J, Weycker D, *et al*. Rates of pneumococcal disease in adults with chronic medical conditions. *Open Forum Infect Dis* 2014;1:ofu024.
12 Choudhury G, Mandal P, Singanayagam A, *et al*. Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia--a propensity-adjusted analysis. *Clin Microbiol Infect* 2011;17:1852–8.
13 Masterton RG, Galloway A, French G, *et al*. Guidelines for the management of hospital-acquired pneumonia in the UK: report of the Working Party on hospital-acquired pneumonia of the British Society for antimicrobial chemotherapy. *J Antimicrob Chemother* 2008;62:5–34.
14 NHS-Choices. A simple guide to payment by results. gateway Ref: 18135. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/213150/PbR-Simple-Guide-FINAL.pdf
15 (PSSRU), PSRU. Hospital and community health services (HCHS) index, 2015. Available: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php?file=sources-of-information
16 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
17 Thorrington D, Andrews N, Stowe J, *et al*. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. *BMC Med* 2018;16:13.
18 Millett ERC, De Stavola BL, Quint JK, *et al*. Risk factors for hospital admission in the 28 days following a community-acquired pneumonia diagnosis in older adults, and their contribution to increasing hospitalisation rates over time: a cohort study. *BMJ Open* 2015;5:e008737.
19 van Hoek AJ, Andrews N, Waight PA, *et al*. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. *J Infect* 2012;65:17–24.
20 Campling J, Jones D, Chalmers JD, *et al*. The impact of certain underlying comorbidities on the risk of developing hospitalised pneumonia in England. *Pneumonia* 2019;11:4.
21 Dela Cruz CS, Wunderink RG, Christiani DC, *et al*. Future research directions in pneumonia. NHLBI Working Group report. *Am J Respir Crit Care Med* 2018;198:256–63.
22 Wunderink RG, Waterer G. Advances in the causes and management of community acquired pneumonia in adults. *BMJ* 2017;358:j2471.
23 Tralhão A, Póvoa P. Cardiovascular events after community-acquired pneumonia: a global perspective with systematic review and meta-analysis of observational studies. *J Clin Med* 2020;9
24 Wagenvoort GHJ, Sanders EAM, de Melker HE, *et al*. Long-Term mortality after IPD and bacteremic versus non-bacteremic pneumococcal pneumonia. *Vaccine* 2017;35:1749–57.
25 Cafiero-Fonseca ET, Stawasz A, Johnson ST, *et al*. The full benefits of adult pneumococcal vaccination: a systematic review. *PLoS One* 2017;12:e0186903–e.
26 Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 2012;67:71–9.
27 Lim WS LH. British Thoracic Society national audit report: adult community acquired pneumonia 2018-2019 national audit period: 1December 2018-31 January 2019 British Thoracic Society Reports; 2019: 1–13.
28 Daniel P, Bewick T, Welham S, *et al*. Adults miscoded and misdiagnosed as having pneumonia: results from the British Thoracic Society pneumonia audit. *Thorax* 2017;72:376–9.
29 Herbert A, Wijlaars L, Zylbersztejn A, *et al*. Data resource profile: Hospital episode statistics admitted patient care (HES APC). *Int J Epidemiol* 2017;46:1093–1093i.
30 Health Do. Health and social care act 2012 The Stationery Office; 2012.
31 Caliendo M, Kopeinig S. Some practical guidance for the implementation of propensity score matching. *J Econ Surv* 2008;22:31–72.
32 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.
33 Eckmann C, Wasserman M, Latif F, *et al*. Increased Hospital length of stay attributable to *Clostridium difficile* infection in patients with four co-morbidities: an analysis of hospital episode statistics in four European countries. *Eur J Health Econ* 2013;14:835–46.
34 Morton JB, Morrill HJ, LaPlante KL, *et al*. Risk stacking of pneumococcal vaccination indications increases mortality in unvaccinated adults with *Streptococcus pneumoniae* infections. *Vaccine* 2017;35:1692–7.
35 Torres OH, Muñoz J, Ruiz D, *et al*. Outcome predictors of pneumonia in elderly patients: importance of functional assessment. *J Am Geriatr Soc* 2004;52:1603–9.
36 Aprahamian I, Cezar NOC, Izbicki R, *et al*. Screening for frailty with the FRAIL scale: a comparison with the phenotype criteria. *J Am Med Dir Assoc* 2017;18:592–6.
37 Chong E, Ho E, Baldevarona-Llego J, *et al*. Frailty and Risk of Adverse Outcomes in Hospitalized Older Adults: A Comparison of Different Frailty Measures. *J Am Med Dir Assoc* 2017;18:638.e7–638.e11.
38 Millett ERC, Quint JK, Smeeth L, *et al*. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. *PLoS One* 2013;8:e75131.
39 Sanz JC, Rodríguez-Avial I, Ríos E, *et al*. Recurrent pneumococcal invasive disease in the region of Madrid during a five-year period. *Infection* 2014;42:475–83.

Taylor & Francis
Taylor & Francis Group

Expert Review of Vaccines

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierv20

A review of evidence for pneumococcal vaccination in adults at increased risk of pneumococcal disease: risk group definitions and optimization of vaccination coverage in the United Kingdom

James Campling, Andrew Vyse, Hui-Hsuan Liu, Hannah Wright, Mary Slack, Ralf-Rene Reinert, Mark Drayson, Alex Richter, Dave Singh, Gavin Barlow, George Kassianos & Gillian Ellsbury

To cite this article: James Campling, Andrew Vyse, Hui-Hsuan Liu, Hannah Wright, Mary Slack, Ralf-Rene Reinert, Mark Drayson, Alex Richter, Dave Singh, Gavin Barlow, George Kassianos & Gillian Ellsbury (2023) A review of evidence for pneumococcal vaccination in adults at increased risk of pneumococcal disease: risk group definitions and optimization of vaccination coverage in the United Kingdom, Expert Review of Vaccines, 22:1, 785-800, DOI: 10.1080/14760584.2023.2256394

To link to this article: https://doi.org/10.1080/14760584.2023.2256394

EXPERT REVIEW OF VACCINES
2023, VOL. 22, NO. 1, 785–800
https://doi.org/10.1080/14760584.2023.2256394

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

A review of evidence for pneumococcal vaccination in adults at increased risk of pneumococcal disease: risk group definitions and optimization of vaccination coverage in the United Kingdom

James Campling[a], Andrew Vyse[a], Hui-Hsuan Liu[b], Hannah Wright[a], Mary Slack[c], Ralf-Rene Reinert[d], Mark Drayson[e], Alex Richter[e], Dave Singh[f], Gavin Barlow[g], George Kassianos[h,i] and Gillian Ellsbury[a]

[a]Medical Affairs, Pfizer Ltd, Walton Oaks, UK; [b]Real-World Evidence, OPEN Health, London, UK; [c]School of Medicine & Dentistry, Griffith University, Southport, Queensland, Australia; [d]Medical Affairs, Pfizer Inc, Pfizer, Paris, France; [e]Institute of Immunology and Immunotherapy, Medical School, University of Birmingham, Edgbaston, Birmingham, UK; [f]Division of Immunology, Immunity to Infection and Respiratory Medicine, University of Manchester, Manchester, UK; [g]Hull York Medical School, University of York, York, UK; [h]Royal College of General Practitioners, London, UK; [i]British Global & Travel Health Association, Bath, UK

ABSTRACT

Introduction: Pneumococcal disease (PD) significantly contributes to morbidity and mortality, carrying substantial economic and public health burden. This article is a targeted review of evidence for pneumococcal vaccination in the UK, the definitions of groups at particular risk of PD and vaccine effectiveness.

Areas covered: Relevant evidence focusing on UK data from surveillance systems, randomized controlled trials, observational studies and publicly available government documents is collated and reviewed. Selected global data are included where appropriate.

Expert opinion: National vaccination programs have reduced the incidence of vaccine-type PD, despite the rising prominence of non-vaccine serotypes in the UK. The introduction of higher-valency conjugate vaccines provides an opportunity to improve protection against PD for adults in risk groups. Several incentives are in place to encourage general practitioners to vaccinate risk groups, but uptake is low-suboptimal particularly among at-risk individuals. Wider awareness and understanding among the public and healthcare professionals may increase vaccination uptake and coverage. National strategies targeting organizational factors are urgently needed to achieve optimal access to vaccines. Finally, identifying new risk factors and approaches to risk assessment for PD are crucial to ensure those at risk of PD can benefit from pneumococcal vaccination.

ARTICLE HISTORY
Received 15 July 2023
Accepted 4 September 2023

KEYWORDS
Clinical risk group; community acquired pneumonia; epidemiology; invasive pneumococcal disease; pneumococcal conjugate vaccine; pneumococcal polysaccharide vaccine; vaccination guidelines; vaccination uptake

1. Introduction

Streptococcus pneumoniae (pneumococcus) infection is a leading cause of morbidity and mortality worldwide [1–3]. Diseases caused by pneumococci range from mucosal infections including otitis media, sinusitis and non-bacteremic pneumonia to life-threatening pneumonia and invasive pneumococcal disease (IPD), most commonly presenting as bacteremic pneumonia, but also sepsis and meningitis. In this review, the term pneumococcal disease (PD) refers to a wider concept of pneumococcal infections (including IPD, community-acquired pneumonia [CAP] caused by pneumococcus, and pneumococcal pneumonia).

The burden of PD is considerable and leads to long-term clinical and economic impact on patients and the healthcare system in the UK. The pneumococcus was recently reported to be the leading pathogen for respiratory hospitalization among adults aged ≥65 years in England (prior to the COVID-19 pandemic) [4]. The clinical burden of PD is notably high among individuals with certain underlying comorbidities [5–10] and increases with age [5]. The increased clinical burden not only reflects higher healthcare resource utilization and costs, but also markedly impacts patients' quality of life [8,11]. Indeed, the presence of other common pandemic viral pathogens including SARS-CoV-2, respiratory syncytial virus and influenza viruses substantially contributed to the epidemiological and clinical burden of respiratory disease, potentially through viral-bacterial interaction [12–14]. However, it was recently reported that non-COVID-19 respiratory infections were still the major cause of acute lower respiratory tract infections (LRTIs) hospitalizations throughout the COVID-19 pandemic [15].

Although the burden of PD has been reported, it is likely to be an underestimate [16]. The causal pathogen is frequently not confirmed in many patients with respiratory tract infections managed in primary and secondary care. As such, under-reporting together with potential under-ascertainment of PD may contribute to invalid estimates of disease prevalence, thus underestimating the true burden of PD [16].

CONTACT James Campling james.campling@pfizer.com Medical Affairs, Pfizer Ltd, Walton Oaks, Dorking Road, Walton-on-the-Hill, Tadworth, Surrey KT20 7NS, UK
This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14760584.2023.2256394

Article highlights

- National vaccination programs have helped reduce the incidence of vaccine-type PD in the UK, but there have been concerns on the emerging incidence of PD caused by non-vaccine serotypes (i.e. non-PCV13, non-PPV23).
- The introduction of higher-valency conjugate vaccine options (i.e. PCV15, PCV20) within the UK provides an opportunity to help address the challenges associated with serotypes replacement. These new pneumococcal conjugate vaccines provide broader serotype coverage, as these contain new serotypes (in addition to PCV13) responsible for PD cases in the UK, particularly in adults aged ≥65 years, and thus potentially offering improved and direct protection against PD for adults in risk groups.
- Two new higher-valency pneumococcal conjugate vaccines, PCV15 and PCV20, are licensed and available in the UK; both vaccines have been introduced into vaccination guidelines in the US and some European countries. In the UK, the JCVI has now recommended that PCV20 should be used for adults in risk groups.
- Within the risk categories defined in the guidelines, occupational risk factors are limited to metal workers and welders. However, other professional activities involving close contact with people with respiratory disease could be considered as relevant for pneumococcal vaccination (e.g. individuals working in residential care homes, elderly care wards, oil rigs, prisons, those living in inner city high pollution settings and healthcare workers), since they are at higher risk of exposure to respiratory infections.
- The effect of risk stacking (defined as the increase in risk of PD with the accumulation of concurrent at-risk conditions) has not yet been formally considered and should be taken into consideration when making recommendations for pneumococcal vaccines. Reassessment of risk groups deemed eligible for pneumococcal vaccination may be beneficial for prevention of PD.
- Several unmet needs and challenges for the management of PD have been identified, including the resurgence of PD cases post COVID-19 restrictions, the continuous pressure on the National Healthcare Service's capacity for delivery of patient care, and global concerns on antimicrobial resistance. Some of these issues may be addressed through pneumococcal vaccination.
- Available data suggest that the PPV23 uptake rate varies by risk factor and remains low particularly in adults with risk conditions. The PPV coverage report published by the UK Health Security Agency estimated that the PPV23 coverage up to 2021 in eligible individuals (aged 2–64 years) ranged between 38.5% for those with chronic liver disease and 56.0% for those with chronic respiratory disease, while uptake rate was 70.7% for those with cochlear implants.
- Barriers affecting vaccination uptake include vaccine hesitancy (inadequate knowledge, low awareness, negative attitudes) toward vaccinations among patients and some GPs and patient access (convenience) to routine vaccinations. We also speculate that low vaccination uptake may be attributable to organizational factors.
- Although various incentives are in place to encourage GPs to vaccinate patients at risk of PD, national strategies are still needed to optimize vaccine uptake and patient access to vaccines may be informed by learnings from vaccine delivery approaches implemented during the COVID-19 pandemic.

PD predominantly affects older adults and young children [3]. Individuals with specific clinical conditions (Table 1) are at elevated risk of PD and PD-associated morbidity and mortality [7,8,17–21]. These risk groups have been targeted for vaccination to reduce the burden of PD [3]. In the UK, five pneumococcal vaccines are authorized for protection against different serotypes, including pneumococcal polysaccharide vaccine (PPV; PPV23) and pneumococcal conjugate vaccine (PCV; including PCV10, PCV13, PCV15, PCV20) [3] (Table 2). Currently, only four licensed vaccines are available, as PCV10 is no longer marketed and in use. Since 2003, PPV23 has been routinely offered to all adults aged ≥65 years and clinical risk groups aged ≥2 years. While in 2010, PCV13 replaced PCV7 (introduced in 2006) for routine infant immunization. Indeed, in the UK, PCV13 is only recommended for adults with very-high-risk conditions (i.e. severely immunocompromised individuals defined as: patients with bone marrow transplant, acute and chronic leukemia, multiple myeloma or genetic disorders affecting the immune system [e.g. IRAK-4, NEMO], and people living with human immunodeficiency virus [PLWHIV] as described in the British HIV Association [BHIVA] guidelines) [3].

In addition to directly protecting children, the sequential introduction of PCV7 and PCV13 into the infant immunization program has induced valuable indirect protection for older age groups and consequently reduced the incidence of vaccine-type (VT)-PD across the full age range [25]. However, the subsequent emergence of non-PCV13 serotypes and concerns about the extent of protection conferred by PPV23 suggested a need to now consider the new higher-valency PCVs for optimal control and prevention of PD among UK adults with underlying comorbidities [17,26]. In late 2021 and early 2022, two new higher-valent vaccines, PCV15 and PCV20, were approved respectively within the UK and licensed for use in adults aged ≥18 years for prevention of PD [22,24]. In light of the benefits of higher-valency PCVs and the evolving epidemiology of PD, the Joint Committee on Vaccination and Immunisation (JCVI) now recommends to include PCV20 for all adults in risk groups and recognizes that PCV20 is likely to prevent more disease than PPV23 and that waning of immunity may occur at a slower rate [23].

The advantages of PCVs over PPVs have been extensively reviewed in the literature [27–30]. Compared with PPVs, PCVs are considered more effective against PD and also impact nasopharyngeal carriage, thus preventing onward transmissions and inducing direct protection [28,30,31]. While PPVs and PCVs contain the same capsular polysaccharides, the polysaccharides within PCVs are conjugated to a carrier protein which provides durable and robust immunogenicity and the ability of generating immunological memory [27–29]. New vaccine candidates are in development, including PCV21, PCV24, and PCV30 (Table 2). Such PCVs will provide direct protection against PD for adults in risk groups against a broader range of serotypes [32]. Higher-valency PCVs that include similar (or higher) numbers of serotypes to PCV20 will likely be attractive options. However, the optimal pneumococcal vaccine will change over time as the epidemiology (e.g. disease incidence, prevalence and serotype behaviors) and vaccine technologies evolve. Alongside PCVs with >20 serotype coverage in development, next-generation whole-cell vaccines and protein-based vaccines are also in early development and whilst currently unproven, theoretically have potential to protect against all serotypes and to minimize possible immune escape [33,34]. Whilst elimination of nasopharyngeal colonization (a central precursor for PD) and inducing indirect protection is an advantage associated with both new and existing conjugate vaccines, aspiring to achieve complete elimination of pneumococcal carriage with future vaccines could in fact lead to the risk of subsequent replacement with other microorganisms that can cause disease, and this may be an undesirable consequence [33,34]. Striking a balance between benefit (e.g. eliminating carriage of those serotypes with most

Table 1. Clinical risk groups recommended for pneumococcal vaccination in the Green Book [3].

	Risk group definitions
Chronic respiratory disease	• COPD including chronic bronchitis and emphysema, bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, and BPD • Children with respiratory conditions caused by aspiration or a neurological disease with a risk of aspiration • Severe asthma requiring continuous use of systemic steroids
Chronic heart disease	Ischemic heart disease, congenital heart disease, hypertension with cardiac complications, and chronic heart failure
Chronic kidney disease	Nephrotic syndrome, chronic kidney disease at stages 4 and 5, and those on kidney dialysis or with kidney transplantation
Chronic liver disease	Cirrhosis, biliary atresia, and chronic hepatitis
Diabetes	Diabetes mellitus requiring insulin or anti-diabetic medication, excluding diabetes that is diet controlled
Immunosuppression	• Immunosuppression caused by disease or treatment (e.g. chemotherapy, bone marrow transplant, asplenia or splenic dysfunction, complement disorder, HIV infection at all stages, multiple myeloma, or genetic disorders affecting the immune system (e.g. IRAK-4, NEMO) • Individuals (any age) on or likely to be on systemic steroids for more than a month at a prednisolone equivalent dose of ≥20 mg per day or children (under 20 kg) on a dose of ≥1 mg per kg per day
Asplenia or splenic dysfunction	Conditions that may lead to splenic dysfunction (e.g. homozygous sickle cell disease and celiac syndrome)
Cochlear implants	Post cochlear implants
CSF leaks	Leakage of CSF caused by trauma or major skull surgery (excluding CSF shunts)
Occupational risk	Continuous occupational exposure to metal fume (welding)

The table was adapted from Green Book [3].
BPD, bronchopulmonary dysplasia; COPD, chronic obstructive pulmonary disease; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus

propensity for disease) and risk (i.e. increasing the likelihood of replacement disease) is imperative, albeit challenging, in vaccine development.

This targeted literature review aimed to describe the current UK landscape in relation to the identification and vaccination of individuals at risk of PD and to identify any opportunities for optimization of vaccine delivery and uptake.

2. Evidence of pneumococcal vaccine effectiveness and impact against PD

In the UK, four licensed vaccines (PPV23 and PCVs) are currently available for use to help prevent PD [3] (Table 2). The efficacy of PCV13 against PD in adults was based on data from the CAPiTA trial (Community-Acquired Pneumonia immunization Trial in Adults), one of the largest adult vaccination randomized control trials containing the most robust data available for assessing efficacy of PCV13 against IPD/CAP in older adults [31]. Substantial efficacy of PCV13 against IPD and pneumococcal CAP was demonstrated in adults aged ≥65 years, with efficacy sustained up to five years without evidence of waning [31,35] (**Table S1**). A post-hoc analysis of CAPiTA also showed significant and persistent efficacy of PCV13 against VT-CAP in at-risk older adults [36].

Evidence demonstrating PPV23 vaccine effectiveness against PD remains inconsistent (**Table S1**). Andrews et al. (2012) and Djennad et al. (2018) showed that PPV23 provided only moderate short-term protection against IPD in UK older adults (aged ≥65 years) and achieved no impact on IPD incidence at the population level. Effectiveness of PPV23 varied by serotype and waned within 2 years after vaccination [37,38]. Whilst there is evidence demonstrating that PPV23 may provide some limited protection against hospitalized CAP in UK adults aged ≥16 years, this was not the case when adults aged ≥65 years were specifically considered [39]. Overall, it is widely accepted that PPV23 provides some limited short-term protection against IPD among adults aged ≥65 years, without significant impact on IPD at the population level [37–42]. More robust evidence is needed to demonstrate PPV23's ability to provide meaningful protection against CAP in UK adults in risk groups [40–43].

The introduction of PCV13 into the UK national routine infant immunization program has considerably reduced the incidence of PCV13 VT-IPD in older age groups through direct and indirect effects; however, the emergence of non-PCV13 serotypes as a consequence of vaccine driven serotype replacement remains a major concern particularly in adults [26,44]. Such serotype replacement has also been reported in France, Germany and Sweden, with widespread concerns that initial substantial vaccine impact is now being eroded [45].

Collectively, such serotype replacement suggests that more effective higher-valent pneumococcal vaccines now need to be considered to replace PPV23 to better protect those UK adults considered at increased risk of PD [46]. The recent JCVI recommendation to include PCV20 for adults aged ≥65 years and all adults in risk groups is therefore timely, with the potential to consider other candidate higher-valency pneumococcal vaccines that are currently in development (e.g. PCV21, PCV24, PCV30) [47–50] in the future should they be licensed (Table 2).

Currently, serotype 3 continues to be responsible for a considerable burden of PD in UK adults [26,51]. Although there is evidence that PCV13 provides some direct protection against serotype 3 PD [42,52–55], its use in UK adults and those in risk groups has been very limited, with PPV23 being the primary vaccine used in this context. The recent recommendation of PCV20 to be included in the routine vaccination program for adults aged ≥65 years and all adults in risk groups may now help address this [23]. The limited impact of PCV13 on serotype 3 carriage further indicates that any indirect protection from pediatric PCV13 programs against serotype 3 disease is compromised [56]. This is likely attributed to the unique physiological properties of serotype 3, such as its thick capsule and surface electronegativity, and its ability to confer protection against host factors [57]. These features are considered to facilitate the ability of serotype 3 to cause disease and escape immune responses [57]. Improving the ability of

Table 2. Details of licensed pneumococcal vaccines and next-generation vaccines in development.

Vaccine	Manufacturer	Serotype coverage	UK recommendation [3]
Licensed pneumococcal vaccines in the UK			
PPV23 (PNEUMOVAX®23)	Merck Sharp & Dohme	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9 V, 10A, 11A, 12F, 14, 15B, 17F,18C, 19A, 19F, 20, 22F, 23F, and 33F	• Licensed for use in adults aged ≥65 years, people aged ≥2 years with at-risk conditions* • Revaccination (every five years) recommended for individuals with certain risk conditions (i.e. asplenia, splenic dysfunction, or CKD) • Revaccination currently not recommended for any other risk groups
PCV20 (APEXXNAR®)	Pfizer	1, 3, 4, 5, 6A, 6B, 7F, 8, 9 V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F	• Licensed for prevention of IPD and pneumonia caused by *Streptococcus pneumoniae* in individuals aged ≥18 years [22] • Recommended for routine adult pneumococcal immunization program; available for all older adults aged ≥65 years and those aged <65 years in clinical risk groups* [23] • The need for revaccination not yet established
PCV15 (VAXNEUVANCE®)	Merck Sharp & Dohme	1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C,19A, 19F, 22F, 23F, and 33F	• Licensed for prevention of IPD and pneumonia caused by *Streptococcus pneumoniae* in infants, children and adolescents from 6 weeks to <18 years of age and individuals aged ≥18 years [24] • The need for revaccination not yet established
PCV13 (PREVENAR13®)	Pfizer	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	• Licensed for Childhood Immunization Program, people aged ≥65 years, and clinical risk groups* • Revaccination not recommended for routine immunization • Additional dose may be recommended for individuals with severe immunocompromise*
PCV10 (SYNFLORIX®)	GSK	1, 4, 5, 6B, 7F, 9 V, 14, 18C, 19F, and 23F	• Not currently recommended in the National Immunization Program • Not currently available, marketed or in use
Next-generation pneumococcal vaccines in development			
PCV30+ (VAX-31)**	VAXCYTE, Inc.	In pre-clinical development	• Not yet commercially available
PCV24 (namely AFX3772)†	GSK	1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9 V, 9N, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23F, and 33F	• Not yet commercially available
PCV21‡	Merck Sharp & Dohme	3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B	• Not yet commercially available

*Risk conditions defined in Green Book (2020) include chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, diabetes, immunosuppression, asplenia or splenic dysfunction, cochlear implants, cerebrospinal fluid leaks, and occupational risk (welding). High-risk conditions include asplenia, splenic dysfunction, and immunocompromising conditions caused by bone marrow transplant, acute and chronic leukemia, multiple myeloma, or genetic disorders (e.g. IRAK-4 or NEMO defects).

**Behrens C, et al. Development of a next generation 30+ Valent Pneumococcal Conjugate Vaccine (VAX-XP) using site-specific carrier protein conjugation. Open Forum Infectious Diseases. 2021;8(Suppl 1):S615. doi: 10.1093/ofid/ofab466.1241

†Chichili GR, et al. Phase 1/2 study of a novel 24-valent pneumococcal vaccine in healthy adults aged 18 to 64 years and in older adults aged 65 to 85 years. Vaccine. 2022;40(31):4190–4198. doi: 10.1016/j.vaccine.2022.05.079

‡Platt H, et al. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomized, double-blind, active comparator-controlled, multicentre, US-based trial. Lancet Infect Dis. 2023;23(2):233–246. doi: 10.1016/S1473–3099(22)00526–6

CKD, chronic kidney disease; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; UK, United Kingdom

pneumococcal vaccines to protect against both serotype 3 disease and carriage may be considered in the future directions of vaccine development.

3. Current pneumococcal vaccine uptake

3.1. Vaccine uptake in risk groups

In England, it was estimated that 12.7% ($n = 6,412,685/50,479,300$) of the general population had one or more risk factors (as defined in the Green Book), and 44.8% ($n = 3,780,552/8,434,300$) in those aged ≥65 years had one or more risk factors in 2009 [6]. In 2009, the estimated proportion of the population in risk groups (aged ≥2 years) ranged from 0.01% ($n = 3,584$) for those with cochlear implants to 6.2% ($n = 3,114,844$) for those with chronic heart disease (CHD) [6].

The number of at-risk individuals has increased since 2009, particularly in those aged ≥65 years. In 2021, a total of 10,601,410 adults aged ≥65 years were eligible for PPV23 vaccination based on registration records with general practitioners (GPs), and the estimated number of at-risk individuals aged 2–64 years ranged from 5,294 for those with cerebrospinal fluid (CSF) leaks to 1,487,496 for those with diabetes [58].

Moreover, PLWHIV are at greater risk of developing IPD than the general population [59,60]. National surveillance

undertaken in England between 1999 and 2017 showed the incidence of IPD was significantly higher among PLWHIV compared than the general population (incidence rate ratio: 14.6, 95% confidence interval [CI]: 13.9, 15.4, $p < 0.001$) [60]. Of 1,453 PLWHIV who developed IPD during the study period, 70.0% developed IPD after ≥3 months of human immunodeficiency virus (HIV) diagnosis. Despite treatment with effective antiretrovirals, PLWHIV had a 4.5-fold higher rate of IPD incidence than the general population. Furthermore, 59.0% of IPD cases were caused by 11 PPV23 serotypes not covered by PCV13 (8, 12F, 9N, 10A, 22F, 15B/C, 11A, 15B, 17F, and 33F) [60]. It should be noted that these serotypes are included in PCV20 with the exception of 9N and 17F. These data indicate that higher-valent pneumococcal vaccines could offer broader protection against PD and highlight the importance of continuing to offer pneumococcal vaccines to PLWHIV according to the national recommendations.

The 2021 PPV23 coverage report published by the UK Health Security Agency (UKHSA) suggested that the rate of pneumococcal vaccination (PV) uptake in eligible adults was suboptimal, particularly among those with risk conditions [58]. PCV13 coverage in those UK adults with very-high-risk conditions is currently not recorded. In England, PPV23 coverage was 70.6% in all adults aged ≥65 years who were vaccinated at any time up to March 2021. Data by age group showed that PPV23 coverage in adults aged 65 years was only 34.2% and increases with age (from 45.2% in adults aged 66 years to 83.0% in adults aged ≥75 years). These data indicate that two thirds of individuals are not immunized in the year when they become eligible but in the subsequent years. Increasing vaccine coverage in older age groups suggests that opportunistic vaccination of PPV23 continues to be offered to adults aged ≥66 years in primary care [58], highlighting the importance of GP's awareness of eligibility for PPV23 and responsibility for routine monitoring of vaccine coverage/uptake. Furthermore, PPV23 coverage in at-risk individuals aged 2–64 years varied by risk category, ranging from 38.5% (chronic liver disease [CLD]) to 70.7% (cochlear implants) [58]. Lower levels of vaccine uptake were observed in eligible individuals with certain risk conditions, such as CSF leaks (38.9% of 5,294 eligible individuals), asplenia or splenic dysfunction (39.1% of 342,938 eligible individuals), immunosuppression (39.1% of 1,034,001 eligible individuals), and CHD (43.3% of 835,750 eligible individuals) [58]. Overall, PPV23 coverage was below the national standard target of 75% [61]. In those with asplenia, splenic dysfunction or chronic kidney disease (CKD), PPV23 coverage is expected to achieve 100% as they should be vaccinated every five years [3], but the uptake is low. Differences in PPV23 coverage across risk groups were likely attributable to variations in clinicians' awareness of eligibility of PPV23 according to clinical indication [58]. Despite several automated systems used to identify patients in primary and secondary care in current practice, there are some barriers to be addressed to increase vaccination uptake, including vaccine hesitancy relating to awareness of and attitudes (complacency, trust) toward vaccinations and access (convenience) to routine vaccinations [62].

Compared with vaccine coverage data published by the UKHSA, uptake rates among risk groups reported in the literature were lower [63,64] (**Table S2**). For example, Matthews et al. (2020) reported that in the UK, the rate of vaccination in risk groups rose from 13.6% to 32.0% between 2011 and 2015 [64]. Individuals with CHD, CKD, CLD, chronic respiratory disease (CRD), or diabetes were significantly less likely to be vaccinated than those with immunosuppression [64]. Vaccination uptake also varied by risk group and the lowest uptake rate included individuals with CSF leaks/shunts [63,64]. Factors influencing PV uptake were age, gender, ethnicity, region, whether individuals have additional clinical risk factors, and whether individuals are receiving annual influenza vaccination [63,64].

Patients with rheumatoid arthritis (RA) are eligible for pneumococcal vaccines, as treatment with disease modifying antirheumatic drugs and corticosteroids for RA is known to increase the susceptibility to infection [3]. However, rates of vaccine coverage remain low in this risk group [65–68] (**Table S2**). Costello et al. (2016) reported that only 50.0% of patients with RA received a PV during the 5-year follow-up period [68]. A UK audit study further found that significantly fewer patients on major immunosuppressants received or were offered pneumococcal immunization than those with other risk factors, despite a high rate of awareness of immunization [65]. These findings suggest that patients with RA may not have been appropriately targeted for pneumococcal immunization by primary care physicians, highlighting the importance of physicians' awareness and education and organizational factors in individual practices for achieving optimal vaccine coverage. Global PV coverage also remains low in RA patients: PPV23 coverage within the recommendations across 17 countries was only 17.2%, with large disparities in vaccination uptake across countries [67]. Factors consistently identified to be associated with higher PPV23 uptake in RA patients included older age (>65 years), prescription of DMARDs, and more comorbidities or additional risk factors [65–68] (**Table S2**).

Currently, there is a lack of robust official data on PV uptake among some of the high-risk groups in the UK, particularly in PLWHIV. In the BHIVA vaccination guidelines published in 2015, PCV13 vaccination is recommended for all PLWHIV, and those who meet the indications for PPV23 vaccination within the national program (typically aged ≥65 years or with a comorbidity other than HIV as defined in the Green Book) should follow general guidance and also receive a single dose of PPV23 at least 3 months after PCV13 [69]. Prior to the recent BHIVA guidelines all PLWHIV were recommended to receive a single dose of PPV23; however, uptake was low. Thornhill et al. (2015) reported that only one out of 189 PLWHIV infected with IPD had a record of PV [59] (**Table S2**). A service evaluation project at James Cook hospital, Middlesborough sought to evaluate the utility of a vaccine passport for PLWHIV [70]. This found that the uptake of pneumococcal vaccine (PCV13 in accordance with BHIVA guidelines) increased from 16.0% to 51.0% following the introduction of a vaccine passport [70].

Lastly, hematopoietic stem cell transplant (HSCT) recipients are at significant risk of PD due to adaptive immune defect

post-HSCT [71]. Joint international/national guidelines therefore recommend a comprehensive course of revaccination schedule for HSCT recipients [71]. While in the UK, there is no revaccination schedule in place for adult HSCT recipients and poor vaccination uptake in HSCT recipients has been demonstrated [72]. Factors affecting uptake include insufficient evidence to inform detailed practical guidance, variations within existing guidelines, and practical challenges of implementing international recommendations at national levels [72]. To address these issues, a joint consensus statement has established a standardized revaccination schedule for adult and pediatric HSCT recipients in the UK: a 3-dose primary schedule is recommended for all HSCT recipients from 3 to 6 months post-HSCT followed by a booster dose given at 18 months post-HSCT with either PCV13 or PPV23 [72]. These findings underline that robust vaccination programs are needed to optimize vaccine uptake, and vaccination post-HSCT to prevent PD remains a priority.

Overall, evidence suggests that there is a large gap in the PPV23 and PCV13 uptake among risk groups eligible for these vaccines. Poor compliance with UK guidelines on the immunization of at-risk individuals, and poor adherence to timely vaccination may continue to be challenging in the long term.

3.2. Factors affecting vaccine delivery/uptake and strategies for optimization

Although the adult pneumococcal immunization program is well established in the UK, the vaccination uptake remains low among risk groups. Inadequate knowledge, negative attitudes, and low levels of awareness among patients and healthcare providers remain key factors affecting PV uptake [58,73,74]. Results from a single center retrospective study showed that the rate of vaccination uptake in patients on dialysis within the last five years was significantly lower than the national average in high-risk groups in 2011 (22.0% versus 53.0%, $p < 0.0001$) [75] (**Table S2**). In this cohort, only 3.0% were up to date with PV. Sites of vaccination may also affect vaccination uptake; for instance, the dialysis unit was the preferred site of vaccination by most of the dialysis patients and GPs interviewed due to patients' regular visits [75]. Other key barriers to vaccine uptake include system organization and accessibility issues (e.g. geographical barriers), competing priorities in healthcare practices, incomplete or inaccessible documentation of vaccination records, and healthcare system delivery challenges [73,74].

Given the significant burden of PD and low levels of pneumococcal vaccination among risk groups, strategies to improve pneumococcal vaccine uptake are required. For instance, strategies targeting organizational factors may help to achieve optimal uptake. A UK audit study demonstrated that practices could achieve or exceed national targets for PV uptake rates for disease-specific risk groups through audit, feedback, and written advice on strategies for organizational change [76] (**Table S2**). After implementation of several methods to increase vaccination rates across 14 practices (e.g. accurate registers for high-risk groups, reminder systems, and practitioner protocols and reminders), rates of PV uptake significantly improved in patients with CHD ($p = 0.002$), diabetes ($p < 0.001$) and splenectomy ($p = 0.03$) and were comparable to the median standards set up across these practices [76]. Combined interventions tailored to overcome practice-specific barriers and approaches targeting individuals (e.g. improving awareness and knowledge of vaccination and attitudes toward immunization among patients and GPs) may be effective to optimize vaccine uptake. Indeed, most patient advocacy groups have endeavored to address vaccination uptake in risk groups through information sheets, websites and campaigns to enhance patients' and GPs' awareness and knowledge [77,78] – these efforts were amplified during the COVID-19 pandemic [79].

Maintaining funding for national vaccination programs is crucial for decreasing practice-associated barriers and improving patient access to vaccines. In the current landscape, funding is only available to support vaccination programs within primary care settings. As of April 2021, a new GP contract has been introduced to support the delivery and organization of vaccination and immunization services across UK primary care, and vaccination and immunization services have become an Essential Service for most routine National Healthcare Service (NHS)-funded vaccinations including pneumococcal vaccination (programs out of scope include the adult and childhood seasonal influenza program and the COVID-19 program which remain a Directed Enhanced Service) [80]. This change will undoubtedly improve PV delivery/uptake. Although opportunistic vaccination has been demonstrated to be a potential route to improve vaccination delivery/coverage during the COVID-19 pandemic, it is relatively rarely administered in secondary care despite many existing opportunities to do so for high-risk patients. Overall, pneumococcal vaccine uptake in UK adults in risk groups remains low; initiatives are needed to improve vaccine delivery.

4. Potential to expand risk group recommendations in the UK

Gaps remain in definitions of clinical risk groups in current UK vaccination guidelines. Understanding how certain disease state or factors increases risks of PD is critical for identifying additional populations at risk of PD. The following sections summarize evidence that may be used to help identify new risk factors for PD and to support the expansion of risk group definitions.

4.1. Risk stacking

The impact of concomitant, multiple risk factors ('risk stacking') for PD on clinical outcomes has been evaluated in the UK [6], US [81], and Germany [82]. Growing evidence has shown that an increasing number of underlying medical conditions is associated with a higher risk of PD and worse clinical outcomes, e.g., the risk of PD among individuals with two or more comorbidities is significantly higher than those with a single high-risk condition [6,81,82]. The concept of 'risk stacking' however is not yet formally recognized within the UK vaccination guidelines.

Using healthcare data in England, Van Hoek et al. (2012) confirmed that having one or more underlying clinical

conditions markedly increased the risk of hospital admission for IPD across all age groups (children aged 2–15 years, OR [95% CI]: 11.7 [10.2, 13.3]; adults aged 16–64 years, OR [95% CI]: 7.6 [7.3, 7.9]); adults aged ≥65 years, OR [95% CI]: 2.7 [2.6, 2.8]). The case fatality ratio (CFR) was higher in those with underlying clinical conditions versus those without risk conditions across all age groups. Notably, the highest CFR was observed among patients with liver disease aged ≥65 years (53.0%) whereas the lowest CFR was seen in non-risk children (1.8%). These findings revealed a 'risk-stacking' phenomenon among risk groups [6].

The effect of risk-stacking on clinical outcomes was evaluated by Shea et al. (2014), using US healthcare medical claims data. In at-risk individuals, absolute rates of all-cause pneumonia significantly increased with the accumulation of concomitant at-risk conditions and were progressively higher with increasing age. Of all age groups, the risk-stacking effect was most pronounced among adults aged 18–49 years; rate ratio increased from 2.5 (95% CI: 2.5, 2.5) in those with one at-risk condition to 6.2 (95% CI: 6.1, 6.3) in those with two at-risk conditions, and 15.6 (95% CI: 15.3, 16.0) in those with ≥3 at-risk conditions [81]. Furthermore, using German claims data, Pelton et al. (2015) reported that rate ratios of all-cause pneumonia among children with risk conditions increased with the number of risk conditions compared with healthy counterparts [82]. Among younger children aged <5 years, the rate ratio increased from 1.5 (95% CI: 1.5, 1.5) for those with one condition to 4.7 (95% CI: 4.6, 4.7) for those with ≥3 conditions; among older children (5–17 years), the rate ratio increased from 2.0 (95% CI: 1.9, 2.1) to 11.3 (95% CI: 11.0, 11.5). Similar patterns for adults were reported. Among adults aged 18–49 years, the rate ratio increased from 1.9 (95% CI: 1.8, 2.0) for those with one condition to 6.2 (95% CI: 5.9, 6.4) for those with ≥3 conditions; among adults aged 50–59 years, the rate ratio increased from 1.7 (95% CI: 1.6, 1.8) for those with one condition to 5.2 (95% CI: 5.0, 5.3) for those with ≥3 conditions; among those aged ≥65 years, the rate ratio increased from 1.8 (95% CI: 1.7, 1.9) for those with one condition to 4.6 (95% CI: 4.5, 4.7) for those with ≥3 conditions [82]. Both studies showed that rate ratios of all-cause pneumonia in individuals with ≥2 risk conditions were comparable with or higher than rates in individuals with a high-risk condition and that rates in individuals with ≥3 risk conditions were substantially higher than those in high-risk individuals.

4.2. Guidelines in other countries

Given the high disease burden of PD, national vaccination guidelines have been implemented worldwide. Vaccination guidance varies across countries by type of vaccine, dosing sequence (including intervals between doses), age, and risk groups deemed eligible for PV [83]. Comparison of vaccination guidelines across countries of interest is summarized in Table 3.

In risk-based guidelines, there are variations in risk factors indicated for PV across countries. For instance, the occupational risk group eligible for vaccination in the UK and Germany is limited to welders and metal workers [87], whereas occupational risk factors are currently not included in France [86]. In the US, individuals living in special environments or social settings (including Alaska Native, Navajo, and White Mountain Apache populations) are considered for vaccination [84]. In Canada, adult residents in long-term care facilities are deemed eligible for vaccination [88]. In Australia, vaccination of aboriginal and Torres Strait Islander people aged ≥50 years without risks conditions is recommended as they are at higher risk of PD compared with non-indigenous adults [90].

Specific recommendations for surrogates of comorbidity, e.g., smoking, alcoholism, illicit drug use and homelessness, are not issued in the UK, whereas some of these risk factors are included in the other countries' vaccination guidelines such as US, Canada and New Zealand (Table 3). Arguably, the most vulnerable individuals in these risk groups will be vaccinated under current UK guidelines; for example, where alcoholism has progressed to liver disease or lung disease has developed in smokers, despite no formal recommendation. Nevertheless, early vaccination of individuals with lifestyle risk factors before the associated diseases progress to the later stages would be preferable.

Age-based vaccination guidelines involve the vaccination of all older adults after a certain age, with a small variation in the recommended starting age of vaccination [83] (Table 3). For healthy older adults, eligible age for PPV23 ranges from ≥60 years in Germany, to ≥65 years in most countries (including UK, US, Canada and New Zealand), and to ≥70 years in Australia [3,83,84,87,90–92]. In contrast, vaccination of healthy older adults is not recommended in France, unless individuals have certain underlying comorbidities [83]. Indeed, older adults (≥65 years) are more susceptible to PD due to immunosenescence (e.g. increased susceptibility to infections and poor responses to vaccines) and present worse clinical outcomes than younger adults [93]. Earlier vaccination may be preferable.

In addition to PPV23, PCV13 is provided for all adults aged ≥65 years without risk conditions in the US, Canada and New Zealand, but not in the UK, France and Germany despite being introduced in the National Childhood Immunization Program (Table 3). As of January 2022, the US Advisory Committee on Immunization Practices (ACIP) recommends the use of PCV15 in series with PPV23 or PCV20 alone in PCV-naïve adults aged ≥65 years or adults aged 19–64 years with certain medical conditions [85]. In 2023, the Canadian and Australian guidelines have also been updated to introduce these two next-generation vaccines [89,90]. As of June 2023, the JCVI recommends to include PCV20 alongside PPV23 in the routine vaccination program for adults aged ≥65 years and all adults in risk groups [23].

4.3. Identification of new risk factors

As the population ages, multimorbidity becomes more prevalent and certain health conditions are more common in different life stages [94]. Using phenotyping algorithms to map the course of the 50 most common health conditions at different life stages, Kuan et al. (2019) illustrated that: hypertension and dyslipidemia commonly occurred in individuals aged 40–49 years; cancer and type 2 diabetes were prominent in individuals aged 60–79 years; CVD and renal

Table 3. Comparisons of pneumococcal vaccination guidelines across countries.

Country/Region	UK	US	France	Germany	Canada	Australia	New Zealand
References	[3,23]	[84,85]	[86]	[87]	[88,89]	[90]	[91]
Vaccines recommended in current guidelines							
PPV23	✓	✓	✓	✓	✓	✓	✓
PCV13	✓	✓	✓	✓	✓	✓	✓
PCV15		✓		✓	✓	✓	
PCV20	✓*	✓			✓	✓	
Structure							
Childhood pneumococcal vaccination program	✓	✓	✓	✓[b]	✓	✓	✓
Age-based guidelines	✓[a]	✓[a, b, c]	✓[d]	✓[a]	✓[a, b, c]	✓[a, b]	✓[a, c]
Risk-based guidelines	✓	✓	✓	✓	✓	✓	✓
Risk groups included in current guidelines							
Asplenia/splenic dysfunction	✓	✓	✓	✓	✓	✓	✓
Immunosuppression	✓	✓	✓	✓	✓	✓	✓
Chronic respiratory disease	✓	✓	✓	✓	✓	✓	✓
Chronic heart disease	✓	✓	✓	✓	✓	✓	✓
Chronic liver disease	✓	✓	✓	✓	✓	✓	✓
Chronic Kidney disease	✓	✓	✓	✓	✓	✓	✓
Diabetes	✓	✓	✓	✓	✓	✓	✓
Cochlear implants	✓	✓	✓	✓	✓	✓	✓
CSF leaks	✓	✓	✓	✓	✓	✓	✓
Occupational risks (exposure to metal fumes, i.e. welders and metal workers)	✓			✓			
Additional risk groups							
Persons living in special environments or social settings		✓[e]					
Residents of long-term care facilities					✓		
Certain ethic groups (indigenous people)						✓[f]	
Smoking		✓			✓		✓
Alcoholism		✓			✓		✓
Illicit drug use					✓		
Homelessness					✓		
Risk-stacking concept							
≥2 risk conditions (Recommended)[g]							✓

*As of June 2023, PCV20 is recommended for adult pneumococcal immunization program by the UK Joint Committee on Vaccination and Immunisation, and it is now available for adults ≥65 years and all adults in clinical risk groups as defined in the Green Book (2020).

[a]PPV23 vaccination of healthy older adults is recommended. Eligible age: ≥60 years for Germany; ≥65 years for UK, US, Canada and New Zealand; ≥70 years for Australia. Revaccination of PPV23 every five years is recommended for most countries, while Germany recommends revaccination with PPV23 at intervals of at least 6 years. In the UK, revaccination of PPV23 is only recommended for the highest risk group of IPD, including those with asplenia, splenic dysfunction and chronic kidney disease.

[b]In the US, PCV20 alone or PCV15 following a dose of PPV23 is recommended for vaccine-naïve adults aged ≥65 years and adults aged 19–64 years with certain medical conditions or risk factors. In Canada and Australia, PCV20 (or PCV15 following a dose of PPV23 as an alternative option) is recommended for vaccine-naïve adults aged ≥65 years and those aged 18–64 years with risk conditions. In Germany, PCV15 is currently recommended for use in children and adolescents aged 2–17 years.

[c]PCV13 is recommended for use in all healthy adults who are aged ≥65 years without risk conditions. In the US, if the decision is made to administer PCV13, it should be given at least 1 year before PPV23. In Canada and New Zealand, it is recommended that a dose of PCV13 should be given first followed by PPV23 at least 8 weeks later.

[d]PPV23 vaccination is only recommended for adults aged ≥18 years with certain medical conditions; revaccination every five years is recommended.

[e]Includes Alaska Native, Navajo, and White Mountain Apache populations.

[f]Indigenous population includes aboriginal and Torres Strait Islander people.

[g]PCV13 and PPV23 are recommended but not funded for the following individuals: immunocompetent adults (aged ≥18 years) at increased risk of pneumococcal disease or its complications due to chronic illness (e.g. chronic heart, renal, liver or pulmonary disease, diabetes or alcohol dependency); adults with CSF leaks; immunocompromised adults at increased risk of pneumococcal disease (e.g. those with nephrotic syndrome, multiple myeloma, lymphoma and Hodgkin's disease); individuals of any age who have had one episode of invasive pneumococcal disease; smokers. CSF, cerebrospinal fluid; PCV, pneumococcal conjugate vaccine; PPV23, pneumococcal polysaccharide vaccine; UK, United Kingdom; US, United States.

disease became more common in individuals aged ≥80 years [94]. These findings imply that clinical risk groups for PD with multiple underlying conditions are likely to expand with an aging population.

Despite the comprehensive list of risk conditions for PD as defined in the Green Book, some risk factors that are currently not included in the guidelines could also predispose individuals to respiratory infections including PD and lead to severe outcomes. These risk factors include prevalent diseases (e.g. COVID-19 infection, stroke, dementia) [95,96], prescription of certain medication (e.g. proton pump inhibitors) [97], and lifestyle or environmental factors (e.g. cigarette smoking, vaping, alcoholism, occupational exposure to inorganic dust or fumes) [98–101]. Among these risk factors, alcoholism and smoking could be considered for the UK guidelines as local data suggest potential associations with IPD and recurrent hospitalization with pneumonia [98–100].

Evidence exists that occupational or environmental exposures to inorganic dust and fumes (including tobacco smoke) increase the risk for IPD [101–103]. A 5-year cumulative occupational exposure to silica dust or fumes was associated with over two-folds of risk of IPD with pneumonia [101]. Tobacco smoking, passive smoking among non-smokers, and vaping are strong independent predictors for IPD, while cessation of tobacco smoking reduced the risk IPD [102–104]. These findings suggest that efforts should be made to reduce environmental or occupational exposures to dust and fumes and control tobacco smoke and vaping. The use of pneumococcal

vaccines could also be considered for UK populations with such exposures to help prevent PD.

Several socioeconomic and demographic characteristics are also associated with increased risk of PD infection, including living with children aged <6 years who attend day-care centers, low educational level, low income, and household crowding [102]. In addition, accumulated evidence showed that homeless people are at higher risk of PD compared with the general population, potentially associated with deprivation, poor living and access to healthcare services, and higher rates of chronic alcohol abuse, illegal drug use and tobacco smoking [105–108]. Currently, PPV23 vaccination of the homeless is only recommended in Canada (Table 3). More research is required to support the consideration of prioritizing vaccination for populations with these characteristics in the UK vaccination guidelines.

Occupational risks in the current UK guidelines cover welders or metal workers [3]. However, other professional activities involving close contact with people with respiratory disease could be considered as relevant for vaccination (including individuals working in residential care homes, elderly care wards, oil rigs, prisons, those living in inner city high pollution settings and healthcare workers), as they are at higher risk of exposure to respiratory infections [109–111]. Indeed, several measures were implemented to control infections during outbreaks, including isolation, hand/respiratory hygiene practice, personal protective equipment, and use of antimicrobials [110]. Utilizing vaccination would be more strategic for employers to prevent PD and its severe outcomes.

In certain patient groups, clinical characteristics and prior history of disease exacerbation may increase patients' susceptibility to PD. In patients with chronic obstructive pulmonary disease (COPD), for whom PPV23 is recommended in the UK, those who had moderate airflow limitation and heightened cardiovascular risk, factors including prior exacerbation history of COPD, body mass index <25 kg/m^2, and greater impairment of lung function (FEV1 <60%), were strongly linked to pneumonia risk [112]. This study indicates that risk of PD could vary within patient group and the risk assessment for PD may be tailored based on individual clinical characteristics.

Moreover, evidence showed that frailty and Charlson Comorbidity Index (CCI) score may serve as prognostic factors for severe clinical outcomes of respiratory diseases (e.g. hospitalization, intensive care unit [ICU] admission, deaths) [5,100,113,114]. Szakmany et al. (2021) assessed the influence of frailty on mortality in patients with pneumonia in Wales between 2010 and 2018. Results showed that increased frailty scores (assessed by either electronic frailty index or hospital frailty risk score) were significant risk factors for ICU admission and in-patient mortality among patients with pneumonia [113]. A study using the Clinical Frailty Scale found that frailty was an independent predictor for 1-year in-hospital mortality for CAP among older patients aged ≥65 years [114]. Similarly, CCI could be a strong predictor for adverse outcomes of PD. Trotter et al. (2008) demonstrated that higher CCI scores were significantly associated with increased odds of 30-day in-hospital mortality among patients with pneumonia in England, after controlling for known confounders (odds ratio (OR) [95% CI] for mild, moderate and severe CCI: 1.6 [1.6, 1.6], 2.5 [2.4, 2.5], 3.7 [3.7, 3.8]). Szakmany et al. (2021) also reported that higher CCI score was significantly linked to higher odds of ICU admission (OR: 2.6, 95% CI: 2.5, 2.8) and in-hospital mortality (OR [95% CI] for CCI 1–10: 1.2 [1.1, 1.2], CCI > 10: 2.5 [2.4, 2.6]). Frailty and multimorbidity are likely to increase notably in the UK population in the coming decades.

These findings indicate that the risk categories currently defined in the UK vaccination guidelines may need to be revised to better manage and prevent clusters of PD, e.g., including additional risk conditions (e.g. COVID-19 infection, stroke, dementia and illicit drug dependency), expanding occupational risks (e.g. healthcare workers) and considering vaccination of hospitalized patients with worse frailty and morbidity scores.

Overall, there is a lack of international consensus around risk group definitions. To address this gap, there may be an opportunity to develop a tool for identifying individuals who are at risk of PD and severe outcomes after respiratory infection. In 2020, a novel risk assessment tool, QCovid®, was developed to predict severe outcomes of COVID-19 infection using a data-driven approach; factors including age, medical conditions, vaccination status and background infection rate are included to establish a risk prediction model [115]. A similar digital tool/calculator may also be considered to identify risk groups for PD.

Lastly, vaccine programs in the UK must be shown to be cost-effective nationally to justify their introduction, and therefore modifying eligible groups for routine vaccination requires a minimum evidence base to assess this. There will also be a budgetary impact due to the change in the number of patients eligible for vaccination. During the COVID-19 pandemic, non-pharmaceutical interventions (i.e. mask wearing and isolation) that were intended to limit the spread of SARS-CoV-2 had a profound impact on other respiratory infections, including the pneumococcus. However, public willingness to routinely adopt such measures, particularly on an ongoing basis, is questionable and vaccination is perhaps a more pragmatic intervention.

5. Current environment

PD causes a significant burden in adults in the UK, despite a relatively high level of health preventive and intervention measures and treatment guidelines [4,26,38]. An understanding of the current landscape and wider challenges and identifying any unmet needs for the management of PD – especially in high-risk groups – will be crucial to help address the resurgence and burden of PD.

5.1. Epidemiological trends of PD before and after the pandemic

Despite the substantial reduction in the IPD cases over time achieved by the well-established routine childhood PCV program in the UK, the overall incidence of IPD has increased since 2013/2014, driven by a rapid increase in non-vaccine serotypes and mainly in the older age groups (≥65 years) [26]. Similarly, there has been an increasing trend of the

incidence of pneumococcal septic arthritis (an uncommon form of IPD) in older adults and those with underlying comorbidities over the last decade, primarily caused by non-vaccine serotypes and PPV23/non-PCV13 serotypes [17]. However, the epidemiological landscape of the pneumococcus recently changed dramatically with the emergence of SARS-CoV-2 and non-pharmaceutical interventions that were intended to limit the spread of this virus.

Following the introduction of non-pharmacological interventions in March 2020, large reductions in IPD were subsequently concomitantly observed across all age groups in England [13]. As the third national lockdown was lifted in July 2021 in England, the incidence of IPD in those aged <15 years rapidly increased to exceed the levels observed before the COVID-19 pandemic [116]. However, levels of IPD in UK adults have re-emerged more slowly and have not yet returned to pre-pandemic levels [117]. A similar pattern of epidemiological trends for IPD was reported in Germany: the incidence of IPD across all age groups largely declined coinciding with the implementation of national COVID-19 measures in 2020 and has exceeded the pre-pandemic levels (2015–2019) after national COVID-19 restrictions were lifted in 2021 [118]. Despite these temporal changes in IPD epidemiology as a consequence of COVID-19 pandemic, distribution of serotypes has remained consistent and reflects those observed before the COVID-19 pandemic in the UK and Germany [13,118,119]. Insight into how pneumococcal pneumonia in the UK was impacted remains limited although there is evidence suggesting that incidence of non-SARS-CoV-2 related all-cause hospitalized CAP remained largely unaltered [17].

5.2. Pressure on the healthcare system

PD imposes a significant economic burden on the NHS in the UK. The estimated mean costs of hospitalization for CAP in 2019 was £3,904 per adult, accounting for a total cost of £731 million per annum to the NHS [120]. For those receiving critical care, the mean cost was £11,654 per person. The mean costs for hospitalized CAP varied by risk group, ranging from £4,458 for patients with diabetes to £5,215 for those with CHD aged <65 years, and £4,356 for those with CHD to £4,751 for those with CLD aged >65 years [120]. However, the costs for PD could be underestimated especially for patients aged ≥65 years due to complications which contribute to additional costs [42]. The COVID-19 pandemic has also significantly increased the pressure on the NHS, and limited its ability to deliver patient care because of absence of staff due to isolation and long-term illness post infection [121,122].

Therefore, improved pneumococcal vaccine uptake in older adults aged ≥65 years or those with the highest risk of PD with higher-valent PCVs could contribute to relieving the continuous pressure on the NHS [42], and more importantly, to help reduce mortality in hospitalized patients and those with unrecognized/undocumented PD in the community.

5.3. Concerns on antimicrobial resistance

Antimicrobial resistance (AMR) is now a widespread, urgent global public health threat of high priority to the WHO and wider global society [123]. Many adults in risk groups have a heightened risk of intercurrent infections including respiratory tract infections which are the leading clinical indication for antibiotic prescriptions in both primary and secondary care worldwide [124,125]. Antibiotics such as co-amoxiclav and cephalosporins are known to be important contributors to AMR [126].

Given that pneumococcal infection is a leading cause of LRTIs worldwide (responsible for 197.05 million episodes and 1,189,937 deaths in 2016) [1], the use of vaccines can help to address the global issue of AMR through direct and indirect effects including [123]:

- prevention of bacterial/viral infections and viral diseases prone to bacterial coinfections or superinfections requiring antibiotics,
- its mechanism of actions less prone to inducing resistance,
- reducing incidence of infections and hence decreasing antimicrobial use,
- prevention of resistant strains from occurring and spreading, and
- prevention of antimicrobial misuse.

Evidence revealed that universal coverage by PCVs in children aged <5 years led to approximately 47.0% reduction in the amount of antimicrobials used for pneumococcal infections [127]. Utilizing PCVs also reduced 64.0% of AMR pneumococcal infection in children and 45.0% in adults aged ≥65 years in 2011 in the US [127]. The significant impact of PCVs on the control of AMR through restricting the need of antimicrobials and reducing the incidence of resistant strains in other countries has also been reported [128]. These studies highlight the important role of vaccinations in the prevention of PD from occurring and spreading as well as addressing the global issue of AMR.

6. Conclusion

The UK JCVI now recommends that PCV20 may be used in addition to PPV23, with a number of even higher valency conjugate vaccines in development that may become available for consideration in the future. Despite the well-established UK immunization programs and guidelines, uptake of PPV23 among clinical risk groups and all adults aged ≥65 years remains unsatisfactory. Improving pneumococcal vaccine uptake in adult risk groups is therefore critical to ensure they are optimally protected. Thereby, national strategies are urgently required to optimize vaccination access and coverage. In light of growing evidence, a number of gaps exist in risk group definitions in current vaccination guidelines which should now be revised to cover wider populations at risks of PD.

7. Expert opinion

Whilst it is well established that individuals with a range of underlying comorbidities are at an increased risk of pneumococcal disease, more robust, detailed evidence is needed.

Detailed insight into incidence in risk-group patient populations is lacking, particularly relating to pneumococcal pneumonia. COVID-19 highlighted the need to better understand the spectrum of comorbidities that increase the risk of respiratory tract infections. Given this, there could be a benefit from a reassessment of the risk groups that are currently eligible for pneumococcal vaccination. Furthermore, the increased likelihood of pneumococcal infection in patients with multiple risk factors suggests that risk stacking should be taken into consideration when making recommendations for pneumococcal vaccines.

Viral-bacterial coinfections and superinfections are relatively common, as preceding or concurrent viral infection of the respiratory tracts is widely known to increase the susceptibility to secondary bacterial coinfection, or vice versa [129,130]. Viral-bacterial coinfections are often synergistic, leading to adverse outcomes [130,131]. Recent evidence showed that individuals aged ≥65 years who had received PCV13 had a lower incidence of COVID-19 infections, hospitalization and mortality compared with non-PCV13 recipients [131]. These findings not only suggest a possible synergistic interaction between pneumococci and SARS-CoV-2, but also highlight some protection afforded by PCV13 against the outcomes of COVID-19 [131]. Given the presence of several common pandemic viral pathogens including SARS-CoV-2, respiratory syncytial virus and influenza viruses, prevention of PD becomes increasingly important to avoid subsequent burden of respiratory diseases caused by viral-bacterial coinfections.

There is a financial incentive in place to encourage GPs to vaccinate UK adults at risk of pneumococcal infection, i.e., adults aged ≥65 years or those in risk groups aged 2–64 years. Data suggest that uptake varies significantly by risk factor and overall uptake is currently low in adults in risk groups but higher in adults eligible for the age-based recommendation. This demonstrates the success of implementing age-based recommendations and the challenges regarding recommendations for specific groups within the population. Current pneumococcal vaccination uptake in risk groups is only reported broadly and is not stratified by risk. Improved vaccine uptake data stratified by specific risk groups would be valuable as it could help to highlight those risk groups where uptake is particularly low at present. This may in part reflect a poor understanding and awareness by both the general public and some healthcare professionals of the threat posed to patients in risk groups by pneumococcal infections or other factors such as concern regarding the efficacy of PPV23.

The recent JCVI recommendation to include PCV20 in addition to PPV23 for UK adults at increased risk of PD provides an opportunity to improve the protection they receive against PD. With several even higher valency PCVs in development, it is anticipated that in the future it may be possible to further improve the extent to which UK adults risk groups are protected against PD. The ability of a single dose of PPV23 to provide long-term protection, particularly for younger adult patients with risk factors is questionable and needs further research.

The NHS is facing capacity challenges particularly following the COVID-19 pandemic, so all opportunities to help prevent infection should be taken. In addition to ensuring that adults with underlying comorbidities are protected against influenza and COVID-19, all opportunistic efforts should be made to ensure adults at increased risk of PD also receive a pneumococcal vaccine.

The response to the COVID-19 pandemic highlighted the variety of ways in which vaccines can be provided to the public, including those at increased risk of respiratory disease. Learnings from this experience and the use of the associated and existing vaccination program framework, should be applied to optimize the delivery of pneumococcal vaccines to adults in risk groups.

Infectious disease control and prevention is the responsibility of everyone involved in patient care and helps to mitigate AMR. Whenever patients in pneumococcal risk groups see their specialist consultant or present acutely to hospital care, there is an opportunity to review their vaccine status. Where necessary a recommendation for pneumococcal vaccine should be documented in follow-up correspondence with their GPs. The role of opportunistic vaccination in the secondary care setting or other innovative approaches should also be explored.

Acknowledgments

The authors thank Dr Peter Elton (Clinical Director) of the Greater Manchester and Eastern Cheshire Strategic Clinical Networks for his contribution to the conceptualization of this article. Additionally, Professor Dave Singh is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC).

Funding

This study was funded by Pfizer Ltd, UK. Medical support was provided by Hui-Hsuan Liu at OPEN Health and was funded by Pfizer.

Declaration of interests

J Campling, A Vyse, H Wright, and G Ellsbury are employees of Pfizer Ltd, UK, and may hold stock or stock options. HH Liu is an employee of OPEN Health. M Slack has received personal fees from GlaxoSmithKine, Pfizer, Merck, AstraZeneca, and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards and has undertaken contract work for Pfizer. RR Reinert is an employee of Pfizer Inc, France, and may hold stock or stock options. M Drayson owns equity/stocks in Abingdon Health outside the submitted work. D Singh has received consultancy fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, EpiEndo, Genentech, GlaxoSmithKline, Glenmark, Gossamer Bio, Kinaset Therapeutics, Menarini, Novartis, Orion, Pfizer, Pulmatrix, Sanofi, Synairgen, Teva, Theravance Biopharma, and Verona Pharma. G Barlow is Senior Clinical Lecturer at Hull York Medical School at the University of York and an Honorary Consultant in Infection at Hull University Teaching Hospitals NHS Trust. Within the last three years, G Barlow has received advisory board or consultation fees from Advanz Pharma, Pfizer UK and Biomerieux. G Kassianos works as a National Immunisation Lead RCGP, President British Global & Travel Health Association, Board Member European Working Scientific Group on Influenza, and Chair RAISE Pan-European Group of experts in influenza, and has participated at meetings organized by all vaccine manufacturers in the UK. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have received an honorarium for their review work. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose.

Author contributions

All authors have (1) substantially contributed to the conception and design of the review article and interpreting the relevant literature and (2) have been involved in writing the review article and have revised it for intellectual content.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Troeger C, Blacker B, Khalil IA, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet Infect Dis. 2018;18(11):1191–1210. doi: 10.1016/S1473-3099(18)30310-4
2. World Health Organization. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. 2019. [cited 2022 December 02]. Available from: https://www.who.int/publications/i/item/10665-310968
3. UK Health Security Agency. Pneumococcal: the Green Book, chapter 25. 2020 [cited2022 August 01]. Available from: https://www.gov.uk/government/publications/pneumococcal-the-green-book-chapter-25
4. Sharp A, Minaji M, Panagiotopoulos N, et al. Estimating the burden of adult hospital admissions due to RSV and other respiratory pathogens in England. Influenza Other Respir Viruses. 2022 Jan;16(1):125–131. doi: 10.1111/irv.12910
5. Trotter CL, Stuart JM, George R, et al. Increasing hospital admissions for pneumonia, England. Emerg Infect Dis. 2008 May;14(5):727–733. doi: 10.3201/eid1405.071011
6. van Hoek AJ, Andrews N, Waight PA, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012 Jul;65(1):17–24. doi: 10.1016/j.jinf.2012.02.017
7. Campling J, Jones D, Chalmers JD, et al. The impact of certain underlying comorbidities on the risk of developing hospitalised pneumonia in England. Pneumonia (Nathan). 2019;11(1):4. doi: 10.1186/s41479-019-0063-z

•• **This article quantifies the risk of adults with certain underlying comorbidities being hospitalized with pneumonia in England.**

8. Campling J, Jones D, Chalmers J, et al. Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England. BMJ Open Respir Res. 2020 Oct;7(1):e000703. doi: 10.1136/bmjresp-2020-000703.

•• **This article evaluates the clinical and financial impact of hospitalized pneumonia in patients with certain underlying comorbidities in England.**

9. Chalmers JD, Campling J, Dicker A, et al. A systematic review of the burden of vaccine preventable pneumococcal disease in UK adults. BMC Pulm Med. 2016 May 11;16(1):77. doi: 10.1186/s12890-016-0242-0
10. Chakrabarti B, Lane S, Jenks T, et al. Predictors of 30-day readmission following hospitalisation with community-acquired pneumonia. BMJ Open Respir Res. 2021 Mar;8(1):e000883. doi: 10.1136/bmjresp-2021-000883
11. Rozenbaum MH, van Hoek AJ, Fleming D, et al. Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. BMJ. 2012 Oct 26;345(oct26 1):e6879. doi: 10.1136/bmj.e6879
12. Chiavenna C, Presanis AM, Charlett A, et al. Estimating age-stratified influenza-associated invasive pneumococcal disease in England: a time-series model based on population surveillance data. PLOS Med. 2019;16(6):e1002829. doi: 10.1371/journal.pmed.1002829
13. Amin-Chowdhury Z, Aiano F, Mensah A, et al. Impact of the coronavirus disease 2019 (COVID-19) pandemic on invasive pneumococcal disease and risk of pneumococcal coinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): prospective national cohort study, England. Clinl Infect Dis. 2020;72(5):e65–e75. doi: 10.1093/cid/ciaa1728
14. Ruuskanen O, Lahti E, Jennings LC, et al. Viral pneumonia. Lancet. 2011 Apr 9;377(9773):1264–1275. doi: 10.1016/S0140-6736(10)61459-6
15. Hyams C, Challen R, Begier E, et al. Incidence of community acquired lower respiratory tract disease in Bristol, UK during the COVID-19 pandemic: a prospective cohort study. Lancet Reg Health Eur. 2022;21:100473. doi: 10.1016/j.lanepe.2022.100473
16. Brendish NJ, Malachira AK, Beard KR, et al. Hospitalised adults with pneumonia are frequently misclassified as another diagnosis. Respir med. 2019 Apr;150:81–84.
17. Hyams C, Amin-Chowdhury Z, Fry NK, et al. Streptococcus pneumoniae septic arthritis in adults in Bristol and bath, United Kingdom, 2006-2018: a 13-year retrospective observational cohort study. Emerg Microbes Infect. 2021 Dec;10(1):1369–1377. doi: 10.1080/22221751.2021.1945955
18. Myint PK, Hawkins KR, Clark AB, et al. Long-term mortality of hospitalized pneumonia in the EPIC-Norfolk cohort. Epidemiol Infect. 2016 Mar;144(4):803–809. doi: 10.1017/S0950268815001971
19. Lopez A, Mariette X, Bachelez H, et al. Vaccination recommendations for the adult immunosuppressed patient: a systematic review and comprehensive field synopsis. J Autoimmun. 2017 Jun;80:10–27.
20. Melegaro A, Edmunds WJ, Pebody R, et al. The current burden of pneumococcal disease in England and Wales. J Infect. 2006 Jan;52(1):37–48. doi: 10.1016/j.jinf.2005.02.008
21. Patterson L, Irvine N, Wilson A, et al. Outbreak of invasive pneumococcal disease at a Belfast shipyard in men exposed to welding fumes, Northern Ireland, April–May 2015: preliminary report. Euro Surveill. 2015;20(21):21138. doi: 10.2807/1560-7917.ES2015.20.21.21138
22. emc. APEXXNAR suspension for injection in pre-filled syringe. 2022 [cited 2022 August18]. Available from: https://www.medicines.org.uk/emc/product/13461/smpc#gref
23. Joint Committee on Vaccination and Immunisation. Minute of the meeting held on 07 June 2023. 2023 [cited 2023 August 08]. Available from: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/1262409204637

•• **The JCVI meeting minutes in June 2023 provide updates on the inclusion of PCV20 alongside PPV23 for routine adult pneumococcal immunization in the UK.**

24. emc. Vaxneuvance. 2023 [cited 2023 September 11]. Available from: https://www.medicines.org.uk/emc/product/13754/smpc
25. Waight PA, Andrews NJ, Ladhani SN, et al. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015;15(5):535–543. doi: 10.1016/S1473-3099(15)70044-7
26. Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. Lancet Infect Dis. 2018 Apr;18(4):441–451. doi: 10.1016/S1473-3099(18)30052-5

• **This article presents the trends of PD and the incidence of PD caused by a range of serotypes in adults aged 65+ years in the UK.**

27. Jochems SP, Weiser JN, Malley R, et al. The immunological mechanisms that control pneumococcal carriage. PLOS Pathog. 2017 Dec;13(12):e1006665. doi: 10.1371/journal.ppat.1006665
28. Davies LRL, Cizmeci D, Guo W, et al. Polysaccharide and conjugate vaccines to Streptococcus pneumoniae generate distinct humoral responses. Sci Transl Med. 2022 Aug 3;14(656):eabm4065. doi: 10.1126/scitranslmed.abm4065

29. Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. Nat Rev Immunol. 2021 Feb;21(2):83–100. doi: 10.1038/s41577-020-00479-7
30. Micoli F, Romano MR, Carboni F, et al. Strengths and weaknesses of pneumococcal conjugate vaccines. Glycoconj J. 2023 Apr;40 (2):135–148. doi: 10.1007/s10719-023-10100-3
31. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015 Mar 19;372(12):1114–1125. doi: 10.1056/NEJMoa1408544
32. Mendes D, Averin A, Atwood M, et al. Cost-effectiveness of using a 20-valent pneumococcal conjugate vaccine to directly protect adults in England at elevated risk of pneumococcal disease. Expert Rev Pharmacoecon Outcomes Res. 2022 Dec;22 (8):1285–1295. doi: 10.1080/14737167.2022.2134120
- **This cost-effectiveness analysis provides the evidence that PCV20 is cost-effective and offers direct protection against PD in UK adult clinical risk groups.**
33. Lagousi T, Basdeki P, Routsias J, et al. Novel protein-based pneumococcal vaccines: assessing the use of distinct protein fragments instead of full-length proteins as vaccine antigens. Vaccines (Basel). 2019 Jan 19;7(1):9. doi: 10.3390/vaccines7010009
34. Pichichero ME. Pneumococcal whole-cell and protein-based vaccines: changing the paradigm. Expert Rev Vaccines. 2017 Dec;16 (12):1181–1190. doi: 10.1080/14760584.2017.1393335
35. Patterson S, Webber C, Michael P, et al. A post hoc assessment of duration of protection in CAPiTA (community acquired pneumonia immunization trial in adults). Trials Vaccinol. 2016;5:92–96. doi: 10.1016/j.trivac.2016.04.004
36. Suaya JA, Jiang Q, Scott DA, et al. Post hoc analysis of the efficacy of the 13-valent pneumococcal conjugate vaccine against vaccine-type community-acquired pneumonia in at-risk older adults. Vaccine. 2018 Mar 7;36(11):1477–1483. doi: 10.1016/j.vaccine.2018.01.049
37. Andrews NJ, Waight PA, George RC, et al. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine. 2012 Nov 6;30(48):6802–6808. doi: 10.1016/j.vaccine.2012.09.019
38. Djennad A, Ramsay ME, Pebody R, et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine and changes in invasive pneumococcal disease incidence from 2000 to 2017 in those aged 65 and over in England and Wales. EClinicalMedicine. 2018 Dec;6:42–50.
39. Lawrence H, Pick H, Baskaran V, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: a case-control test-negative design study. PLOS Med. 2020 Oct;17(10):e1003326. doi: 10.1371/journal.pmed.1003326
40. Tin Tin Htar M, Stuurman AL, Ferreira G, et al. Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies. PLoS One. 2017;12(5):e0177985. doi: 10.1371/journal.pone.0177985
41. Chandler T, Furmanek S, Carrico R, et al. 23-valent pneumococcal polysaccharide vaccination does not prevent community-acquired pneumonia hospitalizations due to vaccine-type streptococcus pneumoniae. Microorganisms. 2022 Mar 4;10(3):560. doi: 10.3390/microorganisms10030560
42. Vyse A, Campling J, Czudek C, et al. A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK. Expert Rev Vaccines. 2021 Oct;20 (10):1311–1325. doi: 10.1080/14760584.2021.1984888
43. Goldblatt D, Miller E. Pneumococcal pneumonia. Thorax. 2020 Jan;75(1):6–7. doi: 10.1136/thoraxjnl-2019-214135
44. Amin-Chowdhury Z, Collins S, Sheppard C, et al. Characteristics of invasive pneumococcal disease caused by emerging serotypes after the introduction of the 13-valent pneumococcal conjugate vaccine in England: a prospective observational cohort study, 2014-2018. Clin Infect Dis. 2020 Nov 5;71(8):e235–e243. doi: 10.1093/cid/ciaa043
45. Klugman KP, Rodgers GL. Time for a third-generation pneumococcal conjugate vaccine. Lancet Infect Dis. 2021;21(1):14–16. doi: 10.1016/S1473-3099(20)30513-2
46. Vyse A, Campling J, Czudek C, et al. The proportion of contemporary invasive pneumococcal disease and pneumococcal pneumonia in UK adults reflected by serotypes included in the 13-valent pneumococcal conjugate vaccine and next generation higher valency pneumococcal conjugate vaccines in development. Vaccine. 2020 Dec 3;38 (51):8068–8070. doi: 10.1016/j.vaccine.2020.10.090
47. ClinicalTrial.gov. A phase 1/phase 2 study of polyvalent pneumococcal conjugate vaccine (V116) in adults (V116-001). 2022 [cited 2022 August 18]. Available from: https://clinicaltrials.gov/ct2/show/NCT04168190?cond=A+Phase+1%2FPhase+2%2C+Randomized%2C+Double-blind+Study+to+Evaluate+the+Safety%2C+Tolerability%2C+and+Immunogenicity+of+a+Polyvalent+Pneumococcal+Conjugate+Vaccine+in+Adults&draw=2&rank=1
48. ClinicalTrial.gov. A single ascending dose study in adults (stage 1) and single ascending dose-finding study (stage 2) in elderly subjects with ASP3772, a pneumococcal vaccine. 2022 [cited 2022 August 18]. Available from: https://clinicaltrials.gov/ct2/show/NCT03803202
49. ClinicalTrial.gov. Safety, tolerability, and immunogenicity study of a 24-valent pneumococcal conjugate vaccine (VAX-24) in adults. 2022 [cited 2022 August 19]. Available from: https://clinicaltrials.gov/ct2/show/NCT05266456?term=VAX-24&draw=2&rank=2
50. Behrens C, Fairman J, Agarwal P, et al. Development of a next generation 30+ valent pneumococcal conjugate vaccine (VAX-XP) using site-specific carrier protein conjugation. Open Forum Infect Dis. 2021;8(Suppl 1):S615. doi: 10.1093/ofid/ofab466.1241
51. Pick H, Daniel P, Rodrigo C, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013-18. Thorax. 2020 Jan;75(1):38–49. doi: 10.1136/thoraxjnl-2019-213725
- **This article presents the trends of PD serotypes in UK adults hospitalized for community-acquired pneumonia and highlights the rising concerns of non-vaccine serotypes and serotype 3.**
52. Gessner BD, Jiang Q, Van Werkhoven CH, et al. A post-hoc analysis of serotype-specific vaccine efficacy of 13-valent pneumococcal conjugate vaccine against clinical community acquired pneumonia from a randomized clinical trial in the Netherlands. Vaccine. 2019 Jul 9;37(30):4147–4154. doi: 10.1016/j.vaccine.2019.05.065
53. McLaughlin JM, Jiang Q, Gessner BD, et al. Pneumococcal conjugate vaccine against serotype 3 pneumococcal pneumonia in adults: a systematic review and pooled analysis. Vaccine. 2019 Oct 8;37(43):6310–6316. doi: 10.1016/j.vaccine.2019.08.059
54. Sings HL, Gessner BD, Wasserman MD, et al. Pneumococcal conjugate vaccine impact on serotype 3: a review of surveillance data. Infect Dis Ther. 2021 Mar;10(1):521–539. doi: 10.1007/s40121-021-00406-w
55. Savulescu C, Krizova P, Valentiner-Branth P, et al. Effectiveness of 10 and 13-valent pneumococcal conjugate vaccines against invasive pneumococcal disease in European children: SpIDnet observational multicentre study. Vaccine. 2022 Jun 23;40(29):3963–3974. doi: 10.1016/j.vaccine.2022.05.011
56. Dagan R, Patterson S, Juergens C, et al. Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: a randomized double-blind trial. Clin Infect Dis. 2013 Oct;57 (7):952–962. doi: 10.1093/cid/cit428
57. Luck JN, Tettelin H, Orihuela CJ. Sugar-coated killer: serotype 3 pneumococcal disease. Front Cell Infect Microbiol. 2020;10:613287. doi: 10.3389/fcimb.2020.613287
58. UK Health Security Agency. Pneumococcal polysaccharide vaccine (PPV) coverage report, England, April 2020 to March 2021. 2021 [cited 2022 July 29]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1035189/hpr1921-ppv-vc.pdf

•• **This government report describes the most current uptake data for pneumococcal vaccine in risk groups in England.**

59. Thornhill J, Sivaramakrishnan A, Orkin C. Pneumococcal vaccination in people living with HIV. Vaccine. 2015 Jun 22;33(28):3159–3160. doi: 10.1016/j.vaccine.2014.07.086
60. Kirwan PD, Amin-Chowdhury Z, Croxford SE, et al. Invasive pneumococcal disease in people with human immunodeficiency virus in England, 1999-2017. Clin Infect Dis. 2021 Jul 1;73(1):91–100. doi: 10.1093/cid/ciaa522
61. Department of Health and Social Care and NHS England. NHS public health functions agreement 2019-20 - public health functions to be exercised by NHS England. 2019. [cited 2022 December 02]. Available from: https://www.gov.uk/government/publications/public-health-commissioning-in-the-nhs-2019-to-2020
62. House of Commons Library. UK vaccination policy. 2022. [cited 2023 June 01]. Available from: https://researchbriefings.files.parliament.uk/documents/CBP-9076/CBP-9076.pdf
63. Pebody RG, Hippisley-Cox J, Harcourt S, et al. Uptake of pneumococcal polysaccharide vaccine in at-risk populations in England and Wales 1999-2005. Epidemiol Infect. 2008 Mar;136(3):360–369. doi: 10.1017/S0950268807008436
64. Matthews I, Lu X, Xia Q, et al. Pneumococcal vaccine coverage among individuals aged 18 to 64 years old with underlying medical conditions in the UK: a retrospective database analysis. BMC Public Health. 2020 Oct 21;20(1):1584. doi: 10.1186/s12889-020-09613-5
65. Sowden E, Mitchell WS. An audit of influenza and pneumococcal vaccination in rheumatology outpatients. BMC Musculoskelet Disord. 2007 Jul 4;8(1):58. doi: 10.1186/1471-2474-8-58
66. McCarthy EM, de Barra E, Bergin C, et al. Influenza and pneumococcal vaccination and varicella status in inflammatory arthritis patients. Ir Med J. 2011 Jul;104(7):208–211.
67. Hmamouchi I, Winthrop K, Launay O, et al. Low rate of influenza and pneumococcal vaccine coverage in rheumatoid arthritis: data from the international COMORA cohort. Vaccine. 2015 Mar 17;33(12):1446–1452. doi: 10.1016/j.vaccine.2015.01.065
68. Costello R, Winthrop KL, Pye SR, et al. Influenza and pneumococcal vaccination uptake in patients with rheumatoid arthritis treated with immunosuppressive therapy in the UK: a retrospective cohort study using data from the clinical practice Research datalink. PLoS One. 2016;11(4):e0153848. doi: 10.1371/journal.pone.0153848
69. British HIV Association. British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. 2015 [cited 2022 December 06]. Available from: https://www.bhiva.org/vaccination-guidelines
70. Chadwick DR, Corbett K, Mann S, et al. Evaluation of a vaccine passport to improve vaccine coverage in people living with HIV. Int J STD AIDS. 2018 Oct;29(12):1190–1193. doi: 10.1177/0956462418779472
71. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009 Oct;15(10):1143–1238. doi: 10.1016/j.bbmt.2009.06.019
72. Miller P, Patel SR, Skinner R, et al. Joint consensus statement on the vaccination of adult and paediatric haematopoietic stem cell transplant recipients: prepared on behalf of the British society of blood and marrow transplantation and cellular therapy (BSBMTCT), the children's cancer and Leukaemia group (CCLG), and British infection Association (BIA). J Infect. 2023 Jan;86(1):1–8. doi: 10.1016/j.jinf.2022.11.005
73. NHS Health Scotland. Interventions to engage people aged 60 years and over in influenza, shingles and pneumococcal immunisation programmes. 2020 [cited 2022 August 01]. Available from: http://www.healthscotland.scot/media/2962/interventions-to-engage-people-aged-60-years-and-over-in-immunisation-programmes-feb20.pdf
74. National Institute for Health and Care Excellence. Vaccine uptake in the general population. 2022 [cited 2022 August 01]. Available from: www.nice.org.uk/guidance/ng218
75. Wilmore SM, Philip KE, Cambiano V, et al. Influenza and pneumococcal vaccinations in dialysis patients in a London district general hospital. Clin Kidney J. 2014 Feb;7(1):27–32. doi: 10.1093/ckj/sft138
76. Siriwardena AN, Rashid A, Johnson M, et al. Improving influenza and pneumococcal vaccination uptake in high-risk groups in Lincolnshire: a quality improvement report from a large rural county. Qual Primary Care. 2003;11:19–28.
77. Myeloma UK. Vaccines and myeloma Infosheet. 2022 [cited 2023 February 14]. Available from: https://www.myeloma.org.uk/documents/vaccines-and-myeloma-infosheet/
78. Cancer Research UK. Immunisations and cancer treatment. 2022 [cited 2022 December 09]. Available from: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/immunisations-and-cancer-treatment
79. Gallant AJ, Nicholls LAB, Rasmussen S, et al. Changes in attitudes to vaccination as a result of the COVID-19 pandemic: a longitudinal study of older adults in the UK. PLoS One. 2021;16(12):e0261844. doi: 10.1371/journal.pone.0261844
80. NHS England. Update on vaccination and immunisation changes for 2021/22. 2021 [cited 2022 December 09]. Available from: https://www.england.nhs.uk/publication/update-on-vaccination-and-immunisation-changes-for-2021-22/
81. Shea KM, Edelsberg J, Weycker D, et al. Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis. 2014 Mar;1(1):ofu024. doi: 10.1093/ofid/ofu024
82. Pelton SI, Shea KM, Farkouh RA, et al. Rates of pneumonia among children and adults with chronic medical conditions in Germany. BMC Infect Dis. 2015 Oct 30;15(1):470. doi: 10.1186/s12879-015-1162-y
83. Bonnave C, Mertens D, Peetermans W, et al. Adult vaccination for pneumococcal disease: a comparison of the national guidelines in Europe. Eur J Clin Microbiol Infect Dis. 2019;38(4):785–791. doi: 10.1007/s10096-019-03485-3
84. Centers for Disease Control and Prevention. The Pink Book. Chapter 17: pneumococcal disease. 2022 [cited 2022 July 28]. Available from: https://www.cdc.gov/vaccines/pubs/pinkbook/pneumo.html#pneumococcal-vaccines
85. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. Adults: Updated recommendations of the advisory Committee on immunization practices — United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71:109–117. doi: 10.15585/mmwr.mm7104a1
86. Ministère des Affaires Sociales et de la Santé. Calendrier des vaccinations et recommandations vaccinales 2022. 2022 [cited 2022 August 01]. Available from: https://solidarites-sante.gouv.fr/IMG/pdf/calendrier_vaccinal_2022_mis_a_jour_juin_2022_v2.pdf
87. STIKO. Recommendations by the Standing vaccination Committee (STIKO) at the Robert Koch Institute. 2023 [cited 2023 August 24]. Available from: https://www.rki.de/EN/Content/infections/Vaccination/recommandations/recommendations_node.html
88. Government of Canada. Pneumococcal vaccine: Canadian immunization guide. 2023 [cited 2023 August 24]. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-16-pneumococcal-vaccine.html#a10
89. Government of Canada. Public health level recommendations on the use of pneumococcal vaccines in adults, including the use of 15-valent and 20-valent conjugate vaccines. 2023 [cited 2023 June 01]. Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/public-health-level-recommendations-use-pneumococcal-vaccines-adults-including-use-15-valent-20-valent-conjugate-vaccines.html
90. Australian Government. Pneumococcal disease. 2023 [cited 2023 August 24]. Available from: https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/pneumococcal-disease
91. New Zealand Government. Immunisation Handbook 2020. Chapter 16: pneumococcal disease.2020 [cited 2022 August 05]. Available from: https://www.health.govt.nz/our-work/immunisation-handbook-2020/16-pneumococcal-disease
92. European Centre for Disease Prevention and Control. Pneumococcal disease: recommended vaccinations. 2022 [cited

2022 July 28]. Available from: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=25&SelectedCountryIdByDisease=-1
93. Crooke SN, Ovsyannikova IG, Poland GA, et al. Immunosenescence and human vaccine immune responses. Immun Ageing. 2019;16(1):25. doi: 10.1186/s12979-019-0164-9
94. Kuan V, Denaxas S, Gonzalez-Izquierdo A, et al. A chronological map of 308 physical and mental health conditions from 4 million individuals in the English national Health Service. Lancet Digital Health. 2019;1(2):e63–e77. doi: 10.1016/S2589-7500(19)30012-3
95. Teh WH, Smith CJ, Barlas RS, et al. Impact of stroke-associated pneumonia on mortality, length of hospitalization, and functional outcome. Acta Neurol Scand. 2018 Oct;138(4):293–300. doi: 10.1111/ane.12956
96. Mullerova H, Chigbo C, Hagan GW, et al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir med. 2012 Aug;106(8):1124–1133. doi: 10.1016/j.rmed.2012.04.008
97. Zirk-Sadowski J, Masoli JA, Delgado J, et al. Proton-pump inhibitors and long-term risk of community-acquired pneumonia in older adults. J Am Geriatr Soc. 2018 Jul;66(7):1332–1338. doi: 10.1111/jgs.15385
98. Mooney JD, Imarhiagbe M, Ling J. Should UK pneumococcal vaccine eligibility criteria include alcohol dependency in areas with high alcohol-related mortality? Vaccines (Basel). 2018 May 2;6(2):25. doi: 10.3390/vaccines6020025
99. Baskaran V, Lim WS, McKeever TM. Effects of tobacco smoking on recurrent hospitalisation with pneumonia: a population-based cohort study. Thorax. 2022 Jan;77(1):82–85. doi: 10.1136/thoraxjnl-2020-216494
100. Millett ER, De Stavola BL, Quint JK, et al. Risk factors for hospital admission in the 28 days following a community-acquired pneumonia diagnosis in older adults, and their contribution to increasing hospitalisation rates over time: a cohort study. BMJ Open. 2015 Dec 1;5(12):e008737. doi: 10.1136/bmjopen-2015-008737
101. Torén K, Blanc PD, Naidoo R, et al. Cumulative occupational exposure to inorganic dust and fumes and invasive pneumococcal disease with pneumonia. Int Arch Occup Environ Health. 2022 Oct;95(8):1797–1804. doi: 10.1007/s00420-022-01848-6
102. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease Active Bacterial Core Surveillance Team. N Engl J Med. 2000 Mar 9;342(10):681–689. doi: 10.1056/NEJM200003093421002
103. McGeoch LJ, Ross S, Massa MS, et al. Cigarette smoking and risk of severe infectious respiratory diseases in UK adults: 12-year follow-up of UK biobank. J Public Health. 2023 Jun 22;fdad090. doi: 10.1093/pubmed/fdad090
104. Miyashita L, Suri R, Dearing E, et al. E-cigarette vapour enhances pneumococcal adherence to airway epithelial cells. Eur Respir J. 2018 Feb;51(2):1701592. doi: 10.1183/13993003.01592-2017
105. Tyrrell G, Lee C, Eurich D. Is there a need for pneumococcal vaccination programs for the homeless to prevent invasive pneumococcal disease? Expert Rev Vaccines. 2021 Sep;20(9):1113–1121. doi: 10.1080/14760584.2021.1966301
106. Ly TDA, Perieres L, Hoang VT, et al. Pneumococcal infections and homelessness. J Prev Med Hyg. 2021 Dec;62(4):E950–E957. doi: 10.15167/2421-4248/jpmh2021.62.4.1805
107. Lemay J-A, Ricketson LJ, Zwicker L, et al. Homelessness in adults with invasive pneumococcal disease in Calgary, Canada. Open Forum Infect Dis. 2019;6(10):ofz362. doi: 10.1093/ofid/ofz362
108. National Institute for Health and Care Excellence. Equality impact assessment. Pneumonia in children and adults: diagnosis and management. 2022 [cited 2023 August 01]. Available from: https://www.nice.org.uk/guidance/GID-NG10357/documents/equality-impact-assessment
109. Thomas HL, Gajraj R, Slack MP, et al. An explosive outbreak of Streptococcus pneumoniae serotype-8 infection in a highly vaccinated residential care home, England, summer 2012. Epidemiol Infect. 2015 Jul;143(9):1957–1963. doi: 10.1017/S0950268814002490
110. Amin-Chowdhury Z, Iyanger N, Ramsay ME, et al. Outbreaks of severe pneumococcal disease in closed settings in the conjugate vaccines era, 2010–2018: a systematic review to inform national guidance in the UK. J Infect. 2019;79(6):495–502. doi: 10.1016/j.jinf.2019.10.009
111. Shields A, Faustini SE, Perez-Toledo M, et al. SARS-CoV-2 seroprevalence and asymptomatic viral carriage in healthcare workers: a cross-sectional study. Thorax. 2020;75(12):1089–1094. doi: 10.1136/thoraxjnl-2020-215414
112. Crim C, Calverley PMA, Anderson JA, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol in COPD patients with moderate airflow limitation: the SUMMIT trial. Respir med. 2017 Oct;131:27–34.
113. Szakmany T, Hollinghurst J, Pugh R, et al. Frailty assessed by administrative tools and mortality in patients with pneumonia admitted to the hospital and ICU in Wales. Sci Rep. 2021 Jun 28;11(1):13407. doi: 10.1038/s41598-021-92874-w
114. Ma HM, Yu RH, Woo J. Recurrent hospitalisation with pneumonia is associated with higher 1-year mortality in frail older people. Intern Med J. 2013 Nov;43(11):1210–1215. doi: 10.1111/imj.12258
115. Qcovid. Qcovid® risk calculator. 2022 [cited 2022 July 28]. Available from: https://qcovid.org/
116. Bertran M, Amin-Chowdhury Z, Sheppard CL, et al. Increased incidence of invasive pneumococcal disease among children after COVID-19 pandemic, England. Emerg Infect Dis. 2022 Aug;28(8):1669–1672. doi: 10.3201/eid2808.220304
117. UK Health Security Agency. Pneumococcal disease: cases caused by strains covered by Prevenar 13 vaccine. 2023 [cited 2023 June 01]. Available from: https://www.gov.uk/government/publications/pneumococcal-disease-cases-caused-by-strains-covered-by-prevenar-13-vaccine/pneumococcal-disease-cases-caused-by-strains-covered-by-prevenar-13-vaccine
118. Perniciaro S, van der Linden M, Weinberger DM. Reemergence of invasive pneumococcal disease in Germany during the spring and summer of 2021. Clin Infect Dis. 2022 Feb 7;75(7):1149–1153. doi: 10.1093/cid/ciac100
119. Amin-Chowdhury Z, Bertran M, Sheppard CL, et al. Does the rise in seasonal respiratory viruses foreshadow the return of invasive pneumococcal disease this winter? Lancet Respir Med. 2022 Jan;10(1):e1–e2. doi: 10.1016/S2213-2600(21)00538-5
120. Campling J, Wright HF, Hall GC, et al. Hospitalization costs of adult community-acquired pneumonia in England. J Med Econ. 2022;25(1):912–918. doi: 10.1080/13696998.2022.2090734
121. Appleby J. NHS sickness absence during the COVID-19 pandemic. BMJ. 2021;372:n471. doi: 10.1136/bmj.n471
122. Propper C, Stoye G, Zaranko B. The wider impacts of the coronavirus pandemic on the NHS. Fiscal Stud. 2020;41(2):345–356. doi: 10.1111/1475-5890.12227
123. Buchy P, Ascioglu S, Buisson Y, et al. Impact of vaccines on antimicrobial resistance. Int J Infect Dis. 2020 Jan;90:188–196.
124. Nowakowska M, van Staa T, Mölter A, et al. Antibiotic choice in UK general practice: rates and drivers of potentially inappropriate antibiotic prescribing. J Antimicrob Chemother. 2019;74(11):3371–3378. doi: 10.1093/jac/dkz345
125. Petersen I, Hayward AC. On behalf of the SACAR surveillance Subgroup. Antibacterial prescribing in primary care. J Antimicrob Chemother. 2007;60(Suppl 1):i43–i47. doi: 10.1093/jac/dkm156
126. UK Health Security Agency. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR). 2022 [cited 2023 August 01]. Available from: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

127. O'Neill J. Tackling globally: final report and recommendation. The review on antimicrobial resistance. 2016 [cited 2022 August 01]. Available from: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf
128. Klugman KP, Black S. Impact of existing vaccines in reducing antibiotic resistance: primary and secondary effects. Proc Nat Acad Sci. 2018;115(51):12896–12901. doi: 10.1073/pnas.1721095115
129. Burk M, El-Kersh K, Saad M, et al. Viral infection in community-acquired pneumonia: a systematic review and meta-analysis. Eur Respir Rev. 2016 Jun;25(140):178–188. doi: 10.1183/16000617.0076-2015
130. Mitsi E, Reine J, Urban BC, et al. Streptococcus pneumoniae colonization associates with impaired adaptive immune responses against SARS-CoV-2. J Clin Invest. 2022 Apr 1;132(7):e157124. doi: 10.1172/JCI157124
131. Lewnard JA, Bruxvoort KJ, Fischer H, et al. Prevention of coronavirus disease 2019 among older adults receiving pneumococcal conjugate vaccine suggests interactions between Streptococcus pneumoniae and severe acute respiratory syndrome coronavirus 2 in the respiratory tract. J Infect Dis. 2022 May 16;225(10):1710–1720. doi: 10.1093/infdis/jiab128

Journal of Medical Economics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijme20

Hospitalization costs of adult community-acquired pneumonia in England

James Campling, Hannah F. Wright, Gillian C. Hall, Tendai Mugwagwa, Andrew Vyse, Diana Mendes, Mary P. E. Slack & Gillian F. Ellsbury

To cite this article: James Campling, Hannah F. Wright, Gillian C. Hall, Tendai Mugwagwa, Andrew Vyse, Diana Mendes, Mary P. E. Slack & Gillian F. Ellsbury (2022) Hospitalization costs of adult community-acquired pneumonia in England, Journal of Medical Economics, 25:1, 912-918, DOI: 10.1080/13696998.2022.2090734

To link to this article: https://doi.org/10.1080/13696998.2022.2090734

JOURNAL OF MEDICAL ECONOMICS
2022, VOL. 25, NO. 1, 912–918
https://doi.org/10.1080/13696998.2022.2090734
Article 0118-FT.R1/2090734

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Hospitalization costs of adult community-acquired pneumonia in England

James Campling[a], Hannah F. Wright[a], Gillian C. Hall[b], Tendai Mugwagwa[c], Andrew Vyse[a], Diana Mendes[c], Mary P. E. Slack[d] and Gillian F. Ellsbury[a]

[a]Vaccines Medical Affairs, Pfizer Ltd. UK, Tadworth, Surrey, UK; [b]Gillian Hall Epidemiology Ltd., London, UK; [c]Health & Value, Pfizer Ltd. UK, Tadworth, Surrey, UK; [d]School of Medicine & Dentistry, Griffith University, Southport, Queensland, Australia

ABSTRACT

Objective: Accurate and up-to-date figures of the cost of community-acquired pneumonia (CAP) hospitalization are needed to understand the associated economic burden for public health decision-makers. Recent estimates are lacking, and previously published estimates differ markedly. Our objective was to estimate the current mean cost to the UK National Health Service (NHS) for adult hospitalized CAP.

Methods: All CAP hospitalizations in 2019 for those aged ≥18 years were identified from English Hospital Episode Statistics (HES). Each hospitalization was mapped to the tariff cost paid to the care provider within the NHS, including critical care costs and accounting for length of stay and complexity of the case. Mean hospitalization costs were estimated in total and in individuals with defined underlying comorbidities.

Results: A mean cost of £3,904 was estimated for 187,251 CAP admissions providing a total cost of approximately £731 million per annum. The mean cost was £3,402, excluding critical care costs, and £11,654 for critical care episodes in the 4.4% of admissions receiving this care. Groups at high risk of CAP had higher mean costs, ranging from £4,458 for people with diabetes to £5,215 for those with heart disease aged <65 years and £4,356 for those with heart disease to £4,751 for those with liver disease aged >65 years who comprised 74.3% of admissions overall.

Conclusion: This estimate of the cost of hospitalization for CAP from the total population and in those with certain underlying comorbidities will allow a valid understanding of the cost-benefit of vaccination and evidence-based prioritization of pneumococcal vaccination to those at highest risk.

PLAIN LANGUAGE SUMMARY

- Community-acquired pneumonia (CAP) is a disease that is most commonly caused in England by the bacterium *Streptococcus pneumoniae*, which infects patients outside of a hospital. Patients who suffer from CAP often require hospitalization, which incurs a cost to the UK National Health Service (NHS). The goal of this study was to establish the annual cost of hospitalized CAP.
- The researchers used England's national healthcare database, known as Hospital Episodes Statistics (HES), to select all adults in England who were hospitalized for CAP in 2019. For the 187,251 patients hospitalized, an average cost of £3,904 per person was estimated, amounting to a total cost of £731 million per year to the NHS. Most people admitted to hospital with CAP were at risk for the disease (due to factors such as increased age or presence of another disease) and the cost of treatment for this subgroup was disproportionately larger than that for treatment of patients not at risk. Furthermore, while approximately 5% of patients admitted for CAP received critical care during treatment, the average cost for these patients was over £8,000 higher than for those outside this subsection.
- The costs of hospitalization reported in this analysis were higher than previously estimated. The researchers highlighted weaknesses in other studies and limitations of the current study which could explain the difference. This work provides up-to-date figures for the cost of treating CAP in hospital in England. Public health decision-makers can use these estimates to determine the cost-benefit of vaccines that can help protect against important causes of CAP, particularly vaccines that target *S. pneumoniae*.

ARTICLE HISTORY
Received 16 March 2022
Revised 13 June 2022
Accepted 14 June 2022

KEYWORDS
Hospital costs; pneumonia; pneumococcal; risk groups; community-acquired pneumonia; NHS cost; cost of illness

JEL CLASSIFICATION CODES
I10; I11

CONTACT James Campling james.campling@pfizer.com Vaccines Medical Affairs, Pfizer Ltd., UK, Walton Oaks, Dorking Road, Tadworth, KT20 7NS, Surrey, UK

Supplemental data for this article is available online at https://doi.org/10.1080/13696998.2022.2090734.

Introduction

Community-acquired pneumonia (CAP) is a common acute infection with an increasing rate of hospitalization in England. *Streptococcus pneumoniae* is the most commonly identified etiology[1] and has reported to be the pathogen responsible for the highest average annual respiratory admissions in England for people aged ≥65 years[2]. Older adults and individuals with certain clinical conditions, such as chronic heart or lung disease, are at an increased risk of CAP[1,3,4]. Intensive care admissions and death are both reported in approximately 8% of hospitalizations for CAP in England (2013–2018)[1], with pneumonia noted as a cause in 18,184 deaths in England in 2020[5]. The clinical and economic burdens resulting from CAP hospitalization are therefore considerable.

An understanding of this economic burden is important, not least to allow analysis of the cost-effectiveness of pneumococcal vaccination. However, published estimates of the cost of CAP hospitalization in UK pneumococcal vaccine cost-effectiveness analyses vary considerably, between £661 and £1,218[6–8]. By comparison, the tariff price paid to a care provider within the NHS internal market for the least complicated non-elective admission for pneumonia was £1,836 in 2019/20 (healthcare resource group [HRG] code: DZ11V)[9] and an analysis of the cost of admission for "pneumonia with an unspecified organism" has been estimated as £3,256[10].

There are valid reasons why estimates of cost for CAP admission may vary including different methodologies, and updated prices and costing methods. However, these differences, along with uplifting to account for inflation, are unlikely to account for the scale of the disparity.

The objective of this study was to address the uncertainty in the cost of CAP hospitalization for adults in England by providing a current estimate based on Hospital Episode Statistics (HES) linked to tariff prices, which is the cost paid by the NHS.

Methods

Data source

This retrospective observational analysis of a cohort of patients admitted for CAP in the calendar year 2019 was based on HES and critical care datasets provided by NHS Digital. HES is a data warehouse which contains information for all admissions, accident and emergency (A&E) attendances, and outpatient appointments at NHS hospitals in England and at treatment centers funded by the NHS[11,12]. The calendar year 2019 was chosen as this was not affected by the COVID-19 pandemic.

The HES Admitted Patient Care (APC) file includes HRGs, admission dates, length of stay, completed consultant episodes within the overall admission spell, and current diagnoses (10th International Classification of Diseases [ICD-10][13]) and procedures (Office of Population Censuses and Surveys (OPCS)-4.9 for procedures[14]) for inpatient admissions. Elective and non-elective admissions and critical care unit stays are flagged. On discharge, the NHS allocates the most relevant HRG code to the admission based on a combination of procedure and diagnostic codes, including comorbidities[12]. HRGs are clinically meaningful groups of diagnoses and interventions that consume similar levels of NHS resources. Therefore, the HRG can reflect the complexity of the case and the most resource-intensive activity occurring within an admission rather than the initial diagnosis. The HRG code is converted into a cost, accounting for length of stay, using the national tariff cost paid to the care provider within the NHS internal system[12]. The dataset used in the study was the final release of HES data for financial years 2018 and 2019, the conversion of procedure and diagnostic codes to HRGs used HRG 4+ grouper software (National Casemix Office, Winchester, UK).

The HES outpatient file includes HRGs which account for first, follow-up single or multi-professional visits, and, separately, outpatient procedures. The HES A&E file includes HRGs for each attendance. The Critical Care Dataset is linked to the APC file and provides the level of care delivered and the number of bed days. Each record includes a patient identifier which links activity across care settings preventing double counting of patients. No ethics approval was required for the study as it was based on anonymous secondary data.

Study population

The study population comprised all patients in England with at least one non-elective inpatient admission with pneumonia recorded as a primary diagnosis position one (reason for admission) in the HES APC during 2019 for patients ≥18 years on admission date (study admission). Every admission was included into the study including patients who were admitted on more than one occasion during the study year. Pneumonia was defined as an ICD-10 code J12 to J18 (see Supplementary Table S1 for all ICD-10 code lists). Each study admission during 2019 was analyzed separately. Admissions which may have been hospital-acquired pneumonia were excluded (a prior admission (elective or non-elective) with discharge <28 days prior to the study admission date ($N = 84{,}228$), or a record of "nosocomial condition" (ICD-10 Y95) during the study admission ($N = 47{,}270$)).

Costs

Costs were derived from the HES dataset by mapping HRGs to an appropriate national tariff (APC, A&E, or outpatient) corresponding to the activity year (i.e. activity in 2018/2019 used tariff 2018/2019, activity in 2019/2020 used tariff in 2019/2020) and applying the appropriate market forces factor to account for regional variation in costs[9,12]. APC HRGs were mapped allowing for the activity type (elective, day case, and non-elective) with extra cost included for excess bed days, and complications and comorbidities as specified by the tariff. Outpatient attendance and procedure, and A&E HRGs were mapped directly to the appropriate tariff. Critical care activity is funded separately so the cost was obtained through the 2018/2019 Reference Costs Grouper using "CCU01 non-specific, general adult critical care" and a

"reported level of care" which allows for increasing costs with a greater number of organs supported.

The primary analyses were completed for the total study population and after stratification by age <65 years or ≥65 years. Age was defined as that on the admission date throughout the analyses. The number of admissions and those with a critical care spell or receiving assisted ventilation at any time during admission were estimated. Average total costs for study admissions were estimated (including HES and critical care activity) from admission date to discharge date on the APC file and, separately, for all activity for a further 30, 60, or 90 days to account for resource use after discharge. The average cost and length of stay were estimated for admissions with and without an episode of critical care. The number of admissions with a critical care episode was estimated and broken down into the number of days spent in critical care (bed days) and the total length of stay in hospital.

The calculation of total costs was repeated for three separate sets of groupings: study admissions with pneumococcal pneumonia; in those aged 65–74 years, 75–84 years, and ≥85 years; and for first study admission in those with a history of chronic comorbidities. Pneumococcal pneumonia was defined as an entry for ICD-10 code J13 (*Streptococcus pneumoniae*) in any position, or ICD-10 code B953 (*Streptococcus pneumoniae* as the cause of diseases classified elsewhere) in position 2, on HES APC for the study admission. The comorbidities included were based on those in previous hospitalized CAP cost estimate analyses but excluding immunocompromised patients which cannot reliably be identified from HES data. The comorbidities were respiratory disease, heart disease, kidney disease, liver disease, and diabetes mellitus identified by an ICD-10 code recorded in the HES APC, outpatient, or A&E file at any time before or during the first study admission. The comorbidity code lists replicated those in Rozenbaum et al.[6] and van Hoek et al.[7] (Supplementary Table S1). However, these studies included pediatric ICD-10 codes, while the current study only included adults. We therefore ran the main analyses with and without these codes.

Results

During 2019, there were 187,251 admissions for CAP in 177,865 people, 74.3% of admissions were in those ≥65 years (Table 1). The mean cost for the CAP hospital admission only was £3,904, increasing to £5,813 when all secondary care costs in the 90 days after discharge were included. The HRG most frequently assigned was DZ11V (lobar, atypical or viral pneumonia, without interventions, with CC [comorbidity and complexity] score 0–3) in 36,532 (19.5%) of study admissions, followed by DZ11U (lobar, atypical or viral pneumonia, without interventions, with CC score 4–6) in 36,526 (19.5%) of admissions (Supplementary Table S2). There was a critical care episode in 4.4% of admissions overall and in 7.4% in those aged <65 years. The mean costs were £3,402 for admissions when critical care episodes were excluded and £11,654 for critical care costs alone. There was a record of pneumococcal pneumonia in 3,572 (1.9%) of admissions, 45.1% of which were in people aged <65 years with a mean

Table 1. Number, critical care, cost, and length of stay of admissions for CAP by age group.

Age band (years)	Total	18–<65	≥65
Admissions (% total)	187,251	48,052 (25.7)	139,199 (74.3)
Patients (% total)	177,865	46,466 (26.1)	131,442 (73.9)
% Male[a]	49.1	50.0	48.8
Admissions with assisted ventilation (% of admissions in age group)[b]	10,027 (5.4)	3,186 (6.6)	6,841 (4.9)
Admissions requiring critical care (% of admissions in age group)	8,319 (4.4)	3,569 (7.4)	4,750 (3.4)
	Cost per admission £		
	Mean (SD)		
	Median (IQR)		
Admission only	3,904 (5,551)	3,450 (8,025)	4,061 (4,371)
	3,032 (1,888–4,633)	1,975 (1,205–3,085)	3,156 (2,256–4,953)
Admission to discharge +30 days	4,783 (6,149)	4,102 (8,395)	5,018 (5,129)
	3,291 (2,051–6,078)	2,270 (1,548–4,154)	4,033 (2,408–6,247)
Admission to discharge + 60 days	5,340 (6,568)	4,514 (8,652)	5,626 (5,644)
	3,755 (2,223–6,483)	2,407 (1,603–4,579)	4,224 (2,530–6,957)
Admission to discharge + 90 days	5,813 (6,976)	4,868 (8,953)	6,139 (6,113)
	4,090 (2,330–7,102)	2,513 (1,670–5,000)	4,419 (2,698–7,483)
Admission only excluding critical care episodes	3,402 (2,354)	2,490 (2,089)	3,717 (2,358)
	2,987 (1,867–4,453)	1,936 (1,039–3,032)	3,121 (2,243–4,837)
Critical care episodes only	11,654 (18,754)	13,316 (22,321)	10,405 (15,427)
	6,688 (3,456–12,597)	6,912 (3,527–14,977)	5,760 (3,456–11,521)
	Length of admission (days)		
	Mean (SD)		
	Median (IQR)		
All admissions	7 (9)	5 (8)	8 (9)
	4 (2–9)	3 (1–6)	5 (2–10)
All admissions excluding critical care episodes	7 (9)	4 (6)	8 (9)
	4 (2–8)	3 (1–5)	5 (2–10)
Admissions with a critical care episode: total length	14 (16)	14 (17)	14 (15)
	10 (5–17)	9 (5–16)	10 (5–17)
Admissions with a critical care episode: length in critical care episode[c]	7 (11)	8 (13)	6 (9)
	4 (2–8)	4 (2–9)	4 (2–7)

[a]Sex not reported in 63 admissions; [b]includes invasive and non-invasive ventilation; [c]bed days in critical care, overnight stays outside critical care.

Table 2. Number, cost, and length of stay of admissions for CAP specified as pneumococcal pneumonia by age group.

Age band (years)	Total (% all admissions)	*N* (% pneumococcal admissions)	
		18–64	≥65
Admissions	3,572 (1.9)	1,610 (45.1)	1,962 (54.9)
% Male[a]	48.4	50.3	46.8
	Length of stay (days)[b]		
	Mean (SD)		
	Median (IQR)		
All admissions including critical care episodes	10 (11)	8 (10)	10 (11)
	6 (4–11)	5 (3–10)	7 (4–12)
All admissions excluding critical care episodes	8 (9)	6 (8)	9 (10)
	5 (3–9)	4 (2–7)	6 (4–11)
	Cost per admission £		
	Mean (SD)		
	Median (IQR)		
Admission only	6,574 (11,692)	7,203 (14,266)	6,060 (9,029)
	3,149 (2,227–6,160)	2,536 (1,901–6,111)	4,104 (2,456–6,160)
Admission to discharge + 30 days	7,245 (11,951)	7,761 (14,428)	6,824 (9,438)
	3,911 (2,376–7,280)	3,036 (1,975–7,189)	4,237 (2,715–7,320)
Admission to discharge + 60 days	7,647 (12,128)	8,090 (14,547)	7,284 (9,701)
	4,145 (2,423–7,875)	3,179 (2,083–7,819)	4,412 (2,896–7,898)
Admission to discharge + 90 days	7,965 (12,261)	8,332 (14,624)	7,665 (9,912)
	4,237 (2,488–8,351)	3,377 (2,139–8,173)	4,643 (2,975–8,572)

[a]No missing data; [b]Bed days in critical care, overnight stays outside critical care.

Table 3. Number and cost of admissions for CAP in people with chronic comorbidities by age group.

Comorbidity[a]	Chronic respiratory disease	Chronic heart disease	Chronic kidney disease	Chronic liver disease	Diabetes mellitus
		18–64 Years of age			
Number (% people in age group)	12,796 (27.5)	11,794 (25.4)	3,445 (7.4)	3,960 (8.5)	7,667 (16.5)
		Cost per admission £			
		Mean (SD)			
		median (IQR)			
Admission only	4,629 (11,443)	5,215 (12,405)	5,124 (8,339)	5,068 (7,856)	4,458 (8,008)
	2,886 (1,891–4,524)	3,015 (1,892–4,943)	3,067 (1,923–5,165)	3,061 (1,937–5,115)	2,766 (1,669–4,575)
Admission to discharge +30 days	5,541 (11,818)	6,262 (12,809)	6,458 (8,938)	6,113 (8,373)	5,395 (8,518)
	3,162 (2,148–6,084)	3,424 (2,198–6,640)	3,955 (2,351–7,322)	3,708 (2,351–6,670)	3,119 (1,937–6,033)
Admission to discharge +60 days	6,229 (12,071)	6,992 (13,089)	7,391 (9,404)	6,865 (8,784)	6,078 (8,936)
	3,581 (2,301–6,988)	4,019 (2,366–7,664)	4,468 (2,533–8,680)	4,222 (2,440–7,776)	3,447 (2,155–6,939)
Admission to discharge +90 days	6,842 (12,418)	7,632 (13,450)	8,190 (10,066)	7,507 (9,317)	6,648 (9,401)
	4,045 (2,400–7,734)	4,326 (2,424–8,606)	4,892 (2,711–9,801)	4,502 (2,600–8,736)	3,806 (2,253–7,664)
		≥65 years of age			
Number (% age group)	62,053 (47.2)	89,841 (68.4)	38,065 (29.0)	7,768 (5.9)	36,458 (27.8)
		Cost per admission £			
		Mean (SD)			
		median (IQR)			
Admission only	4,356 (4,732)	4,428 (4,685)	4,561 (4,028)	4,751 (5,096)	4,416 (4,336)
	3,888 (2,401–5,727)	3,972 (2,424–5,932)	4,166 (2,887–6,103)	4,166 (2,547–6,142)	3,980 (2,423–6,019)
Admission to discharge +30 days	5,431 (5,478)	5,489 (5,460)	5,711 (4,982)	5,970 (5,995)	5,532 (5,245)
	4,240 (2,749–6,655)	4,271 (2,899–6,678)	4,500 (3,053–6,960)	4,596 (3,037–7,147)	4,289 (2,890–6,747)
Admission to discharge +60 days	6,150 (6,024)	6,167 (5,989)	6,442 (5,610)	6,786 (6,630)	6,281 (5,866)
	4,609 (2,999–7,460)	4,619 (3,037–7,445)	4,992 (3,159–7,687)	5,164 (3,167–8,035)	4,684 (3,037–7,552)
Admission to discharge +90 days	6,757 (6,525)	6,740 (6,471)	7,075 (6,206)	7,491 (7,214)	6,900 (6,440)
	4,993 (3,078–8,246)	4,984 (3,098–8,158)	5,643 (3,344–8,594)	5,810 (3,337–9,239)	5,096 (3,098–8,439)

[a]See Supplementary material for comorbidity code lists.

cost of £6,574 across all groups (Table 2). Most people with an admission had one or more comorbidity, 51.4% in those <65 years and 78.3% in those aged ≥65 years. Among the subgroup with comorbidities admission costs were higher in those aged <65 years than in older adults (Table 3). In general costs increased with increasing age and were higher than the overall mean in people with either pneumococcal infections or any comorbid conditions (Figure 1). Costs increased until 75 years of age, although length of stay continued to increase (Table 4).

Review of the data identified a positively skewed distribution of costs per admission and six outliers, each with a total cost of >£200,000. The mean total cost of £3,890 for the admission alone without outliers was estimated for the total population in a post-hoc analysis (see Supplementary Table S3). A sensitivity analysis repeated the comorbidity analysis

after removing the pediatric ICD-10 codes included in previous analyses (Supplementary Table S4).

Discussion

This large study of all 187,251 hospital admissions for CAP in England in 2019 provides a mean cost to the NHS of £3,904. The total cost of hospitalized CAP in England can therefore be estimated as approximately £731 million per annum in 2019 figures. While the proportion of patients who received critical care was small, these episodes increased the overall mean cost of admission by approximately 15% which had a greater impact on the admission costs for those aged <65 years, who were more frequently admitted to critical care (7.4%) compared to all adults (4.4%). Admission costs were higher in at risk populations, including both older people and those with comorbid conditions. Costs increased with age generally, being higher in 65–74-year-olds than in those <65 years. The majority of the study population had at least one chronic comorbidity including approximately 50% of people aged 18–64 years. The higher admission costs in those with chronic comorbidities, as well as that in pneumococcal pneumonia, will partly be the result of higher costs allowed for in these groups within the NHS tariff. The costs in those with a diagnosis of pneumococcal pneumonia may also be biased upwards if the causal organism is more likely to be identified in more severe, complicated, or resistant disease. The proportion with pneumococcal pneumonia (1.9%) is low compared to 37% of admissions for CAP when more routine screening for pneumococcal pneumonia is in place[1] suggesting under ascertainment.

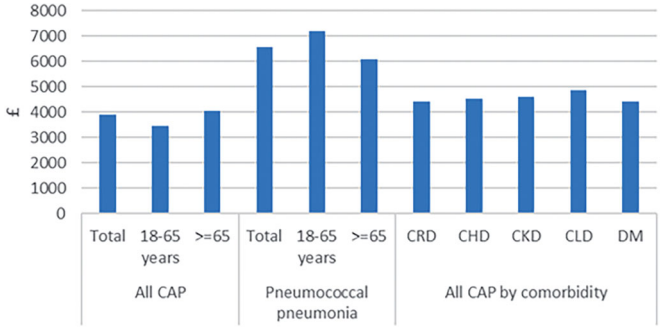


Figure 1. Average cost of CAP hospitalization stratified by age, a diagnosis of pneumococcal pneumonia, and by comorbidity.

The higher risk of hospitalization for CAP in individuals with chronic comorbidities is consistent with previous reports[4,15]. A smaller proportion of <65s in the current study may account for the slightly fewer CAP admissions receiving critical care than reported elsewhere (4.4% compared to 5.2% or 7.7%)[1,16], as the number of critical care stays decrease with age. When time periods after discharge are included costs increase, even in the young, suggesting that the total cost for CAP is greater than that due to the primary admission. This may be partially explained by previous findings that, in people with chronic comorbidities, there is both an increased risk of CAP hospitalization and that hospital admissions increased after CAP[4,17,18]. In addition, high rates, and an increased risk, of cardiac disease are reported in the short-term after CAP hospitalization[19,20].

Our estimate of the cost of CAP admissions is considerably higher than the previous estimates in pneumococcal vaccine cost-effectiveness analyses which ranged from £661 to £1,218. In 2012, Rozenbaum et al.[6] estimated a mean cost of pneumonia admission of £661 in people at increased risk of invasive pneumococcal disease using the HRG code uncomplicated DZ11C (lobar, atypical, or viral pneumonia) and based on 2009–2010 NHS reference costs. This estimate of £661 was subsequently adjusted for inflation to £715 (to 2014 prices) in a 2016 cost-effectiveness analyses by van Hoek and Miller[8] in immunocompetent people aged 65 years and older. Further inflation of the £715 estimate to the 2019 costs used in the current study would provide a figure of £789 based on the Hospital and Community Health Services Index pay and prices percentage increase (see Supplementary Table S5)[21]. To help illustrate the

Table 4. Number, cost, and length of stay of admissions for CAP in older people.

Age band (years)	65–74	75–84	≥85
Admissions (% total)	35,878 (19.2)	51,939 (27.7)	51,382 (27.4)
Patients (% total)	34,102 (19.2)	49,013 (27.6)	48,504 (27.3)
% Male[a]	52.7	51.7	43.1
	Length of stay (days)[b]		
	Mean (SD)		
	Median (IQR)		
All admissions including critical care episodes	6 (8)	8 (10)	9 (10)
	4 (2–8)	5 (2–10)	6 (3–12)
All admissions excluding critical care episodes[b]	6 (8)	8 (9)	9 (10)
	4 (2–7)	5 (2–9)	6 (3–12)
	Cost per admission £		
	Mean (SD)		
	Median (IQR)		
Admission only	3,966 (5,799)	4,091 (4,621)	4,098 (2,584)
	2,907 (1,886–4,391)	3,168 (2,283–4,966)	3,937 (2,424–5,703)
Admission to discharge +30 days	4,916 (6,419)	5,071 (5,369)	5,035 (3,652)
	3,168 (2,077–5,842)	4,051 (2,423–6,278)	4,218 (2,863–6,396)
Admission to discharge + 60 days	5,549 (6,886)	5,709 (5,868)	5,596 (4,285)
	3,552 (2,252–6,556)	4,240 (2,577–7,071)	4,408 (2,975–7,053)
Admission to discharge + 90 days	6,095 (7,348)	6,256 (6,328)	6,052 (4,798)
	3,943 (2,365–7,317)	4,482 (2,774–7,616)	4,674 (3,044–7,462)

[a]No missing data; [b]Bed days in critical care, overnight stays outside critical care.

methodological discrepancy an unrelated estimate provided for infants by van Hoek in 2012 used the same HRG code: DZ11C combined with the cost per bed day and length of stay of about 4 days to provide a cost of CAP of £1,218 based on 2008/2009 NHS reference costs. This example, when adjusted for inflation to 2019 levels, works out to be £1,454[7]. There are several non-inflationary reasons for the difference between our current estimates and these previous studies. The previous studies assumed that all hospitalized CAP was appropriately represented by uncomplicated lobar, atypical or viral pneumonia (HRG code DZ11C, the lowest complexity level available at that time) while the current study includes all complication and comorbidity scores, interventions (multiple, single, and without), and added critical care costs. In practice, only a fifth of study admissions were costed using the lowest complexity level pneumonia HRG code available. Focusing on the lowest complexity levels does not capture the higher resource use and costs associated with patients with more complications and comorbidities resulting in an underestimation. In addition, in all three previous studies, the estimated cost of hospitalized CAP applied in the cost-effectiveness analysis was a cost per admission (or spell) despite the unit of measure in the NHS reference costs at the time being cost per finished consultant episode (FCE)[22,23]. This further underestimates the cost per admission since there can be more than one FCE in a spell. For example, van Hoek and Miller[8] used a mean length of stay of 4 days based on reference costs per FCE for uncomplicated cases, whereas the current study estimated a mean length of an admission of 7 days based on HES data. Conversion of the estimates from cost per FCE to cost per spell would have required adjustment with either the number of FCEs or the length of stay for a spell. NHS reference costs in 2013/2014 (the date of the van Hoek and Miller[8] analysis) did report both cost per FCE and cost per spell[24,25]. Finally, our study included all CAP admissions throughout the year and did not exclude patients who had multiple admissions. We recognize that there is the potential for those patients who were admitted more than once to have higher costs compared to those attending hospital once. This, however, only applied to 5% of the dataset so the potential to skew the overall mean cost would be minimal and it is important to provide a complete datasheet. Our new hospitalization costs provide a current and robust estimate for the actual inpatient healthcare costs paid to hospitals in England for patients that were treated for pneumonia in 2019. This cost data will be valuable for future cost effectiveness analyses for potential future interventions, including adult pneumococcal vaccines. These costs, however, need to be inflated when used in further analyses. We have left this to researchers conducting further analyses to allow for a more straightforward adjustment when the appropriate year and percentage inflation will be known. Cost effectiveness analyses for interventions that target causes of adult CAP in the UK generally only consider hospitalization costs, which provided the rationale this study, however further costs are incurred by the NHS within primary care. Further work analyzing primary care costs is needed to provide an estimate for the total cost to the NHS for pneumonia in England. Furthermore, cost estimates for other diseases related to CAP such as IPD would help strengthen future, specific cost effectiveness analyses.

The strengths of the current analysis are the almost universal coverage of secondary care activity in England[26]. All adult hospitalizations for CAP were included, as well as subgroups and critical care stays. In addition, the reported costs reflect the actual money paid by the Department of Health and Social Care to healthcare providers who treat hospitalized CAP, including critical care costs. Increased costs for more complex admissions are taken into account. As the study was based on the secondary source data HES, it was limited to the data routinely collected. CAP is not specifically coded and was deduced using several variables. Misclassification of pneumonia as a primary diagnosis code has been reported against a case definition which required a chest X-ray[16,27]. This misclassification will include lower respiratory tract infections, such as CAP or COPD, with no radiology workup and may be biased toward older age groups[27]. Some cases of hospital-acquired pneumonia may remain despite exclusion of records with a code for nosocomial disease or recent previous admission. Similarly, CAP diagnosis during a hospitalization for other illness or procedures and readmissions within 28 days may be missed but the use of ICD-10 code Y95 will have minimized this and excluded the majority of cases of hospital acquired pneumonia. Furthermore, in the rare scenario whereby patients were admitted for a new spell of hospitalized CAP between days 29 and 90 post-discharge there would have been double-counting of the spend for these patients. Severity could not be studied as pneumonia severity index or CURB scores are not available in HES. The study data source does not lend itself to a multivariate analysis exploring cost predictors such as age and comorbidities as the costs derived from HRGs are influenced by these variables to some extent. However, such an analysis would provide valuable further insight on the cost of CAP and could form the basis of a subsequent bespoke study.

Conclusions

This analysis provides a contemporary estimate of the cost of hospitalization to the NHS for CAP from the total population and in certain high-risk subgroups. Such estimates are essential to allow a valid understanding of the cost-benefit of vaccination and therefore to inform national vaccine policy of new and existing immunizations that target causes of pneumonia. Information on subgroups allows appropriate, evidence-based, prioritization of pneumococcal vaccination to those at highest risk.

Transparency

Declaration of funding

This study was funded by Pfizer Ltd, UK. Editorial support was provided by Elizabeth Jennings, Lucid Group and was funded by Pfizer Ltd, UK.

Declaration of financial/other interests

JC, HW, TM, AV, DM, GE are employees of Pfizer Ltd, UK, and hold stock or stock options. MS has received personal fees from GlaxoSmithKline, Pfizer, Merck, AstraZeneca, and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards and is currently undertaking contract work for Pfizer. GH received payment from Open Health for her contribution to the current study and has received funding for research and scientific consultancy from several pharmaceutical and healthcare companies outside the submitted work.

All reviewers on this manuscript have received an honorarium from JME for their review work. A reviewer on this manuscript has disclosed that they are a consultant for Merk and their institution has received research funding from Seres Therapeutics. The other reviewers have no conflicts of interest.

Acknowledgements

Dave Heaton provided advice on the HES dataset and data analysis, and Matthew O'Connell for data analysis. Hospital Episode Statistics (HES) Data were re-used with the permission of NHS Digital via Harvey Walsh, Open Health Group.

ORCID

James Campling http://orcid.org/0000-0002-6886-8565
Hannah F. Wright http://orcid.org/0000-0001-8328-7294
Gillian C. Hall http://orcid.org/0000-0001-5081-3710
Tendai Mugwagwa http://orcid.org/0000-0001-7515-8548
Andrew Vyse http://orcid.org/0000-0002-0339-7491
Diana Mendes http://orcid.org/0000-0002-1672-4906
Mary P. E. Slack http://orcid.org/0000-0001-5119-4085
Gillian F. Ellsbury http://orcid.org/0000-0002-6855-4080

References

[1] Pick H, Daniel P, Rodrigo C, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. Thorax. 2020;75(1):38–49.
[2] Sharp A, Minaji M, Panagiotopoulos N, et al. Estimating the burden of adult hospital admissions due to RSV and other respiratory pathogens in England. Influenza Other Respir Viruses. 2021; 16(1):125–131.
[3] Rodrigo C, Bewick T, Sheppard C, et al. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. Eur Respir J. 2015;45(6):1632–1641.
[4] Campling J, Jones D, Chalmers JD, et al. The impact of certain underlying comorbidities on the risk of developing hospitalised pneumonia in England. Pneumonia (Nathan). 2019;11(1):4.
[5] Office for National Statistics. Deaths due to pneumonia; 2020. Available from: https://www.ons.gov.uk/search?q=pneumonia%20statistics.
[6] Rozenbaum MH, van Hoek AJ, Fleming D, et al. Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. BMJ. 2012;345:e6879.
[7] van Hoek AJ, Choi YH, Trotter C, et al. The cost-effectiveness of a 13-valent pneumococcal conjugate vaccination for infants in England. Vaccine. 2012;30(50):7205–7213.
[8] van Hoek AJ, Miller E. Cost-Effectiveness of vaccinating immunocompetent ≥65 year olds with the 13-valent pneumococcal conjugate vaccine in England. PLOS One. 2016;11(2):e0149540.
[9] NHS. National tariff payment system: national prices and prices for emergency care services. 2019. Available from: https://www.england.nhs.uk/publication/national-tariff-payment-system-documents-annexes-and-supporting-documents/.
[10] Jones D, Campling J, Ellsbury G, et al. Establishing the cost of hospitalised community acquired pneumonia (CAP): a hospital episode statistics (HES) analysis. Thorax. 2017;72(S3):A116.
[11] NHS Digital. Hospital episode statistics (HES); 2021. Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics.
[12] Department of Health Payment by Results Team. A simple guide to payment by results. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/213150/PbR-Simple-Guide-FINAL.pdf.
[13] World Health Organisation. International statistical classification of diseases and health problems ICD-102016; 2021. Available from: https://www.who.int/standards/classifications/classification-of-diseases.
[14] Office of Population Censuses and Surveys. OPCS-4 classification of interventions and procedures; 2022. Available from: https://datadictionary.nhs.uk/supporting_information/opcs_classification_of_interventions_and_procedures.html.
[15] Grant LR, Slack MPE, Yan Q, et al. The epidemiologic and biologic basis for classifying older age as a high-risk, immunocompromising condition for pneumococcal vaccine policy. Expert Rev Vaccines. 2021;20(6):691–615.
[16] British Thoracic Society. National audit report: adult community acquired pneumonia audit 2018–2019 national audit period: 1 December 2018 – 31 January 2019; 2019. https://www.brit-thoracic.org.uk/document-library/quality-improvement/audit-reports/adult-community-acquired-pneumonia-201819/.
[17] Campling J, Jones D, Chalmers J, et al. Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England. BMJ Open Resp Res. 2020;7(1):e000703.
[18] Park CM, Kim W, Rhim HC, et al. Frailty and hospitalization-associated disability after pneumonia: a prospective cohort study. BMC Geriatr. 2021;21(1):111.
[19] Bartlett B, Ludewick HP, Lee S, et al. Cardiovascular complications following pneumonia: focus on pneumococcus and heart failure. Curr Opin Cardiol. 2019;34(2):233–239.
[20] Corrales-Medina VF, Alvarez KN, Weissfeld LA, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA. 2015;313(3):264–274.
[21] Personal Social Services Research Unit. Unit costs of health and social care; 2022. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/.
[22] Department of Health and Social Care. National schedule of reference costs 2008–09 for NHS Trusts; 2010. Available from: http://webarchive.nationalarchives.gov.uk/+/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_111607.xls.
[23] Department of Health and Social Care. National schedule of reference costs 2009–10 for NHS Trusts; 2011. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/216308/dh_123455.xls.
[24] Department of Health and Social Care. National schedule of reference costs - year 2013–14 – NHS Trusts and NHS Foundation Trusts (FCE); 2014. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/397469/03a_2013-14_National_Schedule_-_CF-NET_updated.xls.
[25] Department of Health and Social Care. Spell level data: national schedule of reference costs 2013–14 data for NHS Trusts and NHS Foundation Trusts; 2014. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/380038/03b_2013-14_National_Schedule_-_Spells.xls.
[26] Herbert A, Wijlaars L, Zylbersztejn A, et al. Data resource profile: hospital episode statistics admitted patient care (HES APC). Int J Epidemiol. 2017;46(4):1093–1093.
[27] Daniel P, Bewick T, Welham S, et al. Adults miscoded and misdiagnosed as having pneumonia: results from the British Thoracic Society pneumonia audit. Thorax. 2017;72(4):376–379.

Taylor & Francis
Taylor & Francis Group

Expert Review of Vaccines

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierv20

A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK

Andrew Vyse, James Campling, Carole Czudek, Gillian Ellsbury, Diana Mendes, Ralf-Rene Reinert & Mary Slack

To cite this article: Andrew Vyse, James Campling, Carole Czudek, Gillian Ellsbury, Diana Mendes, Ralf-Rene Reinert & Mary Slack (2021) A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK, Expert Review of Vaccines, 20:10, 1311-1325, DOI: 10.1080/14760584.2021.1984888

To link to this article: https://doi.org/10.1080/14760584.2021.1984888

Published online: 19 Oct 2021.

EXPERT REVIEW OF VACCINES
2021, VOL. 20, NO. 10, 1311–1325
https://doi.org/10.1080/14760584.2021.1984888

Taylor & Francis
Taylor & Francis Group

REVIEW

A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK

Andrew Vyse[a], James Campling[a], Carole Czudek[a], Gillian Ellsbury[a], Diana Mendes[b], Ralf-Rene Reinert[c] and Mary Slack[d]

[a]Medical Affairs, Pfizer Ltd, Walton Oaks, Tadworth, KT20 7NS, UK; [b]Health & Value, Pfizer Ltd, Walton Oaks, Tadworth, KT20 7NS, UK; [c]Medical Affairs, Pfizer Inc, Paris, France; [d]School of Medicine & Dentistry, Griffith University, Gold Coast Campus, Queensland 4222, Australia

ABSTRACT

Introduction: The burden of pneumococcal disease in older UK adults remains substantial. Higher valency pneumococcal conjugate vaccines (PCVs) are currently in development with adult formulations for two of these anticipated to become available in 2022. This article collates and reviews relevant candidate data now available that may be used to support cost effectiveness assessments of vaccinating immunocompetent UK adults aged ≥65-years with PCVs.

Areas covered: This article uses published data from surveillance systems, randomized controlled trials and observational studies. It focuses on local data from the UK but where these are either limited or not available relevant global data are considered.

Expert opinion: The body of relevant data now available suggests the UK is well placed to assess the cost effectiveness of vaccinating immunocompetent ≥65-year olds with new generation higher valency PCVs. Recent contemporary data provide important new and robust insights into the epidemiology of pneumococcal disease in older UK adults and help to address much of the uncertainty and data gaps associated with previous analyses. Using these data to make informed decisions about use of new higher valency PCVs for routine use in older adults will be important for public health in the UK.

ARTICLE HISTORY
Received 14 April 2021
Accepted 21 September2021

KEYWORDS
Adult; community acquired pneumonia; cost effectiveness; epidemiology; invasive pneumococcal disease; pneumococcal conjugate vaccines

1. Introduction

Streptococcus pneumoniae (pneumococcus) is a major cause of morbidity and mortality in children and the elderly worldwide [1,2]. Pneumococci are Gram-positive diplococci which can be classified into 100 serotypes, based on their polysaccharide capsule [3]. Diseases caused by pneumococci include invasive infections, such as meningitis, sepsis and bacteremic pneumonia, and mucosal infections, including otitis media, and non-bacteremic pneumonia [4]. Pneumococci are one of the commonest causes of pneumonia [5]. The burden of pneumococcal infection is especially high in older adults, with the vast majority of cases presenting as community acquired pneumonia (CAP) [4]. A pneumococcal conjugate vaccine (PCV) that covered seven serotypes (PCV-7) was introduced in the UK for routine infant immunization in 2006 and then replaced by a 13 valent PCV in 2010 [6]. This resulted in major reductions in vaccine type (VT) pneumococcal disease across the full age range due to both direct and indirect protection [7]. Since 2014 PCV-13 has been indicated for the prevention of invasive pneumococcal disease (IPD) and pneumococcal pneumonia in adults. However, in the UK PCV-13 is currently only recommended for adults at a very high risk of pneumococcal disease [6]. Since 2003 a single dose of the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been routinely offered to all UK adults aged ≥65-years and some clinical risk groups aged ≥2 years [6]. PPV23 is a plain polysaccharide vaccine and, in contrast to PCVs, does not induce a T cell-dependent immune response which is needed for durable protection against pneumococcal disease [8]. Whilst it is generally acknowledged that PPV23 provides limited short-term protection against IPD, studies of the protection that PPV23 provides against noninvasive pneumonia give contradictory conclusions [8–10]. The extent to which PPV23 may provide older adults with meaningful protection against pneumococcal disease therefore continues to be debated with candidate PCVs under development offering potential alternatives. The Joint Committee on Vaccination and Immunization (JCVI) considered routinely vaccinating all immunocompetent UK adults aged ≥65-years with PCV-13 in 2015 but ultimately decided not to recommend proceeding with such an approach [11]. An important contributing factor to this decision was a cost-effectiveness assessment [12], which assumed the incidence of PCV13 VT pneumococcal disease would imminently decline to such a low level in this age group in the UK due to indirect protection from the infant PCV-13 vaccination programme that a PCV-13 programme targeting those aged ≥65-years would not be cost-effective. Whilst this analysis made use of all relevant data available at the time it did recognize areas of uncertainty where data were either limited or lacking. It also assumed that key relevant epidemiological trends reported at the time of the analysis would continue for the foreseeable future.

CONTACT Andrew Vyse andrew.vyse@pfizer.com Pfizer Ltd, Walton Oaks, Tadworth, UK

Article Highlights

- Fifteen and twenty valent pneumococcal conjugate vaccines for use in adult populations are anticipated to become available in 2022. These vaccines include additional pneumococcal serotypes not in PCV-13 that have recently emerged as important causes of pneumococcal disease in the UK, particularly in adults aged ≥65–years, and therefore potentially offer opportunity to better directly protect older UK adults against pneumococcal disease. Candidate data now available that may be considered for use in cost-effectiveness assessments of these vaccines in older immunocompetent UK adults aged ≥65–years are reviewed.
- Robust data giving insight into the incidence, serotype distribution and epidemiological trends over time for invasive pneumococcal disease in UK adults aged ≥65–years to 2016/17 are now available. Some similarly contemporary data for UK adults hospitalised with pneumonia show recent trends and the serotype distribution for pneumococcal pneumonia. However, there is concern there may be substantial under ascertainment in the pneumonia incidence estimates made using these data, with further studies needed that can provide more accurate and robust age stratified estimates of the incidence in UK adults hospitalised with pneumonia.
- A large randomised controlled clinical trial demonstrated the safety and efficacy of PCV-13 against vaccine type pneumococcal disease in older adults aged ≥65–years with a further analysis of data from this trial showing that PCV-13 afforded these adults with protection against serotype 3 pneumonia. These data will help form a basis for estimates of protection likely afforded by next generation higher valency PCVs against pneumococcal disease in older UK adults.
- Relying on indirect protection induced by paediatric PCV programmes alone may not optimally reduce the corresponding disease burden in adults, particularly for certain pneumococcal serotypes, with more consideration needing to be given to the public health value and importance of directly protecting older adults with PCVs.
- Further research is needed to confirm the cost of a hospital admission for community acquired pneumonia for UK adults aged ≥65–years with previous estimates used potentially underestimating this considerably. Additional research is also needed to investigate the epidemiology of pneumonia in UK adults treated outside secondary care.
- Cost effectiveness assessments of adult PCVs can now consider including new candidate data and approaches to reflect the full public health value of these vaccines.
- The global COVID-19 pandemic has added a potential new dimension to decision making for adult vaccines that target causes of respiratory disease. We review evidence emerging that pneumococci may interact with the SARS-CoV-2 virus and result in more severe clinical outcomes, that there is a reduced risk of COVID-19 amongst adults previously vaccinated with PCV-13 and consider the possible implications of the COVID-19 pandemic on future decision making for use of adult PCVs in the UK.

Two next generation higher valency PCVs (PCV-15 and PCV-20) are now in advanced stages of development and are currently anticipated to become available for adult use in the near future before corresponding pediatric licensing [13,14]. These vaccines include additional pneumococcal serotypes not in PCV-13 that have recently emerged as important causes of pneumococcal disease in the UK, particularly in adults aged ≥65-years, and therefore potentially offer the opportunity to better directly protect older UK adults against pneumococcal disease [7,15]. Table 1 shows the individual pneumococcal serotypes included in those PCVs previously (PCV-7) and currently (PCV-13) used in the UK and the two next generation higher valency PCVs (PCV-15 and PCV-20) that are in development. The importance of using vaccination to prevent common respiratory infections in adults has recently taken on greater significance following the COVID-19 pandemic that began in early 2020, with the importance of using COVID-19 vaccines to control the pandemic being paramount. However, it has been hypothesized that any inflammatory damage to the respiratory mucosal tissue caused by common pathogens such as *Streptococcus pneumoniae* and the influenza virus might potentially facilitate infection by SARS-CoV-2 with some evidence now emerging to support a synergy between the pneumococcus and SARS-CoV-2 virus [16–18]. Despite the levels of COVID-19 vaccine uptake now being achieved in older age groups in the UK new strains of SARS-CoV-2 virus with increased transmissibility are starting to emerge. Whilst there is currently no evidence these strains are demonstrating any increased clinical severity in illness the extent of any vaccine escape capability posed by these strains remains a key focus of ongoing research with concerns the virus may continue to circulate in the longer term [19,20]. Evidence gathered during the early part of the pandemic suggested only a low proportion of COVID-19 patients hospitalized in the UK had a bacterial co-infection, with the pneumococcus rarely identified [21,22]. However, this research was undertaken with COVID-19 containment policies and social distancing measures in place, which greatly reduced transmission of *S. pneumoniae* [23]. Potential synergistic interaction between SARS-CoV-2 and other common respiratory pathogens such as seasonal influenza and the pneumococcus may therefore potentially become increasingly prevalent in the UK as social distancing measures are relaxed enabling their reemergence with increased likelihood of co-infection with the SARS-CoV-2 virus. Therefore, in the post pandemic environment it may be increasingly important to consider maximizing use of available adult vaccines that target important causes of respiratory disease. This will not only help better protect individual UK adults against respiratory disease but also contribute to helping ensure the National Health Service (NHS) does not become over-burdened [24,25].

With two candidate next generation higher valency adult PCVs expected to become available shortly the overall aim is to summarize all currently available candidate evidence that could contribute to supporting future cost effectiveness

Table 1. The individual pneumococcal serotypes included in PCVs previously (PCV-7) and currently (PCV-13) used in the UK and the two next generation higher valency PCVs (PCV-15 and PCV-20).

	4	6B	9V	14	18C	19F	23F	1	5	7F	3	6A	19A	22F	33F	10A	15B	8	11A	12F
PCV-7	■	■	■	■	■	■	■													
PCV-13	■	■	■	■	■	■	■	■	■	■	■	■	■							
PCV-15	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■					
PCV-20	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

analyses of these in older immunocompetent UK adults. In this article, we review the full extent of all relevant candidate data available at the end of the second decade of the 21st century, identifying strengths and limitations. New data describing the epidemiology of pneumococcal disease in UK adults have become available since the JCVI last considered routine vaccination for immunocompetent UK adults ≥65-years with PCV-13 and assessed its cost effectiveness. These data provide important new and more contemporary insights for assessing PCV use in the older UK population and supersede much of those data previously used [12]. We therefore consider how those data previously used for key parameter inputs for the cost effectiveness model used for assessing PCV-13 in adults aged ≥65-years in the UK can be updated and identify persisting areas of uncertainty. Where local data gaps continue relevant global data generated outside the UK are summarized. In addition, we comment on new candidate data and approaches being proposed that cost effectiveness assessments of adult PCVs may now want to consider incorporating to try and more accurately reflect the full value of these vaccines. Lastly, we also consider the possible implications of the COVID-19 pandemic on future decision making for use of adult PCVs in the UK.

2. Incidence, serotype distribution, and trends

2.1. IPD (invasive pneumococcal disease)

Public Health England (PHE) has a well-established and long-standing high quality enhanced national routine surveillance system for IPD [7,26], encompassing all ages of patients, with serotyping of invasive pneumococcal isolates. Age stratified data are regularly published in the scientific literature giving robust, accurate and timely insight into the incidence, serotype distribution and epidemiological trends over time for IPD in English and Welsh adults. Van Hoek and Miller [12] used relevant incidence data from the latest published routine IPD surveillance data up to 2013/14 for their analysis of cost effectiveness of PCV-13 in immunocompetent English adults aged ≥65-years [26]. More recent routine IPD surveillance, including data up to 2016/17 are now published providing detailed contemporary data on the epidemiology of IPD in English and Welsh adults aged ≥65-years [7]. Furthermore, data for 27 individual serotypes that caused IPD in those aged ≥65-years in 2016/17 are also presented [7], providing insight into the most common serotypes that caused IPD in England and Wales. This encompasses all the additional serotypes in the two new generation higher valency PCVs that are being developed and are anticipated to shortly become available (i.e. PCV-15 and PCV-20) and provides a basis for assessment of use of these vaccines for preventing IPD in older UK adults [27]. These data show that the serotypes included in PCV-13, PCV-15, and PCV-20 correspond to 21.6, 32.6, and 64.6%, respectively, of the total IPD burden in English and Welsh adults aged ≥65-years in 2016/17. This equates to an incidence of 6.2, 9.4, and 18.7 per 100,000, respectively, for each of these vaccines. The 10 most common serotypes that caused IPD in these adults aged ≥65-years in 2016/17 were 8, 3, 12 F, 22 F, 9 N, 19A, 15A, 33 F, 10A, and 23A [7].

An additional publication using national IPD surveillance data from 2000/01 to 2016/17 [28] presents incidence data for English and Welsh adults aged ≥65 years with estimates further stratifying these data into smaller age groups. However, data are not presented by individual pneumococcal serotype with stratification limited to certain broader groups of serotypes that reflect only those pneumococcal vaccines currently used in the UK. Therefore, whilst these data may help support analyses of PCV-13 in UK adults aged ≥65-years their capacity for assessments of next generation higher valency PCVs is more limited. Additionally, these data also show that the 23 serotypes included in PPV23 corresponded to 73.1% of the total IPD burden in English and Welsh adults aged ≥65-years in 2016/17 equating to an incidence of 21.15 per 100,000. This shows that in 2016/17 the additional serotypes included in PPV23 not currently in next generation PCVs (i.e., serotypes 2, 9 N, 17 F, and 20) caused only a small proportion of the IPD burden in English and Welsh adults aged ≥65-years [27,28].

2.2. Hospitalized CAP (community acquired pneumonia)

Accurate data describing the epidemiology of hospitalized CAP in older adults are particularly important when assessing PCVs for use in older adults since, in contrast to the relatively rare condition of IPD, CAP reflects a much larger disease burden [4,29–31]. Relevant UK data are currently limited to a long-standing study of adults aged ≥16 years with CAP admitted to two university hospitals in the city of Nottingham. This study has been ongoing since September 2008 and was primarily intended to observe disease trends over time. This study stratifies data by age group, describes the trends and distribution over time for both CAP and various individual pneumococcal serotypes identified from cases of pneumococcal CAP using a multiplex urinary antigen detection assay (UAD) [15,32]. This study also provides some insight into incidence of adult CAP and adult pneumococcal CAP but the estimates presented for older adults aged ≥65-years are very low compared to those in recently published studies of similarly aged adults in other comparable countries. For example, a meta-analysis of published data for adults aged ≥65-years hospitalized with pneumonia in industrialized countries [33] and a study of CAP in hospitalized adults aged ≥65-years in the US city of Louisville [34,35] found incidence to be approximately 3 and 4 times higher respectively. Caution needs to be used when comparing incidence estimates in each of these studies since differing case definitions are used and there may be valid epidemiological reasons for such a low hospitalized CAP incidence in this UK population of adults from the city of Nottingham. However, it may also reflect limitations with the approach used by this study to estimate incidence. This has previously led to concerns that substantial under ascertainment may be present in this study and cost effectiveness and modeling studies investigating use of pneumococcal vaccines in UK populations have employed scenarios that double the CAP incidence found in this study [12,36].

There is therefore some uncertainty regarding the published incidence estimates available for adults aged ≥65-years hospitalized with CAP in the UK. Whilst estimates are now available up to 2017/18 [15,32], these should be used with caution due to concerns regarding potential under ascertainment. This suggests using these incidence estimates in conjunction with a suitable multiplier may be most appropriate for assessing adult PCV use in the UK as has been used by other analyses that have considered the burden of hospitalized CAP in UK adults [12,36]. This also highlights that further studies are needed that can provide more robust estimates for hospitalized CAP incidence in older UK adults.

Although the incidence of CAP might be underestimated in the Nottingham study, the distribution of serotypes is likely representative and provide reliable information on epidemiological trends between 2008 and 2018 for UK adults hospitalized with CAP. These are stratified by age group and further stratified into pneumococcal CAP and broad groups of serotypes reflecting those current pneumococcal vaccines used in the UK. Since 2013/14 the multiplex UAD assay used has extended the number of individual serotypes that could be detected to include all contained in PCV-13 and PPV23 [37]. Whilst data for individual serotypes are only presented for all adults aged ≥16-years for each epidemiological year of the study this still provides valuable data describing recent epidemiological trends and distribution for these individual serotypes over time. Importantly this includes all the serotypes in the two new generation higher valency PCVs currently in development that are expected to shortly become available. It also enables an estimation of the current proportion of adult pneumococcal pneumonia these vaccines could potentially address [27].

2.3. Pneumonia in adults in primary care

The previous analysis did not consider the burden of CAP in older UK adults treated in primary care when assessing routine PCV-13 use in adults aged ≥65-years [12]. Previously relevant UK data describing this aspect were both limited and historical, reflecting data from the 20th and very early 21st centuries [31,38–40]. A new study using electronic data records from the UK Clinical Practice Research Datalink [41] reported that clinically diagnosed pneumonia in UK primary care has been increasing over time, particularly since 2010, with an estimated incidence of 2.22 cases per 1000 person-years in 2017 for all age groups combined. However, trends showed incidence of clinically diagnosed pneumonia decreased over time for those aged <15 years but increased in those aged ≥15 years, especially amongst older adults. Collectively these data suggest a potentially large proportion of the burden of adult pneumonia in the UK may be being treated in primary care and future analyses assessing the cost-effectiveness of new PCVs in UK adults may want to include these cases. Whilst the financial cost to the NHS will likely be small compared to that treated in secondary care, pneumonia treated in primary care may still reflect a significant burden to the UK NHS. Given the pneumococcus is a common cause of pneumonia [5], higher valency adult PCVs could usefully contribute toward reducing the burden of adult pneumonia that is seen in primary care. Whilst there are now more contemporary UK data, the body of data providing relevant insight remains limited. To robustly assess this aspect further studies investigating the contemporary epidemiology of pneumonia in UK adults that is treated outside secondary care are therefore needed.

3. Projecting future epidemiological trends for pneumococcal disease in older UK adults and the contribution of indirect protection

Projecting the future longer-term incidence of pneumococcal disease caused by vaccine serotypes was an important and influential component of the previous cost-effectiveness assessment of vaccinating UK adults aged ≥65-years with PCV-13 [12,42]. To make a realistic projection of the future incidence of vaccine-type IPD and CAP in this age group for the next five years this analysis accounted for the indirect protection induced by the childhood pneumococcal vaccination programme. Trends for pneumococcal disease available at the time extended to 2013/14 and were primarily defined using IPD surveillance data from England and Wales. These data showed that collectively PCV-13 vaccine type IPD incidence in older English and Welsh adults aged ≥65-years had been declining steadily with time as a result of indirect protection from routine pediatric immunization. It was reasonably assumed at the time that this trend for IPD incidence in older UK adults would remain consistent and continue for the foreseeable future, so it was extrapolated for the subsequent five years. The future incidence of CAP in this age group was similarly estimated based on the projected IPD incidence and a multiplier approach (the ratio between observed for IPD and CAP between 2008 and 2013). This prediction suggested that PCV-13 vaccine type pneumococcal disease would continue to decline post 2013/14 in older UK adults aged ≥65-years reaching very low near elimination levels by 2018/19. This projected incidence was an important contributor to the conclusion that introducing a routine PCV-13 programme to directly protect the immunocompetent elderly in the UK would not be cost-effective.

More recent data for both IPD and CAP obtained within the UK from English and Welsh residents and English residents respectively present contemporary observed trends for PCV-13 serotype disease in older adults and shows how these have changed since 2013/14 [7,15,28,43,44]. In contrast to the predicted trend, these data show that incidence of PCV-13 serotype pneumococcal disease in older adults did not continue to decline. Rather, the trend unexpectedly reversed, and post 2013/14 incidence began to increase in older adults aged ≥65-years with levels in 2016/17 considerably higher than in 2013/14. This highlights the difficulty of accurately predicting future pneumococcal disease trends that are associated with indirect protection. Furthermore, this collective trend for the serotypes in PCV-13 is largely driven by serotypes 19F, 19A and especially 3 which all began to increase in incidence in older UK adults after 2013/14 [7,15]. There is speculation this could be because higher thresholds of protection maybe required for these serotypes which may have implications for the ability of

PCV-13 to impact carriage of these serotypes in young children [27,45–49]. Pneumococcal disease in UK adults due to the remaining ten PCV-13 serotypes has continued to decline post 2013/14 though the extent to which the very low near elimination levels anticipated by 2018/19 has been achieved is debatable, particularly when adult pneumococcal CAP is considered [7,15].

Adult formulations of higher valency next generation PCVs now in the late stages of development will be available before the corresponding pediatric formulations, with PCV-13 therefore expected to continue to be routinely used in the UK pediatric immunization programme, at least in the short term. This suggests that when assessing the cost effectiveness of vaccinating older UK adults with next generation higher valency PCVs the previous approach used to project the extent to which indirect protection from the pediatric PCV-13 programme may impact the pneumococcal disease burden in older adults in future years will require revision [42]. This will need to reflect the new trends observed post 2013/14 and account for the current observed burden of PCV-13 type pneumococcal disease in older UK adults, which is considerably larger than was previously anticipated, and estimate how trends for these serotypes will likely continue. These data also suggest that relying on indirect protection induced by pediatric PCV programmes alone may not always optimally reduce the corresponding disease burden in adults, particularly for certain serotypes, with more consideration needing to be given to the public health value and importance of directly protecting older adults with PCVs. In this context consideration may need to be given to the observation that some emerging serotypes that are now major causes of pneumococcal disease in older UK adults (e.g., serotypes 8 and 12F) have rarely been detected in younger age groups by recent UK carriage studies, with these younger age groups traditionally considered to be the main carriers and transmitters of the pneumococcus [7,15,50–52]. Whilst this finding may reflect limitations with the methodology used for these carriage studies it nevertheless questions the extent to which indirect protection will be induced against these serotypes specifically by a routine pediatric PCV program. This possibly suggests that direct vaccination may especially be needed to optimally protect older adults against disease caused by these pneumococcal serotypes. Estimating the future extent of indirect protection for older adults induced by pediatric PCV programmes may therefore be more complex than previously thought, need to incorporate insights from the latest and most contemporary local data available and may require more sophisticated approaches.

Future trends for pneumococcal disease in older UK adults aged ≥65-years due to those additional serotypes included in higher valency next generation PCVs but not in PCV-13 will need to be carefully considered when use of these vaccines in older UK adults is assessed. Recent data shows that incidence due to several of these serotypes (e.g., serotypes 8 and 12F) unexpectedly began to rapidly increase post 2013/14 and these are now among the leading contributors to the adult pneumococcal disease burden in the UK [7,15]. This observation is not confined to the UK with serotypes 8 and 12F also having emerged in recent years to become leading causes of IPD in various other European countries [53]. There is, as yet, no clear explanation for this phenomenon nor is it known for how long this trend might continue [7]. Relevant data post 2013/14 should therefore be used to define current trends for pneumococcal disease due to these serotypes individually, explore how they may evolve in the future and for estimating the potential impact of directly vaccinating older adults with higher valency next generation PCVs.

The latest data highlights the unpredictability of pneumococcal disease epidemiology and the difficulties in accurately projecting future trends in older adults [7,43]. Transmission between pediatric and unvaccinated adult age groups may also be more complex than previously thought with previous assumptions about the extent and consistency of indirect protection induced by routine pediatric PCV programmes over time possibly over optimistic [42,54]. New research suggests that carriage of *Streptococcus pneumoniae* in adults may previously have been underestimated, with significant transmission between older adults more likely than had previously been thought. This may have implications for interpreting the dynamics of pneumococcal transmission and the value of vaccinating older age groups with pneumococcal conjugate vaccines [9,55–57].

A further issue that arises when considering possible future epidemiological trends for pneumococcal disease is the extent of population level impact that may potentially be achieved by directly vaccinating older adults with higher valency PCVs. Despite compelling evidence that PCV-13 is efficacious in adults aged ≥65-years it has been difficult to detect a measurable impact on vaccine type IPD following the introduction of routine vaccination with PCV-13 in this age group in the United States in 2014 when trends using US Active Bacterial Core Surveillance are considered. However, these data may need interpreting with caution as coverage of PCV-13 in older US adults has been low until more recently and this may contribute to the lack of impact observed. Furthermore, it is notable that IPD incidence in US adults has remained stable since routine PCV-13 vaccination for older adults began in 2014. This contrasts with data from the UK where older adults are not routinely vaccinated with PCV-13, with a clear trend of increasing incidence post 2013/14 for PCV-13 serotype IPD in those aged ≥65-years [27,58]. Whilst higher valency PCVs are also anticipated to be efficacious, achieving appropriate uptake amongst older UK adults will be important if meaningful impact on the pneumococcal disease burden is to be observed at the population level.

4. Serotype 3

Previously all thirteen serotypes included in PCV-13 were assessed collectively, with PCV-13 considered efficacious against all thirteen when vaccinating immunocompetent UK adults aged ≥65-years [12]. Local data available at the time showed that post introduction of PCV-13 into the UK routine childhood immunization programme in 2010 trends for serotype 3 IPD had declined for all individual age groups [59] and that adult pneumococcal CAP due to serotype 3 had also declined [32]. This therefore suggested that PCV-13 would provide some direct protection against serotype 3 disease for UK adults aged ≥65-years.

However, more recent data now available show that the declining trend for incidence of serotype 3 disease in UK adults ceased in 2013/14 and has subsequently increased substantially [7,15]. Whilst serotype 3 continues to be a rare cause of IPD in young children in the UK, incidence in those aged under 5 years has also risen post 2013/14 [7]. This unexpected change in trend for serotype 3 disease in the UK remains to be explained [7] with recent genomic data suggesting the emergence of a new clade of serotype 3 pneumococci post 2014 [60]. Whilst it is hypothesized this clade might be able to more successfully evade the host immune system and possibly compromise the serotype 3 component of PCV-13 any clinical implications are yet to be determined with further research needed. In addition to these changes in trend for serotype 3 disease, vaccine effectiveness estimated for PCV-13 against serotype 3 IPD in UK children aged <5-years using routine national IPD surveillance data to June 2018 suggested protection was low compared to that for the other serotypes in PCV-13 though this estimate lacks precision due to the rarity of serotype 3 IPD cases in UK children [61]. Collectively these data have subsequently led to the ability of the serotype 3 component of PCV-13 to directly protect against serotype 3 disease to be questioned in the UK with the suggestion that future analyses might legitimately assume the serotype 3 component of PCV-13 to be a non-vaccine serotype [7,15,61]. This assumption was recently used in a study modeling the impact of using a reduced primary dosing schedule of PCV-13 in the UK [36]. However, there are other data that support direct PCV-13 protection against serotype 3 IPD in children [47,49]. These are now supported by a review of publicly available IPD surveillance data from a range of countries which suggest that PCV-13 provides some direct and indirect protection against serotype 3 at the population level [62]. Further evidence that PCV-13 protects pediatrics against serotype 3 disease is additionally now reported by a study of otitis media in children aged 5–35 months which found effectiveness of PCV-13 to be 89% (95%CI 23.9–98.4) [63]. However, the possibility is recognized that routine childhood immunization programmes with PCV-13 may have only limited impact on carriage of serotype 3 pneumococci which may compromise the extent of indirect protection induced against adult serotype 3 disease [48]. In the context of adult pneumococcal disease a recent analysis of data from a large randomized controlled clinical trial (RCT) showed PCV-13 provided some protection against serotype 3 CAP in adults aged ≥65-years (efficacy 61.5%; 95%CI 17.6–83.4) using subjects that met a clinical definition of CAP regardless of radiologic findings [64]. This finding has subsequently been supported by a systematic review and pooled analysis of published literature describing the effectiveness of PCV-13 against serotype 3 CAP in hospitalized adults aged ≥65-years. Whilst this study was based on a relatively small number of serotype 3 CAP cases (n = 67) it estimated vaccine effectiveness to be 53.6% (95%CI 6.2–75.9) and similarly suggested that PCV-13 provides some direct protection against serotype 3 CAP in adults aged ≥65-years [65]. Some local expert opinion in the UK is also now supportive of this conclusion [10].

Published data describing PCV-13 efficacy or effectiveness specifically against serotype 3 IPD in older adults are currently not available. However, pneumococcal vaccines have consistently been found to provide better protection against invasive than noninvasive disease [66] with compelling data from a large RCT showing that collectively for all serotypes PCV-13 efficacy is considerably higher for IPD than for CAP in adults aged ≥65 years [67]. Given the emergence of data showing that PCV-13 is efficacious in protecting older adults against serotype 3 pneumonia some, potentially substantial, protection against serotype 3 IPD in adults aged ≥65-years might therefore also be expected from PCVs that include serotype 3. In this context a recent analysis of Spanish surveillance data between 2009 and 2019 suggests a reduction in serotype 3 IPD has been achieved in those Spanish adult populations aged ≥65-years directly vaccinated with PCV-13 [68].

Overall, emerging data therefore support the ability of PCVs that include a serotype 3 component to provide adults aged ≥65-years with some meaningful protection against serotype 3 pneumococcal disease. Baseline assumptions in analyses that consider a serotype 3 component of adult PCVs as a non-vaccine serotype should therefore be used with caution.

5. Mortality

Previously a 30-day case fatality rate (CFR) of 30% and 10% respectively was used for UK adults aged ≥65-years hospitalized with IPD and CAP [12]. However, relevant data to support these estimates were limited at the time and they were considered uncertain.

The 30% estimate used for 30-day CFR following IPD in UK adults aged ≥65-years was based on a study of IPD patients in England undertaken between 2002 and 2009 which found the 30-day CFR in adults aged ≥65-years to be 31.5% [69]. However, this period reflects the pre PCV era and the first years of PCV-7 use prior to the introduction of PCV-13 into the routine UK childhood immunization programme. The epidemiology and pneumococcal serotype distribution in the UK is now very different and this will have implications for the contemporary 30-day CFR associated with pneumococcal disease [7]. Two recent UK studies are now available that provide more recent insight into the 30-day CFR in UK adults following IPD. Houseman et al [70] showed a trend of declining 30-day CFR between 2006 and 2016 in patients with IPD in the north-east of England. Whilst the trend of declining 30-day CFR was associated with each age group studied, 30-day CFR increased with increasing age and varied by individual serotype. The mean 30-day CFR for adults aged ≥65-years estimated across the full study period was 30% and reflects the estimate previously made by Van Hoek et al [69]. This estimate may not accurately reflect the 30-day CFR following IPD now experienced by UK adults aged ≥65-years ten years after the introduction of PCV-13. More recent UK data are used by Amin-Chowdhury et al [71] where routine national IPD surveillance data from England between 2014 and 2018 were analyzed reflecting the PCV-13 era alone. This study estimated the 30-day CFR following IPD for English adults aged ≥65-years to be 24.8% across the study period. Additionally, 30-day CFR estimates for older adults are further stratified into those aged 65–79y (16.4%) and 80 + y (34.4%) illustrating the increase in

CFR with age in older adults. This study also showed that the emerging serotypes that are becoming important causes of IPD in the UK have a lower 30-day CFR. These new data suggest that the 30-day CFR following IPD in adults aged ≥65-years has declined following the introduction of PCV-13 and suggest an estimate of ~25% for this age group is now more appropriate to use rather than the previous estimate of ~30%. An important factor contributing to the decline in CFR is likely to be serotype replacement following the introduction of PCV-7 in 2006 and PCV-13 in 2010 which targeted those serotypes associated with the most severe outcomes, with new emerging pneumococcal serotypes having a lower propensity for mortality.

The 30-day CFR estimate of 10% previously used for adults aged ≥65-years hospitalized with CAP was based on limited local UK data available at the time [32,72] and data from a large RCT undertaken outside the UK [67]. However, this estimate was acknowledged as being a compromise due to the wide range of CFRs reported by these sources (from 1.8% to ≥20%). Rodrigo et al [32] also only provided CFR data for adults aged ≥16-years rather than for those aged ≥65-years specifically. Relevant new data from the UK now available [15] describes a continuation of the study reported by Rodrigo et al [32] to 2017/18 but again only presents 30-day CFR for adults aged ≥16-years hospitalized with CAP. This was 7.5% and closely reflects the 6% previously reported [32]. Other UK data now available suggest the 30-day mortality for adults hospitalized with CAP is considerably higher. A British Thoracic Society (BTS) audit of CAP in British hospitalized adult patients aged ≥16-years (median age of patients 77 years) undertaken between 2009 and 2014 found overall 30-day mortality to be 18% with a trend that declined with time across the study period [73]. The 6th British Thoracic Society (BTS) national audit of CAP in adults presents data obtained between 1 December 2018 and 31 January 2019 [74]. This reports a 30-day CFR of 13.6% for UK adults hospitalized with CAP but again this is for all adults aged ≥16-years (median age of patients 75 years) and is not further stratified by age. A further finding highlighted by this audit is that mortality in UK adults hospitalized with CAP has been decreasing over time and is currently at its lowest level for 10 years. Therefore, whilst some new UK data are now available, a 30-day CFR estimate following CAP remains uncertain for UK adults aged ≥65-years. Historical UK data describing hospital admissions for pneumonia between 1997 and 2005 also indicate that 30-day mortality is considerably higher in those aged ≥65-years compared to those aged <65-years, highlighting the relevance of having contemporary data specifically for older adults with pneumonia [72]. This also emphasizes a need for future studies that investigate the CFR following hospitalized CAP in UK adults aged ≥65-years specifically to help address this local data gap.

In the absence of published local data describing a 30-day CFR following hospitalization with CAP for UK adults aged ≥65-years two recent studies undertaken outside the UK provide insight for this age group specifically. Arnold et al [34] reports a 30-day CFR of 17% for US adults aged ≥65-years hospitalized with CAP in the city of Louisville between 2014 and 2016. Shi et al [33] presents a meta-analysis of global data from 1996–2017 for older adults hospitalized with pneumonia. The meta-estimate of 30-day mortality for those aged ≥65-years living in industrialized countries was 15.9% (95% CI 13.0–19.3). Lastly, a systematic review of global data describing clinical outcomes for hospitalized patients with CAP is also now available and gives some insight into mortality [75]. This shows that data describing mortality are limited but is an important clinical outcome that occurs in 10–15% of cases overall.

Collectively these data therefore suggest that for future analyses a 30-day CFR for UK adults aged ≥65-years hospitalized with CAP should be at least 10%. Whilst there is evidence that 30-day CFR in UK patients has been declining over the last decade the most contemporary data suggest an estimate of 13–15% could be considered reasonable for UK patients aged ≥65-years who are hospitalized with CAP.

There are currently only very limited and now historical UK data from a single study that provide some insight into mortality following pneumonia treated in primary care [40]. This study estimated 30-day mortality in this context to be 18.5% in participants with a mean age of 57.6 years. However, when deaths in patients with probable hospital discharge diagnoses were excluded this reduced to 5.6%. This lower estimate reflects a 30-day mortality estimate of 5.3% from a study of pneumonia and non-pneumonia lower respiratory tract infections in primary care in the Netherlands that included adults aged 60 + years [76]. Contemporary data on mortality following outpatient pneumonia is therefore lacking, with more research needed to obtain robust estimates that could usefully contribute to cost effectiveness analyses for PCVs in older UK adults if outpatient community pneumonia that is treated in primary care be included.

6. Efficacy, effectiveness, and duration of protection

Van Hoek and Miller used relevant published data available at the time (i.e., data that were available in 2015) to inform their assumptions regarding the efficacy and duration of protection provided by PCV-13 for immunocompetent adults aged ≥ 65-years [12]. Whilst this analysis did not specifically assess PPV23 Van Hoek and Miller concluded that PPV23 had only limited effectiveness and short duration of protection against PPV23 vaccine type IPD and a lack of protection against pneumococcal-attributed CAP, and overall had achieved little impact on pneumococcal disease in those aged ≥ 65-years in the UK [12]. This also reflected the conclusions drawn by the JCVI in October 2015 [11,77]. However, since a single dose of PPV23 is currently routinely offered to all immunocompetent UK adults aged ≥ 65-years cost effectiveness assessments of routine use of next generation higher valency PCVs in older adults may need to include comparison with PPV23. The previous conclusions of Van Hoek and Miller of the effectiveness and duration of protection of PPV23 may therefore need to be reviewed and any relevant new data considered. In this context a more recent assessment of PPV23 effectiveness against IPD has been undertaken in UK adults aged ≥65-years in a large national study using all relevant IPD data to 2016/17.

This analysis similarly concluded that PPV23 has only limited short term protection against PPV23 vaccine type IPD with no evidence of any impact at the population level [28]. Collectively relevant published studies to date investigating PPV23 protection against pneumonia show considerable variation in study design and clinical outcome targeted, making it difficult to draw definitive conclusions. However, there is a lack of consistent evidence demonstrating the effectiveness of PPV23 against CAP in older adults [10,78]. Whilst a recent systematic review [66] considered only data published 2016–2019 and concluded that PCV-13 and PPV23 were similarly effective against vaccine-type pneumonia and a recent review of data published from 2010 to 2020 suggested PPV23 may provide some benefit against vaccine type pneumococcal pneumonia for older adults [79], the issue of inconsistency nevertheless remains when the full wider body of effectiveness data for PPV23 against pneumonia are considered that includes more historical data. However, a new study now provides contemporary data on the vaccine effectiveness of PPV23 against hospitalized vaccine type pneumococcal CAP in UK adults specifically [80]. This was undertaken in a local population in the Greater Nottingham region using data collected between 2013 and 2018. It included adults aged ≥ 16-years but had only limited representation of older adults aged ≥ 65-years. The PPV23 vaccine effectiveness estimated in those aged ≥ 65-years and ≥ 75-years was 20% (95%CI −5%–40%) and 5% (95%CI −37–35%), respectively. The ability to draw robust conclusions in this context is compromised by the small number of adults aged ≥ 65-years included in the study and cannot therefore be considered to provide strong evidence that PPV23 provides some meaningful protection for older UK adults against pneumococcal pneumonia. This study also attempted to investigate duration of protection of PPV23 against CAP in UK adults. However, the relevant data are clearly problematic to interpret and similarly do not permit robust and confident conclusions to be made in this context. The authors conclusion that PPV23 provided UK adults aged ≥ 65-years with moderate long-term protection must therefore be viewed with caution. Overall, there are therefore no compelling new data to suggest the previous position taken by both the JCVI and Van Hoek and Miller that PPV23 provides UK adults aged ≥ 65-years with limited short-term protection against IPD and no protection against pneumococcal CAP should be changed [12,77]. Any new assumption that PPV23 may protect older UK adults aged ≥ 65-years against CAP will need to be strongly supported by high-quality new data.

The previous assessment by Van Hoek and Miller considered that PCV-13 would be efficacious in immunocompetent UK adults aged ≥ 65-years [12]. This was based on data from a large RCT undertaken in adults aged ≥ 65-years in the Netherlands between 2008 and 2013 which showed efficacy of PCV-13 against vaccine-type IPD and CAP to be 75% and 45.6% respectively [67]. These continue to be the highest quality and most robust data available for assessing efficacy of PCV-13 against pneumococcal disease in older adults. Therefore, in the absence of any relevant new high-quality data, this RCT is expected to similarly form the basis for estimates of protection likely afforded by next generation higher valency PCVs against pneumococcal disease in older UK adults. Furthermore, data from a large observational study using a test negative design are also now available and support substantial PCV-13 effectiveness against CAP in adults aged ≥ 65-years (73%; 95%CI 13–92) [81]. These observational effectiveness data are unlikely to supersede the efficacy data presented by Bonten et al [67] but may be valuable to inform scenario analyses.

Some uncertainty persists regarding the duration of protection afforded by PCV-13, with only limited relevant data available. The RCT undertaken by Bonten et al concluded that PCV-13 efficacy occurred soon after vaccination and persisted throughout the duration of the clinical trial (almost 4 years) with no obvious decline in protection [67]. These data were used in the assessment by Van Hoek and Miller [12] but given the limited duration of follow up, lifelong protection following vaccination with PCV-13 was not assumed. Instead a waning scenario was employed which was considered to reflect a conservative approach. This assumed a constant protection for the first nine years post vaccination after which it would drop every 5 years until 20 years post vaccination when subsequent onward levels of protection remain constant [12]. A subsequent post-hoc analysis of the RCT described by Bonten et al is also now available that provides some new data on this aspect [82]. This included one additional year of follow up and found PCV13 was protective against both IPD and CAP in adults aged ≥65-years over the 5-year period with no waning of efficacy observed during the additional year of observation included. Unless any new relevant data subsequently become manifest it is likely these data will be used to inform assumptions regarding duration of protection for assessments of cost-effectiveness for next generation higher valency PCVs. These suggest it may not be unreasonable to assume that protection afforded by higher valency next generation PCVs is unlikely to wane rapidly and will be relatively long lasting with no substantial decline for the first decade. However, at present this remains an important area of uncertainty.

7. Cost and quality of life

In their assessment of the cost-effectiveness of PCV-13 in immunocompetent UK adults aged ≥ 65 years Van Hoek and Miller [12] stated that costs and QALY loss remained uncertain parameters. Those used were based on the analysis of Rozenbaum et al [83] and were derived from NHS reference costs. Van Hoek and Miller made adjustment for inflation, with £715 and £4,800 estimated as the cost of hospital admission with CAP and IPD, respectively. Whilst there is currently no new evidence indicating the cost of hospital admission with IPD should be reviewed, UK government guidance now available on payment by results in the NHS suggests £715 may underestimate the cost of hospital admission with CAP, possibly substantially [84]. Tariff information for a case of lobar, atypical or viral pneumonia with and without complications is listed at £4,165 and £1,675 per day respectively for an ordinary elective spell. For a non-elective spell, the tariff is £3,214 and £936 per day for cases with and without complications. Complications of pneumonia are more common in the elderly and those with long-term health conditions [85]. This suggests that pneumonia cases with complications will be more frequent in adults aged ≥65-years and this should be taken into consideration when estimating the cost of hospitalization, and that the

higher cost estimates associated with complications may be more appropriate in this age group. However, further research is needed to confirm the cost of a hospital admission for CAP for UK adults aged ≥65-years. Until new data become available the estimate of £715 previously used in the cost effectiveness assessment of PCV-13 should be considered with caution since the cost of hospitalization for UK adults aged ≥65-years with CAP could be substantially higher.

Van Hoek and Miller used an overall QALY loss for IPD that declined with increasing age (ranging from 0.14 for those aged 65 years to 0.01 for those aged 100 years) and used an assumption that the QALY loss for CAP in adults aged ≥ 65 years was 0.006 [12]. This estimate of the impact of IPD on patients' health related quality of life (HRQoL) has been used in many other economic evaluations of adult pneumococcal conjugate vaccination [83,86–88]. However, it is based on an assessment of parents views of the impact of IPD on their children's HRQoL rather than being measured in adult patients themselves [89]. Findings of a recent systematic review of the literature suggest the impact of pneumococcal sepsis and bacteremia on adults' HRQoL may be much larger than previously estimated, with adult IPD being associated with negative utility values (i.e., worse than death health states) [90]. Moreover, two new studies both estimate the one-year excess QALY loss due to CAP to be much higher for adults aged ≥65-years at 0.13 [91,92] and assessments of the cost effectiveness of higher valency next generation PCVs should now consider using this value as a baseline figure. Previously economic evaluations of PCV-13 also assumed that patients surviving IPD or CAP would return to a health state reflecting similarly aged healthy individuals. There is growing evidence from both UK and wider global data that adult patients who survive IPD or CAP experience increased morbidity and mortality [93–101]. Future analyses of the cost effectiveness of higher valency next generation PCVs may therefore need to consider ways to capture the reduced health state subsequently experienced by individuals following an episode of pneumococcal disease to reflect the full value these pneumococcal conjugate vaccines can potentially provide.

8. Conclusions

The previous cost effectiveness analysis for PCV-13 undertaken by Van Hoek and Miller was a robust assessment using all relevant data that were available at the time. Wherever possible, local UK data were utilized to ensure the analysis was as bespoke as possible to the UK adult population aged ≥65-years. However, for some parameters relevant insight and data inputs were limited. During the five years since this analysis was undertaken substantial new local and global data have emerged, which supersede those previously used, helping to address some of the areas of uncertainty that previously existed. These new data also provide critical insight into new epidemiological trends for pneumococcal disease in older UK adults that have emerged since 2013/14 and enable the accuracy of previous predictions to be assessed. Some areas of uncertainty continue to persist, particularly regarding the duration of protection afforded by PCVs when older immunocompetent adults are directly vaccinated. Appropriate use of these new, more contemporary data will therefore be critical for supporting any cost effectiveness assessments of vaccinating immunocompetent ≥65 year olds in the UK with new generation higher valency PCVs.

The body of relevant data that now exists suggests the UK is well placed to make robust and informed assessments regarding the cost effectiveness of vaccinating immunocompetent ≥65-year olds with the new generation higher valency PCVs that are expected to shortly become available. These new, more contemporary data that are available provide important inputs for key parameters for cost effectiveness models and provide key insight into new emerging trends and the accuracy of previous predictions. Making informed and robust decisions about use of these new higher valency PCVs for routine use in older adults will be important for public health in the UK.

9. Expert opinion

In addition to the fifteen and twenty valent PCVs that are now in late development, two twenty-four valent PCVs have entered human trials with a thirty valent product also at a preclinical stage [102]. These have the potential to protect individuals against an increasing range of pneumococcal serotypes and suggests the need to make robust and timely assessments of PCVs for potential routine use in older UK adults will continue for both the medium and longer-term future as development of these new higher valency candidates progresses. Research initiatives into adult pneumococcal disease will therefore need to be continued in the UK over the coming decade with ongoing surveillance critical for timely insight into the latest epidemiological trends and the adult pneumococcal disease burden. Whilst a high quality national routine surveillance system is well established in the UK for IPD, surveillance of adult CAP should be expanded beyond the current small local geographical area. Stratification of these surveillance data by individual pneumococcal serotype will also continue to be very important, particularly for assessing new PCVs that include broader ranges of serotypes. Current methodology used in the UK enables all individual serotypes causing IPD to be identified but this is not yet the case for pneumococcal CAP [7,15]. This suggests there is a need to develop new assays that can detect more than the 24 pneumococcal serotypes in urine specimens from patients with CAP that the current generation of multiplex urinary antigen detection assays are capable of [37,103].

The body of relevant data that can now be used to support cost effective analyses of PCVs in immunocompetent UK adults aged ≥ 65 years has increased considerably in the last 5 years. These new data address some of the uncertainty that previously existed when the assessment of PCV-13 was undertaken and will help make subsequent cost-effectiveness analyses for use of new higher valent PCVs in older UK adults much more robust, but data gaps still exist. For example, whilst the UK has a high-quality routine national surveillance system for IPD further studies are needed into the burden of hospitalized CAP in the UK population of older adults, particularly to provide more robust incidence estimates and the proportion that is specifically being caused by the

pneumococcus (and specific pneumococcal serotypes). A knowledge gap that remains in the UK is the burden of pneumococcal pneumonia in immunocompetent older adults that is treated in primary care. Whilst this may not be a key factor that influences cost effectiveness assessments of PCVs it may contribute substantially to the burden of disease currently handled by the primary care health service in the UK, suggesting that vaccinating UK adults aged ≥ 65-years with higher valency PCVs could potentially relieve some of the continuing pressure the NHS finds itself under, in particular during the winter months. Future research initiatives should therefore consider further investigating this topic in the UK. Additional research is also needed to accurately define the current cost of treating a case of hospitalized adult CAP in the UK with the £715 previously used possibly a substantial underestimate.

An important issue highlighted by new data that are now available is the unpredictable epidemiological nature of pneumococcal disease and the difficulty with confidently projecting longer term trends, particularly when certain individual serotypes are considered [7]. Accurately projecting future trends for pneumococcal disease in older UK adults and the extent to which this is influenced by indirect protection induced by routine pediatric PCV programmes therefore remains a challenge and needs to be approached with caution in future cost effectiveness analyses. Whilst great value is often given to the ability of PCVs to induce indirect protection in adult populations, assumptions that indirect protection alone induced by a pediatric PCV programme will rapidly reduce the vaccine type adult disease burden to negligible levels within a few years may be overly optimistic with more consideration for the public health value of directly protecting older adults warranted. This also suggests that new carriage studies will continue to be valuable in the UK to monitor carriage trends in younger age groups over time for individual pneumococcal serotypes, particularly for those that have recently emerged as important causes of disease in older adults but have rarely been detected in carriage studies to date. This may help to better understand the extent to which new generation higher valency PCVs may impact pediatric carriage of the pneumococcus and induce indirect protection once they become available for use in routine pediatric programmes.

Future cost effectiveness assessments of new generation higher valency PCVs in immunocompetent UK adults aged ≥ 65-years may choose to replicate the methodology used previously by Van Hoek and Miller and just update this by incorporating those relevant new data now available [12]. However, data are now emerging that highlight various additional aspects and approaches that subsequent cost effectiveness assessments of PCVs may want to consider incorporating to more accurately reflect the full value of these vaccines. For example, there is growing evidence that older adults who recover from pneumococcal disease do not return to their previous health state and subsequently experience an increased risk of morbidity and mortality, with implications that may influence the cost effectiveness of routine adult PCV programmes when a longer term perspective is considered [96–101]. Future assessments should also consider including the broader socioeconomic consequences that routine vaccination of the elderly with higher valency PCVs could have and the potential additional value they offer in this context [104]. There is also the growing problem of antimicrobial resistance (AMR) and the extent to which routinely vaccinating UK adults with higher valency PCVs could help in reducing use of antimicrobials that would otherwise be used to treat adults with pneumococcal disease [105–107]. Lastly there is compelling evidence now becoming manifest that vaccinating older adults with PCVs is associated with a significant risk reduction of all cause pneumonia and that approaches incorporating this aspect may be needed to estimate the full public health impact PCVs can have on this disease burden in the older adult population and this topic has recently been reviewed in detail [108–111]. Given the importance of including the broader public health impact of vaccines when making public health policy decisions, cost effectiveness analyses of higher valency PCVs that incorporate this approach may provide an important new perspective and insights into the full value of these vaccines.

Historically dynamic transmission models have not been used in cost effectiveness assessments of PCVs in older adults as relevant data have suggested pneumococcal carriage is very rare in older adults with those aged ≥65-years contributing very little to pneumococcal transmission. This has been supported by the body of UK carriage data available to date which has consistently found that carriage in UK adults was only rarely detected using standard methodology [50–52,112]. However, recent research using new methodological approaches is now suggesting that respiratory carriage of *Streptococcus pneumoniae* may have been substantially underestimated in older age groups and is highlighting evidence of a possible transmission reservoir among adults [55–57]. This research is currently at an early stage, but should similar data continue to emerge suggesting a role of older adults in pneumococcal transmission the use of dynamic transmission models in cost effectiveness assessments of PCVs in older adults may need to be considered. Furthermore, this may strengthen the case for vaccinating older age groups with pneumococcal conjugate vaccines specifically given their ability to impact carriage and interrupt transmission [9,26,113–115].

The devastating morbidity and mortality caused by the COVID-19 pandemic has increased public awareness and understanding of the importance of adult vaccination more broadly, particularly for those that can help protect the elderly against important causes of respiratory disease. There is also speculation emerging regarding a potential direct benefit of pneumococcal vaccines on the prevention of COVID-19. Possible SARS-CoV-2-pneumococcus associations with plausible immunological mechanisms are being hypothesized by which pneumococcal vaccines may potentially improve the immune response to SARS-CoV-2 [16,116–118]. This will require careful research before any firm conclusions can be drawn, but some supportive data are available from a study of a nine-valent PCV in South African children and a study of PCV-13 in US adults aged ≥65-years [17,119]. These data suggest that the pneumococcus may have a role in the development of pneumonia associated with COVID-19 and that PCVs

may help prevent COVID-19 associated pneumonia in both pediatric and older adults, particularly severe COVID-19 outcomes. However, the importance of vaccination against SARS-CoV-2 for all eligible individuals remains paramount to controlling the COVID-19 pandemic. Regardless of any possible direct benefit of pneumococcal vaccines for the prevention of COVID-19, a higher valency PCV nevertheless has the potential to help reduce pressure on the NHS, especially in the context of the COVID-19 pandemic and the disease burden this is causing, by decreasing the burden of pneumococcal disease in older UK adults. Furthermore, data are now emerging from the UK showing that co-infection with the pneumococcus and SARS-CoV-2 is associated with a very high case fatality rate, particularly in older adults [120]. This suggests a possible synergistic effect between SARS-CoV-2 and the pneumococcus, with prior pneumococcal infection increasing the risk of infection and severe illness associated with SARS-CoV-2 infection [18]. These data are currently limited to just IPD where such co-infections have so far been infrequent, with further research also needed to investigate SARS-CoV-2 co-infection and mortality in those with noninvasive pneumococcal disease to provide full insight into the public health implications of this observation. However, to date co-infection with the SARS-CoV-2 virus and the pneumococcus has been rarely identified [21,22].

How the COVID-19 pandemic evolves in the UK and how successfully and rapidly it can be brought under control through widespread vaccination, with vaccination of the elderly considered critical [121], may have important implications for adult vaccines in the future and the priority given to new higher valent adult PCVs when they become available. Various COVID-19 vaccines are in development with three now authorized for temporary supply under Regulation 174 in the UK [122,123]. Widespread vaccination with COVID-19 vaccines in the UK has therefore now begun in earnest with immunization of the elderly prioritized [121]. This unprecedented roll out of an adult vaccine in the UK may influence thinking about the future public health role and need to invest in vaccines that protect the health of older adults specifically. However, there is evidence emerging that the COVID-19 pandemic and subsequent social distancing measures and national lockdowns imposed in the UK have been associated with a reduction in transmission of common respiratory infections, including the pneumococcus [23]. A large decline in IPD across all age groups has occurred, with the assumption that noninvasive pneumococcal disease has been similarly impacted [120]. Whilst the burden of adult pneumococcal disease has declined this may only prove to be temporary once relaxation of social distancing measures are permitted, allowing transmission of the pneumococcus to return to pre pandemic levels. How common respiratory pathogens may reemerge in the post COVID-19 era remains very uncertain with a recent modeling study is predicting that large outbreaks of respiratory disease could occur in the years following the removal of social distancing measures as a result of a buildup of susceptible individuals [124]. Whilst this study primarily focused on influenza and RSV, it illustrated the potential for social distancing measures to impact the dynamics and persistence of a much wider range of infections, including the pneumococcus. Finally, it is also becoming evident that circulation of the SARS-CoV-2 virus may persist in the longer term with new strains emerging [19,20]. This suggests co-infections of SARS-CoV-2 virus with the pneumococcus could become more frequent if normal transmission of common respiratory infections resumes once social distancing restrictions are eased. Given there is some evidence suggesting co-infection with the pneumococcus and SARS-CoV-2 virus is associated with more severe illness and outcomes, vaccinating older UK adults with higher valent PCVs could potentially become additionally important in the post COVID era [120].

In conclusion, the global COVID-19 pandemic has added a potential new perspective to decision making for adult vaccines that target causes of respiratory disease. At the time of writing there is much uncertainty about how the epidemiology of the pneumococcus may re-emerge in the UK in the post COVID era and the extent to which strains of the SARS-CoV-2 virus will continue to circulate. Ongoing high-quality surveillance and research will be important to answer these questions and will help inform the public health need and role of higher valency adult PCVs in the UK.

Funding

This article was funded by Pfizer UK

Author contributions

All authors contributed to the conception and design of this review article, interpreting the relevant literature and participated in writing and revising it for intellectual content.

Declaration of interest

A Vyse, J Campling, C Czudek, G Ellsbury, D Mendes and R Reinert are employees of Pfizer which sponsored the manuscript and has an interest in pneumococcal conjugate vaccines. M Slack has received personal fees from GlaxoSmithKine, Pfizer, Merck, AstraZeneca, and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards and has undertaken contract work for Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Amin-Chowdhury Z, Iyanger N, Ramsay ME, et al. Outbreaks of severe pneumococcal disease in closed settings in the conjugate vaccines era, 2010–2018: a systematic review to inform national guidance in the UK. J Infect. 2019 Dec;79(6):495–502. PubMed PMID: 31629865; eng.
2. Martinez-Vega R, Jauneikaite E, Thoon KC, et al. Risk factor profiles and clinical outcomes for children and adults with pneumococcal infections in Singapore: a need to expand vaccination policy? PloS One. 2019;14(10):e0220951.
3. Ganaie F, Saad JS, and McGee L, et al. A new pneumococcal capsule type, 10D, is the 100th serotype and has a large cps fragment from an oral streptococcus mBio . 2020;11(3):e00937–20.

4. Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect. 2014 May;20(Suppl 5):45–51. PubMed PMID: 24313448; eng.
5. Reynolds JH, McDonald G, Alton H, et al. Pneumonia in the immunocompetent patient. Br J Radiol. 2010 Dec;83 (996):998–1009. PubMed PMID: 21088086; PubMed Central PMCID: PMCPMC3473604. eng.
6. Immunisation against infectious disease. Pneumococcal: the Green Book. [cited 2021 Mar 29] Available from: https://www.gov.uk/government/publications/pneumococcalthe-green-book-chapter-25.
7. Ladhani SN, Collins S, Djennad A, et al.Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. Lancet Infect Dis. 2018;18(4):441–451. PubMed PMID: 29395999; eng.
•• This article presents trends and incidence of IPD in UK adults aged 65+ years post 2013/14 with insight provided for a range of individual serotypes.
8. Pilishvili T, Bennett NM. Pneumococcal disease prevention among adults: strategies for the use of pneumococcal vaccines. Am J Prev Med. 2015 Dec;49(Suppl 6):S383–90. PubMed PMID: 26590438; eng.
9. Isturiz RE, Schmoele-Thoma B, Scott DA, et al. Pneumococcal conjugate vaccine use in adults. Expert Rev Vaccines. 2016;15 (3):279–293. PubMed PMID: 26651847; eng.
10. Goldblatt D, and Miller E. Pneumococcal pneumonia Thorax . 2020;75(1):6–7.
11. JCVI. Interim statement on adult pneumococcal vaccination. Located at:https://www.gov.uk/government/publications/jcvi-interim-statement-on-adult-pneumococcal-vaccination.
12. van Hoek AJ, Miller E. Cost-effectiveness of vaccinating immunocompetent ≥65 year olds with the 13-valent pneumococcal conjugate vaccine in England. PloS One. 2016;11(2):e0149540. PubMed PMID: 26914907; PubMed Central PMCID: PMCPmc4767406. eng.
••This article presents the first and to date only cost-effectiveness assessment of routinely vaccinating UK adults aged 65+ years with a pneumococcal conjugate vaccine
13. Peterson JT, Stacey HL, MacNair JE, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine compared to 13-valent pneumococcal conjugate vaccine in adults ≥65 years of age previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Hum Vaccin Immunother. 2019;15 (3):540–548. PubMed PMID: 30427749; PubMed Central PMCID: PMCPMC6605723. eng.
14. Thompson A, Lamberth E, Severs J, et al. Phase 1 trial of a 20-valent pneumococcal conjugate vaccine in healthy adults. Vaccine. 2019 Sep 30;37(42):6201–6207. PubMed PMID: 31495592; eng.
15. Pick H, Daniel P, Rodrigo C, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. Thorax. 2020 Jan;75(1):38–49. PubMed PMID: 31594801; eng.
•This article presents insight into trends for UK adults hospitalised with pneumonia and pneumococcal pneumonia
16. Sultana J, Mazzaglia G, Luxi N, et al. Potential effects of vaccinations on the prevention of COVID-19: rationale, clinical evidence, risks, and public health considerations. Expert Rev Vaccines. 2020 Oct;19 (10):919–936. PubMed PMID: 32940090; eng.
17. Lewnard JA, Bruxvoort KJ, Fischer H, et al. Prevention of COVID-19 among older adults receiving pneumococcal conjugate vaccine suggests interactions between streptococcus pneumoniae and SARS-CoV-2 in the respiratory tract. J Infect Dis. 2021 Mar 9. DOI:10.1093/infdis/jiab128. PubMed PMID: 33693636; PubMed Central PMCID: PMCPMC7989304. eng.
• This article presents evidence that pneumococci may interact with the SARS-CoV-2 virus and that there is a reduced risk of COVID-19 amongst adults vaccinated with PCV–13
18. Howard LM. Is there an association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and streptococcus pneumoniae? Clinl Infect Dis. 2020. DOI:10.1093/cid/ciaa1812
19. Tang JW, Tambyah PA, Hui DSC, et al. Emergence of a new SARS-CoV-2 variant in the UK. J Infect. 2021;82(4):e27–e28.
20. Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization. Nature. 2021. 2021 07 08. DOI:10.1038/s41586-021-03777-9.
21. Lansbury L, Lim B, Baskaran V, et al. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020 Aug;81(2):266–275. PubMed PMID: 32473235; PubMed Central PMCID: PMCPMC7255350. eng.
22. Russell CD, Fairfield CJ, Drake TM, et al. Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. Lancet Microbe. 2021. 2021 06 02. DOI:10.1016/S2666-5247(21)00090-2.
23. Brueggemann AB, Jansen van Rensburg MJ, Shaw D, et al. Changes in the incidence of invasive disease due to streptococcus pneumoniae, haemophilus influenzae, and neisseria meningitidis during the COVID-19 pandemic in 26 countries and territories in the invasive respiratory infection surveillance initiative: a prospective analysis of surveillance data. Lancet Digital Health. 2021;3(6):e360–e370.
24. Verhagen MD, Brazel DM, Dowd JB, et al. Forecasting spatial, socio-economic and demographic variation in COVID-19 health care demand in England and Wales. BMC Med. 2020 Jun 29;18(1):203. PubMed PMID: 32594909; PubMed Central PMCID: PMCPMC7321716. eng.
25. Majeed A, Maile EJ, Bindman AB, et al. The primary care response to COVID-19 in England's national health service. J R Soc Med. 2020 Jun;113(6):208–210. PubMed PMID: 32521196; PubMed Central PMCID: PMCPMC7439588. eng.
26. Pa An W, Ladhani NJ, Sheppard CL, et al. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015;15(5):535–543.
27. Vyse A, Campling J, Czudek C, et al. The proportion of contemporary invasive pneumococcal disease and pneumococcal pneumonia in UK adults reflected by serotypes included in the 13-valent pneumococcal conjugate vaccine and next generation higher valency pneumococcal conjugate vaccines in development. Vaccine. 2020 Dec 3;38 (51):8068–8070. PubMed PMID: 33190949; eng.
28. Djennad A, Ramsay ME, Pebody R, et al. Effectiveness of 23-valent Polysaccharide pneumococcal vaccine and changes in invasive pneumococcal disease incidence from 2000 to 2017 in those aged 65 and over in England and Wales. EClinicalMedicine. 2018;6:42–50.
• This article presents trends and incidence of IPD in adults aged 65+ years stratified by broad serotype groups
29. Chalmers J, Campling J, Ellsbury G, et al. Community-acquired pneumonia in the United Kingdom: a call to action [journal article]. Pneumonia. 2017 Oct 05;9(1):15.
30. McLaughlin JM, Swerdlow DL, Isturiz RE, et al. Decision-making for PCV in adults. Human vaccines & immunotherapeutics. 2019;15(3):584–593. doi: PubMed PMID: 30352017.
31. Melegaro A, Edmunds WJ, Pebody R, et al. The current burden of pneumococcal disease in England and Wales. J Infect. 2006;52(1):37–48.
32. Rodrigo C, Bewick T, Sheppard C, et al. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. Eur Respir J. 2015 Jun;45(6):1632–1641. PubMed PMID: 25792633; eng.
33. Shi T, Denouel A, Tietjen AK, et al. Global and regional burden of hospital admissions for pneumonia in older adults: a systematic review and meta-analysis. J Infect Dis. 2019 Mar 8. DOI:10.1093/infdis/jiz053. PubMed PMID: 30849172; eng.
34. Arnold FW, Reyes Vega AM, and Salunkhe V, et al. Older adults hospitalized for pneumonia in the United States: incidence, epidemiology, and outcomes The American Geriatrics Society . 2020;68 (5):1007–1014.
35. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. Clin Infect Dis. 2017 Nov 13;65(11):1806–1812. PubMed PMID: 29020164; eng.

36. Choi YH, Andrews N, Miller E, et al. Estimated impact of revising the 13-valent pneumococcal conjugate vaccine schedule from 2+1 to 1 +1 in England and Wales: a modelling study. PLoS Med. 2019;16(7): e1002845–e1002845. PubMed PMID: 31269018; eng.
37. Eletu SD, Sheppard CL, Rose S, et al. Re-validation and update of an extended-specificity multiplex assay for detection of streptococcus pneumoniae capsular serotype/serogroup-specific antigen and cell-wall polysaccharide in urine specimens. Access microbiology. 2020;2(3):acmi000094. doi: PubMed PMID: 32974571; PubMed Central PMCID: PMCPMC7470314. eng.
38. Woodhead MA, Macfarlane JT, McCracken JS, et al. Prospective study of the aetiology and outcome of pneumonia in the community. Lancet. 1987 Mar 21;1(8534):671–674. PubMed PMID: 2882091.
39. Macfarlane J, Holmes W, Gard P, et al. Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. Thorax. 2001 Feb;56(2):109–114. PubMed PMID: 11209098; PubMed Central PMCID: PMCPMC1746009. eng.
40. Myles PR, McKeever TM, Pogson Z, et al. The incidence of pneumonia using data from a computerized general practice database. Epidemiol Infect. 2009 May;137(5):709–716. PubMed PMID: 18840320.
41. Sun X, Douiri A, Gulliford M, et al. Pneumonia incidence trends in UK primary care from 2002 to 2017: population-based cohort study. Epidemiol Infect. 2019 Sep 9;147:e263. PubMed PMID: 31496464; PubMed Central PMCID: PMCPMC6805760. eng.
42. Treskova M, Scholz SM, Kuhlmann A, et al. Cost effectiveness of elderly pneumococcal vaccination in presence of higher-valent pneumococcal conjugate childhood vaccination: systematic literature review with focus on methods and assumptions. Pharmacoeconomics. 2019 Sep;37(9):1093–1127. PubMed PMID: 31025189; eng.
43. Ladhani SN, Ramsay ME. Smart scheduling: optimizing national immunization programs to achieve maximum impact. Clin Infect Dis. 2020 Feb 3;70(4):684–686. PubMed PMID: 31209467; eng.
44. Thorrington D, Andrews N, Stowe J, et al. Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control. BMC Med. 2018 Feb 8;16(1):13. PubMed PMID: 29415741; PubMed Central PMCID: PMCPMC5804014. eng.
45. Adebanjo TA, Pondo T, Yankey D, et al. Pneumococcal conjugate vaccine breakthrough infections: 2001–2016. Pediatrics. 2020 Mar;145(3). DOI:10.1542/peds.2019-0836. PubMed PMID: 32054822; PubMed Central PMCID: PMCPMC7055927 Merck, Pfizer, and Sanofi Pasteur for consulting on the epidemiology and vaccine prevention of bacterial diseases; the other authors have indicated they have no potential conflicts of interest to disclose. eng.
46. Andrews NJ, Waight PA, Burbidge P, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. Lancet Infect Dis. 2014 Sep;14(9):839–846. PubMed PMID: 25042756; eng.
47. Sings HL, De Wals P, Gessner BD, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine against invasive disease caused by serotype 3 in children: a systematic review and meta-analysis of observational studies. Clin Infect Dis. 2019 May 30;68(12):2135–2143. PubMed PMID: 30357326; PubMed Central PMCID: PMCPMC6541704. eng.
48. Dagan R, Patterson S, Juergens C, et al. Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: a randomized double-blind trial. Clin Infect Dis. 2013 Oct;57(7):952–962. PubMed PMID: 23804191; eng.
49. Sings, HL , De Wals, P, and Gessner, BD Corrigendum to: effectiveness of 13-valent pneumococcal conjugate vaccine against invasive disease caused by serotype 3 in children: a systematic review and meta-analysis of observational studies. Clinl Infect Dis. 2021. DOI:10.1093/cid/ciaa1767.
50. Southern J, Andrews N, Sandu P, et al. Pneumococcal carriage in children and their household contacts six years after introduction of the 13-valent pneumococcal conjugate vaccine in England. PloS One. 2018;13(5):e0195799. PubMed PMID: 29799839; PubMed Central PMCID: PMCPMC5969732. eng.
51. van Hoek AJ, Sheppard CL, Andrews NJ, et al. Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England. Vaccine. 2014;32(34):4349–4355. PubMed PMID: 24657717; eng.
52. Flasche S, Van Hoek AJ, Sheasby E, et al. Effect of pneumococcal conjugate vaccination on serotype-specific carriage and invasive disease in England: a cross-sectional study. PLoS Med. 2011;8(4): e1001017–e1001017. PubMed PMID: 21483718; eng.
53. European Centre for Disease Prevention and Control. Invasive pneumococcal disease.In: ECDC. Annual epidemiological report for 2015. Stockholm: ECDC; 2017.
54. Flasche S, Lipsitch M, Ojal J, et al. Estimating the contribution of different age strata to vaccine serotype pneumococcal transmission in the pre vaccine era: a modelling study. BMC Med. 2020 Jun 10;18(1):129. PubMed PMID: 32517683; PubMed Central PMCID: PMCPMC7285529. eng.
55. Arguedas A, Trzciński K, O'Brien KL, et al. Upper respiratory tract colonization with streptococcus pneumoniae in adults. Expert Rev Vaccines. 2020 Apr;19(4):353–366. PubMed PMID: 32237926; eng.
56. Almeida ST, Paulo AC, Froes F, et al. Dynamics of pneumococcal carriage in adults: a new look at an old paradigm. J Infect Dis. 2020 Sep 2. DOI:10.1093/infdis/jiaa558. PubMed PMID: 32877517; eng.
57. Metcalf BJ, Chochua S, Walker H, et al. Invasive pneumococcal strain distributions and isolate clusters associated with persons experiencing homelessness during 2018. Clin Infect Dis. 2020 Nov 5. DOI:10.1093/cid/ciaa1680. PubMed PMID: 33150366; eng.
58. Matanock A, Lee G, Gierke R, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal Polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep. 2019;68(46):1069–1075.
59. Waight PA, Andrews NJ, Ladhani SN, et al. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015;15(5):535–543. PubMed PMID: 25801458; eng.
60. Groves N, Sheppard CL, Litt D, et al. Evolution of streptococcus pneumoniae serotype 3 in England and Wales: a major vaccine evader. Genes (Basel). 2019 Oct 25;10(11). DOI:10.3390/genes10110845. PubMed PMID: 31731573; PubMed Central PMCID: PMCPMC6896183. eng.
61. Andrews N, Kent A, Amin-Chowdhury Z, et al. Effectiveness of the seven-valent and thirteen-valent pneumococcal conjugate vaccines in England: the indirect cohort design, 2006–2018. Vaccine. 2019 Jul 1. DOI:10.1016/j.vaccine.2019.06.071. PubMed PMID: 31272872; eng.
62. Sings HL, Gessner BD, Wasserman MD, et al. Pneumococcal conjugate vaccine impact on serotype 3: a review of surveillance data. Infect Dis Ther. 2021 Mar;10(1):521–539. PubMed PMID: 33587245; PubMed Central PMCID: PMCPMC7954992. eng.
63. Dagan R, van der Beek BA, Ben-Shimol S, et al. Effectiveness of the seven- and thirteen valent pneumococcal conjugate vaccines against vaccine-serotype otitis media. Clin Infect Dis. 2021 Jan 28. DOI:10.1093/cid/ciab066. PubMed PMID: 33507250; eng.
64. Gessner BD, Jiang Q, Van Werkhoven CH, et al. A post-hoc analysis of serotype-specific vaccine efficacy of 13-valent pneumococcal conjugate vaccine against clinical community acquired pneumonia from a randomized clinical trial in the Netherlands. Vaccine. 2019 May 30. DOI:10.1016/j.vaccine.2019.05.065. PubMed PMID: 31155413.

    • This analysis of data from a large randomised controlled clinical trial showed PCV-13 provided some protection against serotype 3 CAP in adults aged 65+ years
65. McLaughlin JM, Jiang Q, Gessner BD, et al. Pneumococcal conjugate vaccine against serotype 3 pneumococcal pneumonia in adults: a systematic review and pooled analysis. Vaccine. 2019 Oct 8;37(43):6310–6316. PubMed PMID: 31522807; eng.

66. Berild JDW BA, Vestrheim DF, Slotved H-C, et al. A systematic review of studies published between 2016 and 2019 on the effectiveness and efficacy of pneumococcal vaccination on pneumonia and invasive pneumococcal disease in an elderly population. Pathogens. 2020;9:259.
67. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015 Mar 19;372(12):1114–1125. PubMed PMID: 25785969; eng.
••This large randomized, controlled, phase 4 clinical trial demonstrated the safety and efficacy of PCV-13 among adults aged ≥65 years in preventing vaccine type community-acquired pneumonia, non-bacteremic/ non-invasive pneumonia, and vaccine-type invasive pneumococcal disease.
68. De Miguel S, Domenech M, González-Camacho F, et al. Nationwide trends of invasive pneumococcal disease in Spain (2009–2019) in children and adults during the pneumococcal conjugate vaccine era. Clin Infect Dis. 2020 Sep 29. DOI:10.1093/cid/ciaa1483. PubMed PMID: 32990303; eng.
69. van Hoek AJ, Andrews N, Waight PA, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012;65(1):17–24.
70. Houseman C, Chapman KE, Manley P, et al. Decreasing case fatality rate following invasive pneumococcal disease, North East England, 2006–2016. Epidemiol Infect. 2019 Jan;147:e175. PubMed PMID: 31063115; PubMed Central PMCID: PMCPMC6518772. eng.
71. Amin-Chowdhury Z, Collins S, Sheppard C, et al. Characteristics of invasive pneumococcal disease (IPD) caused by emerging serotypes after the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in England; prospective observational cohort study, 2014–18. Clin Infect Dis. 2020:ciaa043. DOI:10.1093/cid/ciaa043. PubMed PMID: 31955196; eng.
72. Trotter CL, Stuart JM, George R, et al. Increasing hospital admissions for pneumonia, England. Emerg Infect Dis. 2008 May;14 (5):727–733. PubMed PMID: 18439353; PubMed Central PMCID: PMCPMC2600241. eng.
73. Daniel P, Woodhead M, Welham S, et al. Mortality reduction in adult community-acquired pneumonia in the UK (2009–2014): results from the British thoracic society audit programme. Thorax. 2016 Nov;71(11):1061–1063. PubMed PMID: 27534681; eng.
74. BTS. 2019. Available from: https://www.brit-thoracic.org.uk/quality-improvement/clinical-audit/
75. Lawrence H, Lim WS, McKeever TM, et al. Variation in clinical outcomes and process of care measures in community acquired pneumonia: a systematic review. Pneumonia. 2020;12(1):10. PubMed PMID: 32999854; PubMed Central PMCID: PMCPMC7517805. eng.
76. Hak E, Bont J, Hoes AW, et al. Prognostic factors for serious morbidity and mortality from community-acquired lower respiratory tract infections among the elderly in primary care. Fam Pract. 2005 Aug;22(4):375–380. PubMed PMID: 15805127; eng.
77. JCVI. Minute of the meeting on 07 October 2015.
78. Tin Tin Htar M, Stuurman AL, Ferreira G, et al. Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies. PloS One. 2017;12(5):e0177985.
79. Niederman MS, Folaranmi T, Buchwald UK, et al. Efficacy and effectiveness of a 23-valent polysaccharide vaccine against invasive and noninvasive pneumococcal disease and related outcomes: a review of available evidence. Expert Rev Vaccines. 2021 Feb 20:1–13. DOI:10.1080/14760584.2021.1880328. PubMed PMID: 33478306; eng.
80. Lawrence H, Pick H, Baskaran V, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: a case-control test-negative design study. PLoS Med. 2020 Oct;17(10):e1003326. PubMed PMID: 33095759; eng.
81. McLaughlin JM, Jiang Q, Isturiz RE, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine against hospitalization for community-acquired pneumonia in older US adults: a test-negative design. Clin Infect Dis. 2018 Oct 30;67(10):1498–1506. PubMed PMID: 29790925; PubMed Central PMCID: PMCPMC6206101. eng.
82. Patterson S, Webber C, Patton M, et al. A post hoc assessment of duration of protection in CAPiTA (community acquired pneumonia immunization trial in adults). Trials Vaccinol. 2016. 2016 01 01;5:92–96.
83. Rozenbaum MH, van Hoek AJ, Fleming D, et al. Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. BMJ (Clin Res Ed). 2012 Oct 26;345: e6879. PubMed PMID: 23103369; PubMed Central PMCID: PMCPmc3482156. eng.
84. Payment by results in the NHS: tariff for 2013 to 2014 2013. Available from: https://www.gov.uk/government/publications/payment-by-results-pbr-operational-guidance-and-tariffs
85. Corrales-Medina VF, Musher DM, Shachkina S, et al. Acute pneumonia and the cardiovascular system. Lancet. 2013 Feb 9;381 (9865):496–505. PubMed PMID: 23332146; eng.
86. Melegaro A, Edmunds WJ. Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales. Vaccine. 2004 Oct 22;22(31–32):4203–4214. PubMed PMID: 15474710; eng.
87. Rubin JL, McGarry LJ, Strutton DR, et al. Public health and economic impact of the 13-valent pneumococcal conjugate vaccine (PCV13) in the United States. Vaccine. 2010 Nov 10;28 (48):7634–7643. PubMed PMID: 20883739; eng.
88. Kuchenbecker U, Chase D, Reichert A, et al. Estimating the cost-effectiveness of a sequential pneumococcal vaccination program for adults in Germany. PloS One. 2018;13(5):e0197905. PubMed PMID: 29795647; eng.
89. Bennett JE, Sumner W 2nd, Downs SM, et al. Parents' utilities for outcomes of occult bacteremia. Arch Pediatr Adolesc Med. 2000 Jan;154(1):43–48. PubMed PMID: 10632249.
90. Shiri T, McCarthy ND, Petrou S, et al. The impact of childhood pneumococcal vaccination on hospital admissions in England: a whole population observational study. BMC Infect Dis. 2019 Jun 10;19(1):510. PubMed PMID: 31182036; PubMed Central PMCID: PMCPMC6558731. eng.
91. Mangen MJ, Huijts SM, Bonten MJ, et al. The impact of community-acquired pneumonia on the health-related quality-of-life in elderly. BMC Infect Dis. 2017 Mar 14;17(1):208. PubMed PMID: 28292280; PubMed Central PMCID: PMCPmc5351062. eng.
92. Glick HA, Miyazaki T, Hirano K, et al. One-year quality of life post-pneumonia diagnosis in Japanese adults. Clin Infect Dis. 2020 May 24. DOI:10.1093/cid/ciaa595. PubMed PMID: 32447366; eng.
93. Bruns AH, Oosterheert JJ, Cucciolillo MC, et al. Cause-specific long-term mortality rates in patients recovered from community-acquired pneumonia as compared with the general Dutch population. Clin Microbiol Infect. 2011 May;17(5):763–768. PubMed PMID: 20807226.
94. Floeystad HK, Holm A, Sandvik L, et al. Increased long-term mortality after survival of invasive pneumococcal disease: a population-based study. Infectious Diseases. 2017 May;49 (5):365–372. doi: PubMed PMID: 28095723.
95. Sandvall B, Rueda AM, Musher DM, et al. Long-term survival following pneumococcal pneumonia. Clin Infect Dis. 2013 Apr;56 (8):1145–1146. PubMed PMID: 23300240.
96. Wagenvoort GH, Sanders EA, de Melker HE, et al. Long-term mortality after IPD and bacteremic versus non-bacteremic pneumococcal pneumonia. Vaccine. 2017 Mar 27;35(14):1749–1757. PubMed PMID: 28262334; eng.
97. Campling J, Jones D, Chalmers J, et al. Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England. BMJ Open Respir Res. 2020;7(1):e000703.
98. Peyrani P, Ramirez J. Long-term mortality in hospitalized patients with community-acquired pneumonia. Am J Med Sci. 2017 May;353 (5):421. PubMed PMID: 28502325; eng.
99. Peyrani P, Arnold FW, Bordon J, et al. Incidence and mortality of adults hospitalized with community-acquired pneumonia according to clinical course. Chest. 2020 Jan;157(1):34–41. PubMed PMID: 31610158; eng.
100. Hughes GJ, Wright LB, Chapman KE, et al. Serotype-specific differences in short- and longer-term mortality following invasive

pneumococcal disease. Epidemiol Infect. 2016 Sep;144 (12):2654–2669. PubMed PMID: 27193457; PubMed Central PMCID: PMCPMC4988273. eng.

101. Myint PK, Hawkins KR, Clark AB, et al. Long-term mortality of hospitalized pneumonia in the EPIC-norfolk cohort. Epidemiol Infect. 2016 Mar;144(4):803–809. PubMed PMID: 26300532; PubMed Central PMCID: PMCPMC6217917. eng.
102. Klugman KP, Rodgers GL. Time for a third-generation pneumococcal conjugate vaccine. Lancet Infect Dis. 2021 Jan;21(1):14–16. PubMed PMID: 32702301; eng.
103. Kalina WV, Souza V, Wu K, et al. Qualification and clinical validation of an immunodiagnostic assay for detecting 11 additional streptococcus pneumoniae serotype-specific Polysaccharides in human urine. Clin Infect Dis. 2020 Dec 3;71(9):e430–e438. PubMed PMID: 32072165; PubMed Central PMCID: PMCPMC7713672. eng.
104. Sevilla JP, Stawasz A, and Burnes D, et al. Indirect costs of adult pneumococcal disease and the productivity-based rate of return to the 13-valent pneumococcal conjugate vaccine for adults in Turkey. Human Vaccines & Immunotheraputics. 2020 Aug 2;16 (8):1923–1936. Human Vaccines & Immunotheraputics Human Vaccines & Immunotheraputics.
105. Doherty TM, Hausdorff WP, Kristinsson KG, et al. Effect of vaccination on the use of antimicrobial agents: a systematic literature review. Ann Med. 2020 Sep;52(6):283–299. PubMed PMID: 32597236; eng.
106. Suaya JA, Mendes RE, Sings HL, et al. Streptococcus pneumoniae serotype distribution and antimicrobial nonsusceptibility trends among adults with pneumonia in the United States, 2009–2017. J Infect. 2020 Oct;81(4):557–566. PubMed PMID: 32739491; eng.
107. Vekemans J, Hasso-Agopsowicz M, Kang G, et al. Leveraging vaccines to reduce antibiotic use and prevent antimicrobial resistance: a WHO action framework. Clinl Infect Dis. 2021. DOI:10.1093/cid/ciab062.
108. Kolditz M, Schmitt J, Pletz MW, et al. Impact of the 13-valent pneumococcal conjugate vaccine on incidence of all-cause pneumonia in adults aged ≥60 years - a population-based retrospective cohort study. Clin Infect Dis. 2018 Nov 21. DOI:10.1093/cid/ciy993. PubMed PMID: 30462172.
109. Theilacker C, Vyse A, Jodar L, et al. Evaluations of the public health impact of adult vaccination with pneumococcal vaccines should include reductions in all-cause pneumonia. Clin Infect Dis. 2020 May 23;70(11):2456–2457. PubMed PMID: 31624826; eng.
110. Gessner BD, Isturiz R, Snow V, et al. The rationale for use of clinically defined outcomes in assessing the impact of pneumococcal conjugate vaccines against pneumonia. Expert Rev Vaccines. 2021:null–null. DOI: 10.1080/14760584.2021.1889376.
• This study evaluated the public health impact of PCV-13 using data from a randomized clinical trial and found substantial reductions of pneumonia and invasive pneumococcal disease following PCV-13 immunization among adults aged 65+ years.
111. Gessner BD, Jiang Q, Van Werkhoven CH, et al. A public health evaluation of 13-valent pneumococcal conjugate vaccine impact on adult disease outcomes from a randomized clinical trial in the Netherlands. Vaccine. 2018 May 31. DOI:10.1016/j.vaccine.2018.05.097. PubMed PMID: 29861177; eng.
112. Hussain M, Melegaro A, Pebody RG, et al. A longitudinal household study of streptococcus pneumoniae nasopharyngeal carriage in a UK setting. Epidemiol Infect. 2005 Oct;133 (5):891–898. PubMed PMID: 16181510; PubMed Central PMCID: PMCPMC2870321. eng.
113. Whitney CG, Pilishvili T, Farley MM, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet. 2006 Oct 28;368(9546):1495–1502. PubMed PMID: 17071283; eng.
114. Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis. 2010;201(1):32–41. PubMed PMID: 19947881; eng.
115. E An M, Waight PA, Slack MP, et al. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. Lancet Infect Dis. 2011;11(10):760–768.
116. Root-Bernstein R. Possible cross-reactivity between SARS-CoV-2 Proteins, CRM197 and Proteins in pneumococcal vaccines may protect against symptomatic SARS-CoV-2 disease and death. Vaccines (Basel). 2020 Sep 24;8(4). DOI:10.3390/vaccines8040559. PubMed PMID: 32987794; PubMed Central PMCID: PMCPMC7712751. eng.
117. Cucchiari D, Pericàs JM, and Riera J, et al. Pneumococcal superinfection in COVID-19 patients: a series of 5 cases. Medicina clinica. 2020 Dec 11;155(11):502–505. doi: doi:.
118. Sharov KS. SARS-CoV-2-related pneumonia cases in pneumonia picture in Russia in March-May 2020: secondary bacterial pneumonia and viral co-infections. J Glob Health. 2020 Dec;10(2):020504. PubMed PMID: 33110587; PubMed Central PMCID: PMCPMC7568231 (available upon request from the corresponding author) and declares no conflicts of interest. eng.
119. Nunes MC, Cutland CL, and Klugman KP, et al. Pneumococcal conjugate vaccine protection against coronavirus-associated pneumonia hospitalization in children living with and without HIV mBio . 2021;12(1):e02347–20.
120. Amin-Chowdhury Z, Aiano F, Mensah A, et al. Impact of the COVID-19 pandemic on invasive pneumococcal disease and risk of pneumococcal coinfection with SARS-CoV-2: prospective national cohort study, England. Clin Infect Dis. 2020 Nov 16. DOI:10.1093/cid/ciaa1728. PubMed PMID: 33196783; eng.
• This article presents evidence that UK adults with IPD who were co-infected with the SARS-CoV-2 virus had an elevated risk of mortality
121. JCVI Priority Groups COVID–19.
122. Soiza RL, Scicluna C, Thomson EC, et al. Efficacy and safety of COVID-19 vaccines in older people. Age Ageing. 2020. DOI:10.1093/ageing/afaa274.
123. MHRA COVID Vaccines Page.
124. Baker RE, Park SW, Yang W, et al. The impact of COVID-19 nonpharmaceutical interventions on the future dynamics of endemic infections. Proceedings of the National Academy of Sciences of the United States of America; 2020 Dec 1;117, (48):, 30547–30553. doi: 10.1073/pnas.2013182117. PubMed PMID: 33168723; PubMed Central PMCID: PMCPMC7720203.

Taylor & Francis
Taylor & Francis Group

Expert Review of Pharmacoeconomics & Outcomes Research

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierp20

Cost-effectiveness of using a 20-valent pneumococcal conjugate vaccine to directly protect adults in England at elevated risk of pneumococcal disease

Diana Mendes, Ahuva Averin, Mark Atwood, Reiko Sato, Andrew Vyse, James Campling, Derek Weycker, Mary Slack, Gillian Ellsbury & Tendai Mugwagwa

To cite this article: Diana Mendes, Ahuva Averin, Mark Atwood, Reiko Sato, Andrew Vyse, James Campling, Derek Weycker, Mary Slack, Gillian Ellsbury & Tendai Mugwagwa (2022) Cost-effectiveness of using a 20-valent pneumococcal conjugate vaccine to directly protect adults in England at elevated risk of pneumococcal disease, Expert Review of Pharmacoeconomics & Outcomes Research, 22:8, 1285-1295, DOI: 10.1080/14737167.2022.2134120

To link to this article: https://doi.org/10.1080/14737167.2022.2134120

EXPERT REVIEW OF PHARMACOECONOMICS & OUTCOMES RESEARCH
2022, VOL. 22, NO. 8, 1285–1295
https://doi.org/10.1080/14737167.2022.2134120

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Cost-effectiveness of using a 20-valent pneumococcal conjugate vaccine to directly protect adults in England at elevated risk of pneumococcal disease

Diana Mendes [a], Ahuva Averin [b], Mark Atwood[b], Reiko Sato [c], Andrew Vyse [a], James Campling [a], Derek Weycker [b], Mary Slack [d], Gillian Ellsbury [a] and Tendai Mugwagwa [a]

[a]Pfizer Ltd, Tadworth, UK; [b]Policy Analysis Inc. (PAI), Chestnut Hill, MA, USA; [c]Pfizer Inc, Collegeville, PA, USA; [d]School of Medicine & Dentistry, Griffith University, Gold Coast Campus, 4222, Australia

ABSTRACT

Objectives: Despite the current pneumococcal vaccination program in England for older adults and adults with underlying conditions, disease burden remains high. We evaluated cost-effectiveness of 20-valent pneumococcal conjugate vaccine (PCV20) compared to current pneumococcal recommendations for adults in England.

Methods: Lifetime outcomes/costs of invasive pneumococcal disease (IPD) and community-acquired pneumonia (CAP) among adults aged 65–99 years and adults aged 18–64 years with underlying conditions in England were projected using a deterministic cohort model. Vaccination with PCV20 was compared with 23-valent pneumococcal polysaccharide vaccine (PPV23) from the National Health Service perspective.

Results: PCV20 was cost saving compared with PPV23 in base case and most sensitivity analyses. In the base case, replacing PPV23 with PCV20 prevented 7,789 and 140,046 cases of IPD and hospitalized CAP, respectively, and 22,199 associated deaths, resulting in incremental gain of 91,375 quality-adjusted life-years (QALYs) and incremental savings of £160M. In probabilistic sensitivity analyses, PCV20 (vs. PPV23) was cost saving in 85% of simulations; incremental cost per QALY was below £30,000 in 99% of simulations.

Conclusions: PCV20 vaccination in adults aged 65–99 years and those aged 18–64 years with underlying comorbidities in England is expected to prevent more hospitalizations, save more lives, and yield lower overall costs than current recommendations for PPV23.

ARTICLE HISTORY
Received 3 June 2022
Accepted 4 October 2022

KEYWORDS
Streptococcus pneumoniae; vaccination; immunization; cost-effectiveness; pneumococcal conjugate vaccine

1. Introduction

Streptococcus pneumoniae (pneumococcus) causes significant morbidity and mortality in both children and adults in the United Kingdom (UK) [1]. Invasive pneumococcal disease (IPD) is the most serious manifestation causing severe illness with a high risk of mortality [2–4]. Community-acquired pneumonia (CAP), however, is far more common and associated with significant morbidity and mortality [5–8]. Between 2010 and 2017, there were more than 4,000 cases of IPD in England and Wales annually [3]. Estimates of the burden of hospitalized CAP vary considerably, ranging from 80,000 to half a million cases, and a recent study of UK adults found 37% of persons hospitalized with CAP between 2013 and 2018 had pneumococcal pneumonia [5,6,9].

To reduce the risk of pneumococcal infection in the UK, routine vaccination is currently recommended by the Joint Committee on Vaccination and Immunisation (JCVI) for infants, at-risk children and adults (i.e. aged ≥2 years), and all older adults (i.e. aged ≥65 years) [10]. Two vaccines are currently available for use in the UK: a 23-valent pneumococcal polysaccharide vaccine (PPV23) manufactured by Merck Sharpe & Dohme (MSD), for which evidence suggests protection against vaccine-type IPD (VT-IPD) only [11–26], and Pfizer's 13-valent pneumococcal conjugate vaccine (PCV13), which has been shown to protect against VT-IPD and vaccine-type CAP (VT-CAP) [27].

PPV23 has been recommended for all persons aged ≥2 years with underlying conditions (e.g. chronic comorbidities and immunosuppressive conditions) since 1992 and for all older adults since 2003 [28]. Although PPV23 coverage is high (65% among adults aged ≥65 years), surveillance data suggest that its use has provided only low to moderate short-term direct protection against IPD and has not had a population-level impact on IPD burden given that serotypes unique to PPV23 continue to account for a large proportion of IPD among older adults [2,29]. Immunization of children aged <2 years with PCVs – including 7-valent PCV (PCV7) from 2006–2009 and PCV13 from 2010 to present – has prevented a significant number of cases of pneumococcal disease and associated deaths through the direct protection of young children and indirect protection of older children and adults [3,30]. Nonetheless, the burden of both IPD and CAP remains substantial among adults [6,9,30].

CONTACT Ahuva Averin aaverin@pai2.com Policy Analysis Inc. (PAI), 822 Boylston Street, Suite 206, Chestnut Hill, MA

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14737167.2022.2134120

Two new, higher valent PCVs – PCV15 and PCV20 – have recently been approved by the Medicines and Healthcare products Regulatory Agency for use among adults in the UK, however, at the time of writing JCVI has not published revised pneumococcal vaccination guidelines since their approval. PCV15 (manufactured by MSD) includes the serotypes in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) plus two additional serotypes (22F, 33F) and PCV20 (manufactured by Pfizer) includes the serotypes in PCV15 plus five additional serotypes (8, 10A, 11A, 12F, 15B). Although PCV13 is only recommended among a very limited subgroup of high-risk UK adults, it is anticipated that these new PCVs may reduce disease burden in adults versus PPV23 – due to their broader serotype coverage than existing conjugate vaccines and expected greater, longer-lasting protection compared to PPV23 [2,31–36] – and thus may be a cost-effective use of healthcare resources. However, analyses of cost-effectiveness of use of higher-valent PCVs among adults in England have not been previously published. Accordingly, we evaluated the cost-effectiveness of PCV20 alone as well as various other strategies against a single dose of PPV23 in a population of adults currently eligible for pneumococcal vaccination in England.

2. Methods

2.1. Model description

A deterministic model with a Markov-type process was used to depict the lifetime risk of clinical outcomes and economic costs of pneumococcal disease in a hypothetical closed population comprising all adults aged 65–99 years and adults aged 18–64 years with underlying conditions in England (i.e. those adults currently eligible for vaccination with PPV23) (Figure 1). The model population is stratified at model entry by age (i.e. in one-year increments) and risk profile (i.e. low, moderate, or high risk). Persons may transition to a higher risk group, but not to a lower risk group, during the modeling horizon. Persons in the model population may be assumed to receive any of the following at model entry or subsequently: PCV20, PCV20→PPV23 (i.e. PCV20 at model entry [i.e. year 1] followed by PPV23 at start of year 2), PCV15→PPV23 (i.e. PCV15 at model entry followed by PPV23 in year 2), PPV23, PPV23+PPV23 (i.e. PPV23 at model entry and again at start of year 6), or no vaccine.

Expected clinical outcomes and economic costs are projected annually for the model population, based on age, risk profile, disease/fatality rates, vaccination status, and unit costs of vaccinations and medical care. IPD includes bacteremia and meningitis, and all-cause CAP is stratified by care setting. Vaccinated persons may be at lower risk of future IPD and all-cause CAP; the magnitude of vaccine-associated risk reduction depends on clinical presentation, vaccine type(s), proportion of disease that is vaccine-preventable, age, time since vaccination, and risk profile. Risk of death from IPD, all-cause CAP, and other causes depends upon age and risk profile. Expected medical treatment costs for IPD and all-cause CAP are generated based on event rates and unit costs in relation to care setting. Vaccination costs are tallied in the year of vaccine administration. Clinical outcomes and economic costs projected for each vaccination strategy include IPD and all-cause CAP cases and attributable deaths, life-years (LYs), quality-adjusted LYs (QALYs), and costs of vaccination and medical treatment.

2.2. Model estimation

A summary of methods employed to estimate key model parameters is set forth below; corresponding parameter values are summarized in Table 1. A detailed description of methods employed to estimate all model parameters is provided in Supplement A.

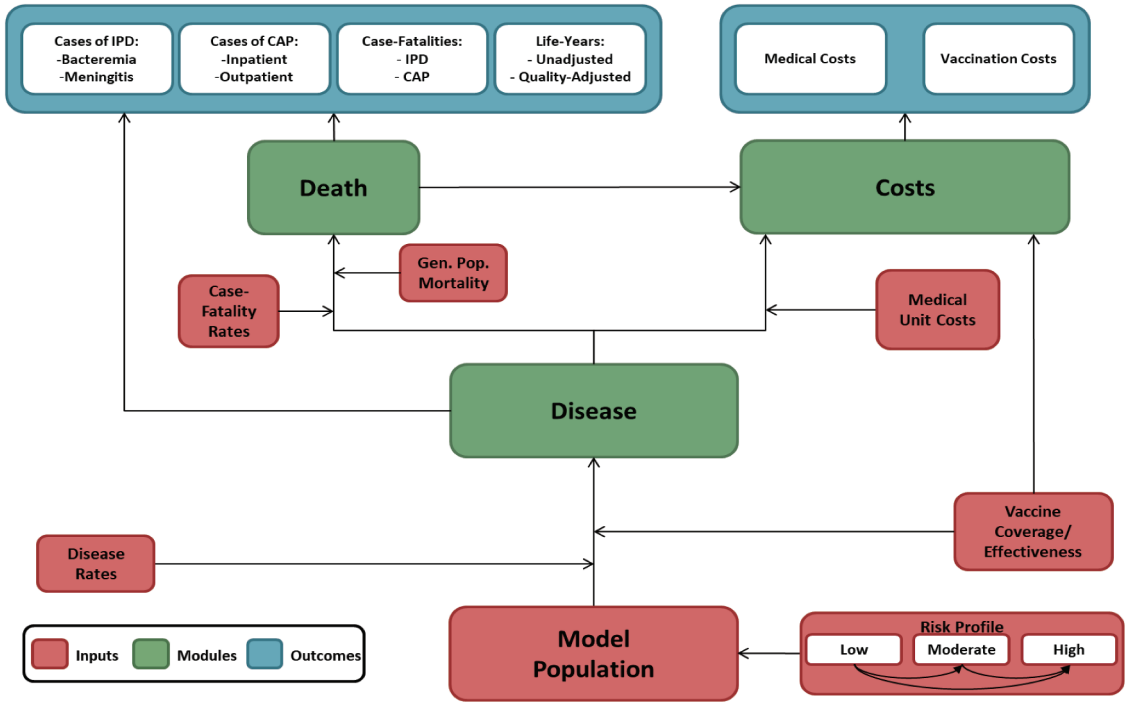


Figure 1. Model schematic.

Table 1. Base case model input values.

	Age and Risk Profile												
	18–49 Years		50–64 Years		65–74 Years			75–84 Years			85-99 Years		
	Moderate	High	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
No. of adults (in thousands)	1,254.6	449.5	1,784.1	1,315.7	3,392.3	1,220.8	963.3	1,970.8	1,005.5	818.2	626.0	456.0	379.1
Annual disease incidence (per 100,000)													
Bacteremia	18.7	42.0	17.6	48.9	4.8	18.8	62.3	8.1	21.9	94.7	15.0	40.5	175.4
Meningitis	2.1	4.7	1.7	4.8	0.3	1.1	3.6	0.3	0.7	3.0	0.1	0.3	1.5
All-cause hospitalized CAP	247.7	452.4	700.6	1,279.3	769.7	2,301.4	4,202.5	939.7	2,809.7	5,130.8	1,498.7	4,481.2	8,183.1
Annual mortality/case-fatality (per 100)													
General population	0.1	0.2	0.6	0.8	1.1	1.7	2.3	3.0	4.5	6.0	9.6	14.4	19.2
Bacteremia	6.0	7.2	12.8	15.4	14.0	17.5	21.0	22.0	27.5	33.0	32.3	40.3	48.4
Meningitis	6.0	7.2	12.8	15.4	14.0	17.5	21.0	22.0	27.5	33.0	32.3	40.3	48.4
All-cause hospitalized CAP	3.4	4.1	6.7	8.0	7.9	9.9	11.8	10.3	12.9	15.5	14.5	18.1	21.7
General population health-state utilities	0.7745	0.7346	0.7234	0.6852	0.9283	0.7308	0.7082	0.8921	0.6799	0.6607	0.8191	0.6038	0.5643
Vaccine coverage													
PCV20*	43.4%	37.5%	43.4%	37.5%	42.9%	79.0%	83.7%	73.3%	89.6%	95.5%	77.9%	85.9%	85.7%
PPV23**	43.4%	37.5%	43.4%	37.5%	42.9%	79.0%	83.7%	73.3%	89.6%	95.5%	77.9%	85.9%	85.7%
VE PCV vs. VT-IPD													
Year 1	81.5%	65.2%	79.2%	63.3%	75.0%	75.0%	60.0%	75.0%	75.0%	60.0%	75.0%	75.0%	60.0%
Year 5	81.5%	65.2%	79.2%	63.3%	75.0%	75.0%	60.0%	75.0%	75.0%	60.0%	75.0%	75.0%	60.0%
Year 10	63.1%	50.5%	61.2%	49.0%	58.0%	58.0%	46.4%	58.0%	58.0%	46.4%	58.0%	58.0%	46.4%
Year 15	37.2%	29.8%	36.2%	28.9%	34.3%	34.3%	27.4%	34.3%	34.3%	27.4%	34.3%	34.3%	27.4%
Year 16+	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
VE PCV vs. VT-CAP													
Year 1	55.6%	44.5%	51.3%	41.1%	45.0%	45.0%	36.0%	45.0%	45.0%	36.0%	45.0%	45.0%	36.0%
Year 5	55.6%	44.5%	51.3%	41.1%	45.0%	45.0%	36.0%	45.0%	45.0%	36.0%	45.0%	45.0%	36.0%
Year 10	43.0%	34.4%	39.7%	31.8%	34.8%	34.8%	27.9%	34.8%	34.8%	27.9%	34.8%	34.8%	27.9%
Year 15	25.4%	20.3%	23.5%	18.8%	20.6%	20.6%	16.4%	20.6%	20.6%	16.4%	20.6%	20.6%	16.4%
Year 16+	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
VE PPV23 vs. VT-IPD													
Year 1	32.7%	17.0%	32.4%	16.9%	55.9%	31.1%	16.2%	50.8%	28.2%	14.7%	37.6%	20.9%	10.9%
Year 5	24.9%	13.0%	24.7%	12.8%	42.6%	23.7%	12.3%	38.7%	21.5%	11.2%	28.7%	15.9%	8.3%
Year 10+	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

*Vaccine uptake of PCVs was the same in sequential strategies involving PCV20→PPV23 and PCV15→PPV23; in such strategies, 100% of persons who received PCV and were alive in year 2 were assumed to receive PPV23
**Vaccine uptake was the same in the PPV23 strategy with revaccination; 100% of persons who received the initial dose of PPV23 were assumed to receive the second dose assuming they were alive in year 6

2.2.1. Population

The model population size (N = 15.6 M) and age distribution were based on the estimated population in England in 2022, the year when PCV20 became available for adults [37]. Persons in each age group were allocated into low-, moderate- (immunocompetent with underlying medical conditions), and high-risk (immunocompromised) subgroups based on risk factors defined in The Green Book of Immunisation against infectious disease, Chapter 25 [28] and published risk distributions [38] (see Supplement A for a comprehensive description of conditions considered).

2.2.2. Rates of IPD

Annual incidence of IPD was estimated by age (in one-year increments) and risk profile using the most recent age-specific disease rates available [2,3], age-specific distributions by risk profile, and age-specific odds ratios (ORs) for IPD by risk profile [38]. IPD rates were apportioned between bacteremia and meningitis based on a recent prospective study [4].

2.2.3. Rates of all-cause CAP

Annual incidence of all-cause hospitalized CAP was estimated by age and risk profile using age-specific rates of radiologically confirmed pneumonia from a recent prospective study conducted in Bristol, UK [5], age-specific distributions by risk profile [38], and age-specific fully adjusted ORs for all-cause hospitalized CAP by risk profile [39]. All-cause outpatient CAP was not considered in base case analyses.

2.2.4. Effectiveness of PCVs

For PCVs, vaccine effectiveness (VE) was based principally on randomized control trial data from the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) [27], which provides efficacy estimates for PCV13 and has been used in previous PCV20 cost-effectiveness analyses [40]. Initial effectiveness of PCVs against VT-IPD and VT-CAP for low- and moderate-risk persons aged ≥18 years was based on data from CAPiTA and post hoc analyses [27,41]. Initial VE against VT-IPD and VT-CAP for high-risk persons aged 18–99 years was assumed to be equal to 80% of corresponding values for low-/moderate-risk persons [42,43]. Initial VE-PCV was assumed to persist for 5 years, consistent with CAPiTA [27,44], and to wane thereafter, as follows: 5% annual decline during years 6–10, 10% annual decline during years 11–15, and no efficacy from year 16 through the end of the modeling horizon [41].

2.2.5. Effectiveness of PPV23

For VE-PPV23, we used the most recent real-world effectiveness studies conducted among UK adults, which are in line with assumptions for VE-PPV23 employed in previously published cost-effectiveness analyses. Risk-specific VE-PPV23 against VT-IPD for persons aged ≥18 years was derived from the study by Djennad et al. [2]. VE-PPV23 against VT-CAP was assumed to be zero based on findings by Lawrence et al. which do not provide robust evidence that PPV23 confers any meaningful protection against hospitalized CAP to older UK adults and is consistent with findings of a recent meta-analysis [26,45]. Beyond year 1 of the modeling horizon, VE-PPV23 against VT-IPD was assumed to decline [2] linearly, as follows: decline to 76.2% of initial VE by year 5, and decline to no efficacy by year 10.

2.2.6. Serotype coverage

Age-specific vaccine serotype coverage for IPD was based on prospectively collected surveillance data for 2016/2017 [2,3]. Vaccine serotype coverage for all-cause CAP was based on serotype coverage for pneumococcal CAP and the proportion of CAP due to pneumococcus in 2017/2018 [6]. Serotype coverage for pneumococcal CAP was assumed to be the same irrespective of age.

Herd effects for serotypes unique to PCV15 and PCV20 (vs. PCV13) were assumed to begin one year after the corresponding pediatric immunization program is expected to be implemented (i.e. model years 3 and 4, respectively). Serotype coverage for PPV23 was also reduced to account for the impact of herd effects on serotypes common to PPV23 and PCV20. Reductions in serotype coverage due to herd effects from childhood vaccination were based on the observed impact of PCV13 on the five additional serotypes in PCV13 not in PCV7 (excluding serotype 3) [3]. Reduction in serotype coverage was assumed to peak by year 10 and to be sustained at that level thereafter.

2.2.7. Costs

Costs of IPD (bacteremia, £4,542; meningitis, £5,600) and all-cause hospitalized CAP (£4,192) were derived based on average costs per finished consultant episode (FCE) from the 2019/2020 National Health Service (NHS) reference costs [46] and the average number of FCEs per admission from the Hospital Episode Statistics for England [9]. Prices of PPV23 (£16.80), PCV13 (£49.10), PCV15 (£50.30), and PCV20 (£56.50) were based on list values [47,48]. Vaccine administration cost (£10.06) was based on the General Practice Contract (2019) [49].

2.2.8. Utilities

Age- and risk-specific general population health-state utility values (HSUVs) were based on a published study of HSUVs for English adults [50]. For persons who experienced IPD or all-cause CAP, an annual utility decrement (0.13) was applied during the year in which the event occurred [51]. Both utilities and disutilities were estimated based on data sources which employed the EQ-5D instrument.

2.3. Analyses

2.3.1. Base Case

Clinical outcomes and economic costs were projected for the model population under PCV20 alone, PCV20→PPV23, PCV15→PPV23, and PPV23+PPV23 (hypothetical recommendations) and PPV23 (single dose, currently recommended for eligible NHS patients). Vaccine coverage for each strategy was assumed on par with current PPV23 coverage levels [29]. Future costs, LYs, and QALYs were discounted at 3.5% annually; analyses were conducted from the NHS (i.e. healthcare system) perspective. Cost-effectiveness was assessed considering the £20,000–30,000/QALY gained threshold range employed by the National Institute for Health and Care Excellence (NICE) and JCVI [52].

2.3.2. Subgroup and Sensitivity

Subgroup analyses were conducted comparing PCV20 versus PPV23 among all adults aged 65–99 years and adults aged 18–64 years with underlying conditions, respectively. Selected sensitivity analyses comparing PCV20 versus PPV23 were conducted in which alternative input values were employed for key model parameters. Probabilistic sensitivity analyses (PSA) were conducted (1,000 replications) for all strategies considered to account for uncertainty surrounding estimates of key model parameters. Inputs employed in sensitivity analyses and corresponding methods of estimation are described in Supplement A.

3. Results

3.1. Base case

Clinical and economic outcomes and full incremental cost-effectiveness results for all strategies evaluated are presented in Table 2. The cost-efficiency frontier – which comprises the PPV23 single dose strategy, PCV20 alone strategy, and PCV20→PPV23 strategy – indicates that the PCV15→PPV23 and PPV23+PPV23 strategies are dominated by strategies involving PCV20 (Figure 2). Although PCV20→PPV23 is on the cost-efficiency frontier, it was not cost-effective because its incremental cost-effectiveness ratio (ICER) compared with PCV20 alone (£686,948/QALY) was above the upper bound of the cost-effectiveness range. PCV20 alone was therefore deemed the most relevant hypothetical vaccination strategy.

Compared with PPV23 (single dose), PCV20 alone would prevent an additional 7,789 IPD cases, 140,046 hospitalized CAP cases, and 22,199 pneumococcal-related deaths and save £538.31 million in medical care costs (Table 3). Total vaccination costs with PCV20 would increase by £378.70 million, and thus use of PCV20 would save the NHS £159.61 million. With total net costs lower by £159.61 million

Table 2. Results of base case analyses of alternative vaccination strategies among moderate- and high-risk adults aged 18–64 years and all adults aged 65–99 years in England (N = 15,635,909).

A. Clinical and Economic Outcomes

	PPV23 (1 dose)	PCV20	PCV20→PPV23	PPV23+PPV23	PCV15→PPV23
Clinical Outcomes					
No. of cases					
IPD	117,807	110,018	109,709	117,031	113,644
All-cause hospitalized CAP	7,483,128	7,343,082	7,343,116	7,483,223	7,384,442
No. of deaths					
IPD	37,612	35,191	35,106	37,377	36,247
All-cause hospitalized CAP	1,122,633	1,102,854	1,102,860	1,122,651	1,108,621
Life-years (discounted)	179,787,906	179,906,103	179,906,580	179,788,893	179,867,258
Quality-adjusted life-years (discounted)	132,546,963	132,638,338	132,638,681	132,547,656	132,608,379
Economic Outcomes (in millions)					
Medical care	£19,971.1	£19,432.8	£19,431.6	£19,968.7	£19,604.2
Vaccination	£256.2	£634.9	£871.4	£424.0	£812.2
Medical + vaccination	£20,227.3	£20,067.7	£20,303.0	£20,392.7	£20,416.4

B. Incremental Cost-Effectiveness

Strategy	Cost (in millions)	QALYs	Incremental Cost (in millions)	Incremental QALYs	ICER
PCV20	£20,067.7	132,638,338	–	–	–
PPV23 (1 dose)	£20,227.3	132,546,963	£159.6	−91,375	Dominated
PCV20→PPV23	£20,303.0	132,638,681	£235.3	343	£686,948
PPV23+PPV23	£20,392.7	132,547,656	£89.7	−91,024	Dominated
PCV15→PPV23	£20,416.4	132,608,379	£113.4	−30,302	Dominated

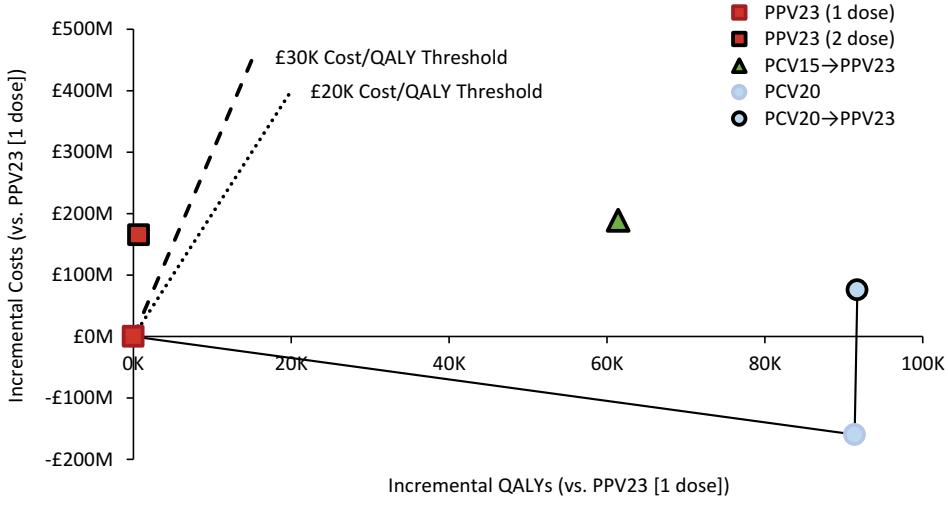


Figure 2. Cost-effectiveness plane for alternative vaccination strategies among moderate- and high-risk adults aged 18–64 years and all adults aged 65–99 years in England (N = 15,635,909).

Table 3. Incremental results of base case, subgroup, and sensitivity analyses comparing PCV20 alone vs. PPV23 (single dose) among moderate- and high-risk adults aged 18–64 and all adults aged 65–99 years in England (N = 15,635,909).

		Subgroup		Sensitivity Analyses*								
	Base Case	Moderate- and High-Risk Aged 18–64 Years	All Aged 65–99 Years	Hosp. CAP Rates from Pick et al.	2x Hosp. CAP Rates from Pick et al.	Plus Outpatient CAP	LT Consequences of IPD & CAP	VE-PPV23 vs. VT-CAP from Lawrence et al.	VE-PCV20 vs. ST3 CAP from Gessner et al.	Differential Discounting	Alt. Vaccine Waning	RWE of Vaccines
Clinical Outcomes												
No. of cases												
IPD	−7,789	−1,892	−5,897	−8,021	−7,927	−7,789	−7,043	−7,815	−7,651	−7,789	−6,617	−5,874
All-cause hospitalized CAP	−140,046	−22,355	−117,691	−41,037	−80,087	−140,046	−119,221	−105,222	−165,231	−140,046	−118,323	−194,477
All-cause outpatient CAP	–	–	–	–	–	−61,501	–	–	–	–	–	–
No. of deaths												
IPD	−2,420	−287	−2,134	−2,516	−2,475	−2,420	−2,217	−2,431	−2,384	−2,420	−2,003	−1,810
All-cause hospitalized CAP	−19,779	−1,936	−17,843	−6,209	−12,021	−19,779	−49,847	−15,201	−23,599	−19,779	−16,511	−27,754
Life-years (discounted)	118,197	24,262	93,935	41,291	69,316	118,197	284,236	91,657	136,570	145,090	103,952	155,186
Quality-adjusted life-years (discounted)	91,375	19,081	72,293	30,981	52,837	91,588	192,331	69,875	105,485	109,906	80,521	120,158
Economic Outcomes (in millions)												
Medical care	−£538.3	−£85.8	−£452.5	−£178.2	−£318.7	−£540.4	−£469.4	−£411.8	−£627.1	−£538.3	−£470.5	−£723.0
Vaccination	£378.7	£78.7	£300.0	£378.7	£378.7	£378.7	£378.7	£378.7	£378.7	£378.7	£378.7	£378.7
Medical + vaccination	−£159.6	−£7.2	−£152.4	£200.5	£60.0	−£161.7	−£90.7	−£33.1	−£248.4	−£159.6	−£91.8	−£344.3
Cost-Effectiveness												
Cost per LY	Dominant	Dominant	Dominant	£4,857	£865	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
Cost per QALY	Dominant	Dominant	Dominant	£6,473	£1,135	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant

LT: long-term; RWE: real world effectiveness; ST3: serotype 3

*Detailed information on parameter values employed in sensitivity analyses can be found in Supplement A

and discounted QALYs higher by 91,375, PCV20 was dominant versus PPV23; incremental net monetary benefit was £1.99 billion at £20,000/QALY gained and £2.90 billion at £30,000/QALY gained.

3.2. Subgroup and Sensitivity

PCV20 was found to be cost-effective – if not cost saving – versus PPV23 in all subgroup and sensitivity analyses (Table 3). Sensitivity analyses also suggest that PCV20 alone would remain cost saving (vs. PPV23) at prices up to 4.4 times (£73.23) the PPV23 list price, and would be cost-effective at prices up to 15.8 to 21.5 times (£264.82 and £360.61) the PPV23 list price at £20,000/QALY and £30,000/QALY, respectively. In PSA, PCV20 alone was cost saving versus PPV23 in 85% of simulations and cost-effective in 99% of simulations (WTP = £30,000/QALY) (Figure 3). The cost-effectiveness acceptability frontier indicates that PCV20 is always the optimal strategy (Figure 4).effective

4. Discussion

With recent approval of next generation PCVs with expanded serotype coverage, we undertook a new evaluation to examine the potential cost-effectiveness of pneumococcal vaccination strategies – including PCV20 alone and others – relative to PPV23 alone (single dose). Our findings suggest replacing PPV23 with PCV20 alone for vaccination of adults aged 65–99 years as well as adults aged 18 to 64 years with underlying conditions in England would save lives and reduce health care resources and costs to the NHS. Furthermore, PCV20 alone was the most efficient vaccination strategy among those explored,

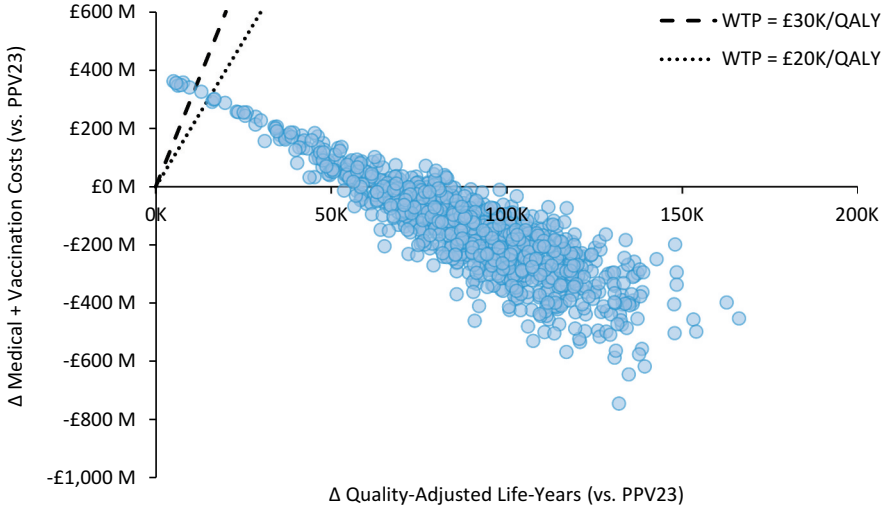


Figure 3. Scatterplot for cost-effectiveness of PCV20 alone versus PPV23 (single dose) among moderate- and high-risk adults aged 18–64 years and all adults aged 65–99 years in England (N = 15,635,909).
WTP: willingness-to-pay

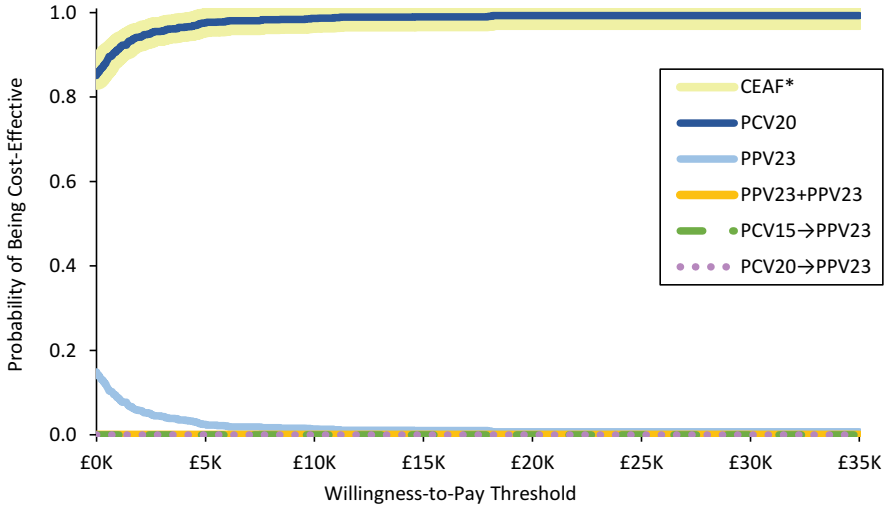


Figure 4. Cost-effectiveness acceptability curve for alternative pneumococcal vaccination strategies among moderate- and high-risk adults aged 18–64 years and all adults aged 65–99 years in England (N = 15,635,909).
CEAF: cost-effectiveness acceptability frontier
*The CEAF illustrates the probability of greatest net monetary benefit

dominating the strategy involving revaccination with PPV23 (2 doses total), as well as PCV15 in sequence with PPV23. Our finding that PCV20 alone is a cost saving replacement for PPV23 reflects the latest pre-COVID serotype coverage for pneumococcal disease among adults [2,3,6] and the expected greater and longer-lasting protection provided by PCV20 compared to PPV23, which largely offsets the 7% difference in IPD serotype coverage between vaccines (PPV23 non-PCV20 serotypes: 2, 9N, 17F, and 20; PCV20 non-PPV23 serotypes: 6A/6C) [2,27,44,53,54].

To the best of our knowledge, this is the first study to report on cost-effectiveness of PCV20 use among adults in England, however, several analyses have been conducted focused on the United States (US). Findings presented by the US Advisory Committee on Immunization Practices (ACIP) pneumococcal work group suggest that use of PCV20 alone among US adults aged ≥65 years as well as those aged <65 years with risk factors would be cost saving compared to the 2019 US adult pneumococcal vaccines recommendation [55–57]. Based on consideration of all domains included in the evidence-to-recommendation framework, including cost-effectiveness analyses, the ACIP recently recommended the use of PCV20 alone among moderate- and high-risk adults aged 19–64 years and all adults aged ≥65 years [55].

Base case analyses described herein were conducted taking a conservative approach to several aspects of model parameterization. Although higher-valent PCVs have been neither licensed nor recommended for infants and children in England, herd effects from future pediatric use of PCV20 and PCV15 were considered. In addition, base case analyses did not account for the considerable burden of outpatient CAP [58]. Long-term clinical consequences and costs of pneumococcal disease also were not included though common following acute illness [7,59,60]. Finally, despite evidence suggesting that risk of death may remain elevated for several years following an acute hospitalization for IPD or CAP [7,8,60] – especially among the elderly and those with comorbidities (i.e. 65% of the English population) [8,37–39] – we considered only in-hospital pneumonia deaths.

Robust estimates of the incidence of hospitalized CAP in the UK are limited. In base case analyses, we employed recently published estimates from the first prospective study of CAP in the UK by Hyams et al. [5] which suggest that CAP incidence is three to five times higher than previous estimates based on data from Nottingham, which were employed in the 2016 JCVI analyses [5,6,61,62]. To evaluate the impact of CAP incidence rates on model outcomes, we conducted sensitivity analyses in which we conservatively assumed CAP incidence rates based on Pick et al. (Nottingham data) and twice the rates from Pick et al., respectively. The latter analysis was similar to one conducted by JCVI in 2016 to address concerns of likely substantial CAP under ascertainment [6]. Despite the low incidence rates, PCV20 was found to be cost-effective versus PPV23, with ICERs of approximately £6,500/QALY and £1,100/QALY, respectively. The difference in rates reported by Pick et al. and Hyams et al. is believed to be largely attributable to differences in study design. The Nottingham study was designed primarily to measure serotype distribution and trends for CAP [1,6,61]. The study by Hyams et al., however, was designed to estimate CAP incidence and also employed a novel, potentially more robust approach to estimate the population denominator used to calculate incidence rates [5]. Estimates by Hyams et al. are comparable to rates reported in other industrialized countries and are better aligned with the number of hospital admissions for pneumonia in the UK (based on ICD-10 code J18) [9,63].

Because the observed decline in serotype 3 disease among UK adults after the introduction of PCV13 among infants was lower than the decline in disease due to the other five serotypes that are in PCV13 but not in PCV7, and because incidence of IPD due to serotype 3 began increasing again in 2013/2014, there is some concern that PCV13 – and therefore also PCV20 – may be less effective in preventing serotype 3 disease [3]. However, as summarized in a recently published review article, evidence suggests that PCV13 is indeed effective against IPD and CAP due to serotype 3 [64–67]. We therefore conducted a scenario analysis using estimates of VE-PCV20 against serotype 3 CAP based on the study by Gessner et al. and found PCV20 alone to be dominant versus PPV23 [67].

Assumed effectiveness of PPV23 against CAP is an area of parameter uncertainty. Consistent with findings of multiple meta-analyses, assumptions employed in recently published economic evaluations, and the 2015 JCVI position, we assumed that PPV23 conferred no benefit against CAP in the base case [11–25,54,68,69]. However, given recent literature suggesting some limited effectiveness of PPV23 against VT-CAP, we conducted a scenario analysis based on estimates from the study by Lawrence et al. which employed real-world data from the UK [45,70]. Although the differences in cases and deaths due to hospitalized CAP and medical care costs were reduced, PCV20 remained dominant (vs. PPV23). Due to the high degree of uncertainty surrounding recent literature – both within and across studies – findings from analyses in which PPV23 is assumed to provide some protection against CAP should be considered with caution until higher-quality data in support of this assumption become available. We also note that in line with NICE and JCVI methodological guidance [52,71], analyses considering no vaccine (i.e. as a standalone strategy) vs. PPV23 were not conducted because PPV23 is the current standard of care in the UK.

To account for uncertainty in the future price of PCV20, we considered alternative prices and found that PCV20 alone remained cost saving (vs. PPV23) at prices up to 4.4 times the PPV23 list price and was cost-effective at prices up to 21.5 times the PPV23 list price (assuming WTP = £30,000/QALY). As PPV23 recently changed to being centrally procured [72], it may now be procured at a discounted price, in which case the price of PPV23 employed in our analyses may somewhat overestimate the current cost of adult pneumococcal vaccination to the NHS.

The true reduction in hospitalization costs with PCV20 (vs. PPV23) is underestimated in our base case analysis as the cost of IPD and CAP cases treated in intensive care – estimated at 5.2% of all hospitalized CAP cases in 2018/19 [73] – was not accounted for. Published literature suggests intensive care hospitalizations for pneumonia span 11 days on average at a cost of £1,500 per bed-day [74,75]. Given that patients with

IPD generally experience more severe symptoms, it is likely that the proportion of patients admitted to intensive care for IPD is even greater, however, we have not found published estimates on IPD intensive care admissions. In addition, new research suggests NHS reference costs fail to account for the opportunity cost of hospitalization [76,77]. This may be especially relevant in the context of pneumonia, which tends to peak during winter when many hospitals are at capacity. Further research is also needed to estimate the impact of pneumonia on social care.

Societal costs of pneumococcal disease were also omitted from these analyses in line with JCVI guidance [52], thus excluding the benefits of vaccination in avoiding productivity loss to patient and carers. The adoption of a societal perspective in health technology assessments of vaccines has been discussed in the literature [78,79]. A recent cost-effectiveness analysis of COVID-19 vaccination by Public Health England and London School of Hygiene & Tropical Medicine researchers demonstrates the relevance of the broader impact of vaccinations [75].

The burden of pneumococcal disease in England has been greatly reduced in the past two years due to measures implemented to reduce transmission of COVID-19 (i.e. lockdowns, social distancing measures, mask-wearing) [80]. However, in light of recent reports of out-of-season respiratory syncytial virus outbreaks across the globe [81–85] as well as data showing PCV13-type IPD cases increased in 2021 (vs. prior years) in England and elsewhere [86–88], there is concern that major outbreaks of common respiratory disease may occur in England as pandemic restrictions are further relaxed [89]. It is therefore critical that delivery of adult vaccinations be prioritized, especially for older adults and others at elevated risk [90].

5. Conclusions

Results of our analyses suggest that the use of PCV20 in lieu of a single dose of PPV23 among all adults aged 65–99 years and adults aged 18–64 years with underlying conditions in England would be cost saving (i.e. more effective and less costly than the current program). Other strategies considered were either too costly or less efficient than PCV20. The prolonged duration of protection and greater effectiveness against vaccine-type IPD and CAP with use of PCV20 results in greater protection of vulnerable adults, and therefore has the potential to substantially reduce the clinical, resource, and financial burden of pneumococcal disease on the NHS.

Funding

This study was funded by Pfizer Inc.

Declaration of interest

The research described herein and manuscript development was supported by Pfizer Inc. D Mendes, R Sato, A Vyse, J Campling, G Ellsbury, and T Mugwagwa are employees and shareholders of Pfizer; no other relationships or activities that could appear to have influenced the submitted work. M Slack has received personal fees from GSK, Pfizer, Merck, AstraZeneca and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards (outside the scope of the submitted work). M Slack has also worked as a contractor for Pfizer and received remuneration from Pfizer. M Atwood, A Averin, and D Weycker are employees of Policy Analysis Inc. (PAI), which received financial support from Pfizer Inc. for this study (including manuscript preparation). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Authorship was designated based on guidelines promulgated by the International Committee of Medical Journal Editors (2004). All persons who met criteria for authorship were included in the author list. The contribution of each of these persons to this study is as follows: (1) conception and design (all authors), acquisition of data (A Averin, D Mendes, A Vyse, T Mugwagwa), analysis or interpretation of data (all authors); and (2) preparation of manuscript (all authors), critical review of manuscript (all authors). All authors have read and approved the final version of the manuscript. The study sponsor, Pfizer Inc., reviewed the study research plan and study manuscript; data management, processing, and analyses were conducted by PAI. All final analytic decisions and the decision to submit for publication were made solely by study investigators.

ORCID

Diana Mendes http://orcid.org/0000-0002-1672-4906
Ahuva Averin http://orcid.org/0000-0002-4490-7021
Reiko Sato http://orcid.org/0000-0003-2785-7103
Andrew Vyse http://orcid.org/0000-0002-0339-7491
James Campling http://orcid.org/0000-0002-6886-8565
Derek Weycker http://orcid.org/0000-0002-5405-2215
Mary Slack http://orcid.org/0000-0001-5119-4085
Gillian Ellsbury http://orcid.org/0000-0002-6855-4080
Tendai Mugwagwa http://orcid.org/0000-0001-7515-8548

References

1. Chalmers J, Campling J, Ellsbury G, et al. Community-acquired pneumonia in the United Kingdom: a call to action. Pneumonia. 2017;9(1):15.
2. Djennad A, Ramsay ME, Pebody R, et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine and changes in invasive pneumococcal disease incidence from 2000 to 2017 in those aged 65 and over in England and Wales. EClinicalMedicine. 2018;6:42–50.
3. Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. Lancet Infect Dis. 2018;18(4):441–451.
4. Amin-Chowdhury Z, Collins S, Sheppard C, et al. Characteristics of invasive pneumococcal disease caused by emerging serotypes after the introduction of the 13-valent pneumococcal conjugate vaccine in england: a PROSPECTIVE OBSERVATIONAL COHORT STUDY, 2014–2018. Clinl Infect Dis. 2020;71(8):e235–e243.
5. Hyams C, Begier E, Gonzalez MG Incidence of acute lower respiratory tract disease hospitalisations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective methodology. BMJ Open. 2022 Jun 15;12(6):e057464. DOI: 10.1136/bmjopen-2021-057464.

6. Pick H, Daniel P, Rodrigo C, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. Thorax. 2020;75(1):38–49.
7. Myint PK, Hawkins KR, Clark AB, et al. Long-term mortality of hospitalized pneumonia in the EPIC-Norfolk cohort. Epidemiol Infect. 2016;144(4):803–809.
8. Averin A, Shaff M, Weycker D, et al. Mortality and readmission in the year following hospitalization for pneumonia among US adults. Respir Med. 2021;185:106476.
9. NHS Digital. Hospital Admitted Patient Care Activity 2019-20. 2020.
10. Health and Social Care Public Health Agency. Changes to the infant pneumococcal conjugate vaccine schedule: information for healthcare practitioners. 2019.
11. Boccalini S, Bechini A, Levi M, et al. Cost-effectiveness of new adult pneumococcal vaccination strategies in Italy. Hum Vaccin Immunother. 2013;9(3):699–706.
12. Cho B-H, Stoecker C, Link-Gelles R, et al. Cost-effectiveness of administering 13-valent pneumococcal conjugate vaccine in addition to 23-valent pneumococcal polysaccharide vaccine to adults with immunocompromising conditions. Vaccine. 2013;31(50):6011–6021.
13. Evers SMAA, Ament AJHA, Colombo GL, et al. Cost-effectiveness of pneumococcal vaccination for prevention of invasive pneumococcal disease in the elderly: an update for 10 Western European countries. Eur J Clin Microbiol Infect Dis. 2007;26(8):531–540.
14. Fry AM, Zell ER, Schuchat A, et al. Comparing potential benefits of new pneumococcal vaccines with the current polysaccharide vaccine in the elderly. Vaccine. 2002;21(3):303–311.
15. Heo JY, Seo YB, Choi WS, et al. Cost-effectiveness of pneumococcal vaccination strategies for the elderly in Korea. PLOS ONE. 2017;12(5):e0177342.
16. S-l H, Kondo M, Okubo I. Economic Evaluation of Immunisation Programme of 23-Valent Pneumococcal Polysaccharide Vaccine and the Inclusion of 13-Valent Pneumococcal Conjugate Vaccine in the List for Single-Dose Subsidy to the Elderly in Japan. PLOS ONE. 2015;10(10):e0139140.
17. Johnstone J, Marrie TJ, Eurich DT, et al. Effect of pneumococcal vaccination in hospitalized adults with community-Acquired Pneumonia. Arch Internal Med. 2007;167(18):1938–1943.
18. Kuhlmann A, Theidel U, Pletz MW, et al. Potential cost-effectiveness and benefit-cost ratios of adult pneumococcal vaccination in Germany. Health Econ Rev. 2012;2(1):4.
19. Moberley S, Holden J, Tatham DP, et al. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;1. DOI:10.1002/14651858.CD000422.pub3.
20. Örtqvist Å, Hedlund J, Burman L-Å, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Lancet. 1998;351(9100):399–403.
21. Simberkoff MS, Cross AP, Al-Ibrahim M, et al. Efficacy of Pneumococcal Vaccine in High-Risk Patients. N Engl J Med. 1986;315(21):1318–1327.
22. Smith KJ, Wateska AR, Nowalk MP, et al. Modeling of Cost Effectiveness of Pneumococcal Conjugate Vaccination Strategies in U.S. Old Adults Am J Prev Med. 2013;44(4):373–381.
23. Stoecker C, Kim L, Gierke R, et al. Incremental cost-effectiveness of 13-valent pneumococcal conjugate vaccine for adults age 50 Years and older in the United States. J Gen Intern Med. 2016;31(8):901–908.
24. Stoecker C, Kobayashi M, Matanock A, et al. Cost-effectiveness of continuing pneumococcal conjugate vaccination at age 65 in the context of indirect effects from the childhood immunization program. Vaccine. 2020;38(7):1770–1777.
25. Latifi-Navid H, Latifi-Navid S, Mostafaiy B, et al. Pneumococcal disease and the effectiveness of the PPV23 vaccine in adults: a two-stage bayesian meta-analysis of observational and RCT reports. Sci Rep. 2018;8(1):11051.
26. Tin Htar M T, Stuurman AL, Ferreira G, et al. Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies. PLOS ONE. 2017;12(5):e0177985.
27. Bonten MJM, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372(12):1114–1125.
28. Ramsay M. The Green Book for immunisation against infectious disease: chapter 25, Pneumococcal. Public Health England. 2020.
29. UK Health Security Agency. Pneumococcal Polysaccharide Vaccine (PPV) coverage report, England, April 2019 to March 2020. Health Prot Rep. 2020;15(19).
30. Waight PA, Andrews NJ, Ladhani SN, et al. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015;15(5):535–543.
31. Adler H, German EL, Mitsi E, et al. Experimental human pneumococcal colonization in older adults is feasible and safe, not immunogenic. Am J Respir Crit Care Med. 2021;203(5):604–613.
32. Andrews NJ, Waight PA, George RC, et al. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine. 2012;30(48):6802–6808.
33. Collins AM, Wright AD, Mitsi E, et al. First human challenge testing of a pneumococcal vaccine. double-blind randomized controlled trial. Am J Respir Crit Care Med. 2015;192(7):853–858.
34. German EL, Solórzano C, Sunny S, et al. Protective effect of PCV vaccine against experimental pneumococcal challenge in adults is primarily mediated by controlling colonisation density. Vaccine. 2019;37(30):3953–3956.
35. Jackson LA, Gurtman A, van Cleeff M, et al. Influence of initial vaccination with 13-valent pneumococcal conjugate vaccine or 23-valent pneumococcal polysaccharide vaccine on anti-pneumococcal responses following subsequent pneumococcal vaccination in adults 50 years and older. Vaccine. 2013;31(35):3594–3602.
36. Jochems SP, Weiser JN, Malley R, et al. The immunological mechanisms that control pneumococcal carriage. PLoS Pathog. 2017;13(12):e1006665.
37. Office for National Statistics (UK). 2018-based National Population Projections. 2019.
38. van Hoek Aj, Andrews N, Waight PA, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012;65(1):17–24.
39. Campling J, Jones D, Chalmers JD, et al. The impact of certain underlying comorbidities on the risk of developing hospitalised pneumonia in England. Pneumonia. 2019;11(1):4.
40. Stoecker C Economic Assessment of PCV15 & PCV20. Meeting of the ACIP: 2021 Jun 25; Virtual.
41. Mangen MJ, Rozenbaum MH, Huijts SM, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J. 2015;46(5):1407–1416.
42. Klugman KP, Madhi SA, Huebner RE, et al. A Trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003;349(14):1341–1348.
43. French N, Gordon SB, Mwalukomo T, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-Infected adults. N Engl J Med. 2010;362(9):812–822.
44. Patterson S, Webber C, Patton M, et al. A post hoc assessment of duration of protection in CAPiTA (Community Acquired Pneumonia immunization Trial in Adults). Trials Vaccinol. 2016;5:92–96.
45. Lawrence H, Pick H, Baskaran V, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: a case-control test-negative design study. PLoS Med. 2020;17(10):e1003326.
46. Department of Health. NHS reference costs 2019 to 2020. 2021.
47. Joint Formul Comm British Nat Formul. 2017.
48. MIMS Database. 2022.
49. NHS England. Directed enhanced service specification: seasonal influenza and pneumococcal polysaccharide vaccination program 2019/20. 2019 Mar 29.
50. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health. 2011;14(4):539–545.

51. Mangen M-J-J, Huijts SM, Bonten MJM, et al. The impact of community-acquired pneumonia on the health-related quality-of-life in elderly. BMC Infect Dis. 2017;17(1):208.
52. Joint Committee on Vaccination and Immunisation. Code of Practice June 2013.
53. Essink B, Sabharwal C, Cannon K, et al. Pivotal phase 3 randomized clinical trial of the safety, tolerability, and immunogenicity of 20-valent pneumococcal conjugate vaccine in adults aged ≥18 years. Clinl Infect Dis. 2022;75(3):390–398.
54. Joint Committee on Vaccination and Immunisation. Minutes of the meeting on 2015 Oct 07.
55. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. adults: updated recommendations of the advisory committee on immunization practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(4):109–117.
56. Matanock A, Lee G, Gierke R, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep. 2019;68(46):1069–1075.
57. Leidner AJ Summary of three economic models assessing pneumococcal vaccines in US adults. Pneumococcal Vaccines. Meeting of the ACIP: September 29, 2021; Atlanta, GA.
58. Sun X, Douiri A, Gulliford M. Pneumonia incidence trends in UK primary care from 2002 to 2017: population-based cohort study. Epidemiol Infect. 2019;147:e263.
59. Campling J, Jones D, Chalmers J, et al. Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England. BMJ Open Respir Res. 2020;7(1):e000703.
60. Hughes GJ, Wright LB, Chapman KE, et al. Serotype-specific differences in short- and longer-term mortality following invasive pneumococcal disease. Epidemiol Infect. 2016;144(12):2654–2669.
61. Rodrigo C, Bewick T, Sheppard C, et al. Impact of infant 13-valent pneumococcal conjugate vaccine on serotypes in adult pneumonia. Eur Respir J. 2015;45(6):1632–1641.
62. van Hoek AJ, Miller E . Cost-effectiveness of vaccinating immunocompetent ≥65 year olds with the 13-valent pneumococcal conjugate vaccine in England. PLOS ONE. 2016;11(2):e0149540.
63. Shi T, Denouel A, Tietjen AK, et al. Global and regional burden of hospital admissions for pneumonia in older adults: a systematic review and meta-analysis. J Infect Dis. 2019;222(Supplement_7):S570–S576.
64. Vyse A, Campling J, Czudek C, et al. A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK. Expert Rev Vaccines. 2021;20(10):1311–1325.
65. McLaughlin JM, Jiang Q, Gessner BD, et al. Pneumococcal conjugate vaccine against serotype 3 pneumococcal pneumonia in adults: a systematic review and pooled analysis. Vaccine. 2019;37(43):6310–6316.
66. Sings HL, De Wals P, Gessner BD, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine against invasive disease caused by serotype 3 in children: a systematic review and meta-analysis of observational studies. Clinl Infect Dis. 2018;68(12):2135–2143.
67. Gessner BD, Jiang Q, Van Werkhoven CH, et al. A post-hoc analysis of serotype-specific vaccine efficacy of 13-valent pneumococcal conjugate vaccine against clinical community acquired pneumonia from a randomized clinical trial in the Netherlands. Vaccine. 2019;37(30):4147–4154.
68. Sisk JE, Whang W, Butler JC, et al. Cost-effectiveness of vaccination against invasive pneumococcal disease among people 50 through 64 years of age: role of comorbid conditions and race. Ann Intern Med. 2003;138(12):960–968.
69. Smith KJ, Zimmerman RK, Lin CJ, et al. Alternative strategies for adult pneumococcal polysaccharide vaccination: a cost-effectiveness analysis. Vaccine. 2008;26(11):1420–1431.
70. Suzuki M, Dhoubhadel BG, Ishifuji T, et al. Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study. Lancet Infect Dis. 2017;17(3):313–321.
71. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. Jan 2022.
72. Public Health England. Pneumococcal polysaccharide vaccine: change to the supply route from. Jun 2021.
73. Lim WS, Lawrence H. National audit report: adult community-acquired pneumonia audit 2018-2019. Brit Thoracic Soc. 2019;10(4).
74. Ostermann H, Garau J, Medina J, et al. Resource use by patients hospitalized with community-acquired pneumonia in Europe: analysis of the REACH study. BMC Pulm Med. 2014;14(1):36.
75. Sandmann FG, Davies NG, Vassall A, et al. The potential health and economic value of SARS-CoV-2 vaccination alongside physical distancing in the UK: a transmission model-based future scenario analysis and economic evaluation. Lancet Infect Dis. 2021;21(7):962–974.
76. Sandmann FG, Shallcross L, Adams N, et al. Estimating the hospital burden of norovirus-associated gastroenteritis in England and its opportunity costs for nonadmitted patients. Clinl Infect Dis. 2018;67(5):693–700.
77. Sandmann FG, Robotham JV, Deeny SR, et al. Estimating the opportunity costs of bed-days. Health Econ. 2018;27(3):592–605.
78. Bloom DE, Brenzel L, Cadarette D, et al. Moving beyond traditional valuation of vaccination: needs and opportunities. Vaccine. 2017;35:A29–A35.
79. Jit M, Hutubessy R. Methodological challenges to economic evaluations of vaccines: is a common approach still possible? Appl Health Econ Health Policy. 2016;14(3):245–252.
80. Brueggemann AB, Jansen van Rensburg MJ, Shaw D, et al. Changes in the incidence of invasive disease due to streptococcus pneumoniae, haemophilus influenzae, and *Neisseria meningitidis* during the COVID-19 pandemic in 26 countries and territories in the invasive respiratory infection surveillance initiative: a prospective analysis of surveillance data. Lancet Digital Health. 2021;3(6):e360–e370.
81. Eden J-S, Sikazwe C, Xie R, et al. Off-season RSV epidemics in Australia after easing of COVID-19 restrictions. Nat Commun. 2022;13(1):2884.
82. Fourgeaud J, Toubiana J, Chappuy H, et al. Impact of public health measures on the post-COVID-19 respiratory syncytial virus epidemics in France. Eur J Clin Microbiol Infect Dis. 2021;40(11):2389–2395.
83. Hsu H-T, Huang F-L, Ting P-J, et al. The epidemiological features of pediatric viral respiratory infection during the COVID-19 pandemic in Taiwan. J Microbiol Immunol Infect. 2021. DOI:10.1016/j.jmii.2021.09.017.
84. Lavoie PM, Reicherz F, Solimano A, et al. Potential resurgence of respiratory syncytial virus in Canada. Can Med Assoc J. 2021;193(29):E1140.
85. Olsen SJ, Winn AK, Budd AP, et al. Changes in influenza and other respiratory virus activity during the COVID-19 PANDEMIC - United States, 2020-2021. MMWR Morb Mortal Wkly Rep. 2021;70(29):1013–1019.
86. UK Health Security Agency. Pneumococcal disease: cases caused by strains covered by Prevenar 13 vaccine 2021. [cited 2021 Dec 15]. Available from: https://www.gov.uk/government/publications/pneumococcal-disease-cases-caused-by-strains-covered-by-prevenar-13-vaccine/pneumococcal-disease-cases-caused-by-strains-covered-by-prevenar-13-vaccine
87. Casanova C, Küffer M, Leib SL, et al. Re-emergence of invasive pneumococcal disease (IPD) and increase of serotype 23B after easing of COVID-19 measures, Switzerland, 2021. Emerg Microbes Infect. 2021;10(1):2202–2204.
88. Perniciaro S, van der Linden M, Weinberger DM. Re-emergence of invasive pneumococcal disease in germany during the spring and summer of 2021. Clinl Infect Dis. 2022;75(7):1149–1153.
89. Baker RE, Park SW, Yang W, et al. The impact of COVID-19 non-pharmaceutical interventions on the future dynamics of endemic infections. Proc Nat Acad Sci. 2020;117(48):30547.
90. Privor-Dumm LA, Poland GA, Barratt J, et al. A global agenda for older adult immunization in the COVID-19 era: a roadmap for action. Vaccine. 2021;39(37):5240–5250.

Taylor & Francis
Taylor & Francis Group

Expert Review of Vaccines

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierv20

Public health and budgetary impact of 20-valent pneumococcal conjugate vaccine for adults in England

Tendai Mugwagwa, Ahuva Averin, Mark Atwood, Reiko Sato, Andrew Vyse, James Campling, Derek Weycker, Mary Slack, Gillian Ellsbury & Diana Mendes

To cite this article: Tendai Mugwagwa, Ahuva Averin, Mark Atwood, Reiko Sato, Andrew Vyse, James Campling, Derek Weycker, Mary Slack, Gillian Ellsbury & Diana Mendes (2022) Public health and budgetary impact of 20-valent pneumococcal conjugate vaccine for adults in England, Expert Review of Vaccines, 21:9, 1331-1341, DOI: 10.1080/14760584.2022.2104250

To link to this article: https://doi.org/10.1080/14760584.2022.2104250

EXPERT REVIEW OF VACCINES
2022, VOL. 21, NO. 9, 1331–1341
https://doi.org/10.1080/14760584.2022.2104250

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Public health and budgetary impact of 20-valent pneumococcal conjugate vaccine for adults in England

Tendai Mugwagwa [a], Ahuva Averin [b], Mark Atwood[b], Reiko Sato [c], Andrew Vyse [a], James Campling [a], Derek Weycker [b], Mary Slack [d], Gillian Ellsbury [a] and Diana Mendes [a]

[a]Pfizer Ltd, Tadworth, UK; [b]Policy Analysis Inc. (PAI), Chestnut Hill, MA, USA; [c]Pfizer Inc, Collegeville, PA, USA; [d]School of Medicine & Dentistry, Griffith University, Gold Coast Campus, Southport, Queensland, Australia

ABSTRACT

Background: Despite use of 23-valent pneumococcal polysaccharide vaccine (PPV23) in England, disease burden among at-risk adults remains high. We evaluated the public health and budgetary impact of 20-valent pneumococcal conjugate vaccine (PCV20) compared to the current adult pneumococcal vaccination program.

Methods: Five-year outcomes and costs of invasive pneumococcal disease (IPD) and community-acquired pneumonia (CAP) among adults aged 65–99 years and adults aged 18–64 years with underlying conditions in England were projected using a deterministic cohort model. Hypothetical vaccination with PCV20 versus PPV23 was compared from the National Health Service (NHS) perspective.

Results: Replacing PPV23 with PCV20 would prevent 785 IPD hospitalizations, 11,751 CAP hospitalizations, and 1,414 deaths over 5 years, and would reduce medical care costs by £48.5 M. With vaccination costs higher by £107.2 M, projected net budgetary impact is £58.7 M. The budgetary impact would be greatest in year 1 (£26.3 M), and would decrease over time (to £1.6 M by year 5). The average budget increase (£11.7 M/year) represents <0.01% of the Department of Health and Social Care total budget and <3% of the vaccine budget.

Conclusions: Use of PCV20 among adults currently eligible for PPV23 in England would substantially reduce the burden of pneumococcal disease, with modest budgetary impact.

ARTICLE HISTORY
Received 25 May 2022
Accepted 18 July 2022

KEYWORDS
Streptococcus pneumoniae; vaccination; immunization; budgetary impact; public health

1. Introduction

Pneumococcal disease causes significant morbidity and is a leading cause of mortality among children and adults in the United Kingdom (UK) [1]. Surveillance data show that the incidence of invasive pneumococcal disease (IPD) – the most severe manifestation of pneumococcal disease – increased among persons of all ages in England and Wales in the pre-COVID-19 era (from 7.12 per 100,000 in 2013/14 to 9.87 per 100,000 in 2016/17) [2]. Rates of community-acquired pneumonia (CAP) – the less severe but far more common manifestation of pneumococcal disease – are also high, with annual rates ranging from 158 to >1,300 hospitalizations per 100,000 persons and 222 to 1,820 outpatient cases per 100,000 persons [3–5]. With each CAP-related hospitalization requiring an average of 10 hospital bed-days, 18% of patients requiring mechanical ventilation, and 5% of patients requiring critical care, the public health and economic burden of pneumococcal disease to the National Health Service (NHS) is substantial [6,7].

The pneumococcal disease burden in England is especially important given the longstanding human resource and budgetary constraints on the NHS, which tend to be highest during winter months and have been heightened as a result of the ongoing COVID-19 pandemic [8–11]. While IPD rates declined during the early period of the pandemic (i.e. March 2020-July 2021), data from the UK Health Security Agency suggest cases of IPD have been gradually returning to pre-pandemic levels since the summer of 2021 when strict COVID-19 prevention protocols were eased [12–14]. The rise in IPD cases – and presumably other manifestations of pneumococcal disease, including CAP – is concerning, because even as less severe strains of COVID-19 have become predominant, patients who develop IPD/COVID-19 co-infection may suffer worse outcomes, including higher risk of death [15,16]. Therefore, efforts to reduce the burden of pneumococcal disease among vulnerable populations that may, in turn, improve public health, free up hospital beds, and reduce costs to the NHS are increasingly important.

Data clearly show that currently recommended 23-valent pneumococcal polysaccharide vaccine (PPV23) provides older UK adults with only limited short-term protection against IPD [17]. Moreover, the proportion of IPD attributable to PPV23 serotypes has been increasing among this population despite widespread use of PPV23 among adults for whom vaccination is recommended [2,18,19]. Local UK data also do not provide any compelling evidence that PPV23 provides older UK adults

CONTACT Ahuva Averin aaverin@pai2.com Policy Analysis Inc. (PAI), 822 Boylston Street, Suite 206, Chestnut Hill, MA 02467, USA

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14760584.2022.2104250

with meaningful protection against pneumococcal CAP [17]. An alternative vaccine to PPV23 is therefore needed to better protect vulnerable adults against pneumococcal disease.

Although the addition of 13-valent pneumococcal conjugate vaccine (PCV13) to the UK adult pneumococcal program (i.e. for sequential use with PPV23) was not recommended in 2015 due to predicted reductions in vaccine-preventable disease from pediatric herd effects [20], the increasing burden of adult IPD and the availability of higher-valent pneumococcal conjugate vaccines (PCVs) has prompted a review of the adult vaccination program. New PCVs – including 20-valent PCV (PCV20) – recently received regulatory approval for use among UK adults based on immune-bridging to PCV13, which demonstrated efficacy against vaccine-type pneumococcal disease in adults ≥65 years in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) [21,22]. PCV20 has the potential to substantially reduce the burden of pneumococcal disease in England because its serotype coverage approaches that of PPV23 and PCVs protect adults against both IPD and pneumococcal CAP [21,23,24]. We therefore conducted a budgetary impact analysis (BIA) to project the costs of routine immunization of all adults aged 65-99 years and at-risk adults aged 18–64 years in England, as well as potential cost offsets that may be realized via reductions in disease burden, to assess whether routine immunization of adults with PCV20 is viable within the NHS budget.

2. Methods

2.1. Model description

A deterministic model with a Markov-type process was used to depict the 5-year risk of clinical outcomes and economic costs associated with various strategies for adult pneumococcal vaccination in a hypothetical population comprising all adults aged 65–99 years and adults aged 18–64 years with underlying conditions in England (Figure 1). The model population is stratified at model entry by age (i.e. in one-year increments) and risk profile (i.e. low, moderate [immunocompetent with underlying medical conditions], or high risk [immunocompromised]). Persons may transition to a higher risk group, but not to a lower risk group, during the modeling horizon. Persons in the model population may be assumed to receive either PCV20, PPV23, or no vaccine during the modeling horizon.

Expected clinical outcomes and economic costs are projected annually for the model population, based on age, risk profile, disease/fatality rates, vaccination status, and unit costs of vaccination and medical care. IPD includes bacteremia and meningitis, and all-cause CAP is stratified by care setting. Vaccinated persons may be at lower risk of future IPD and all-cause CAP; the magnitude of vaccine-associated risk reduction depends on clinical presentation, vaccine type(s), age, time since vaccination, and risk profile. Risk of death from IPD, all-cause CAP, and other causes depends upon age and risk profile. Expected medical treatment costs for IPD and all-cause CAP are generated based on event rates and unit costs in relation to care setting. Vaccination costs are tallied in the year of vaccine administration. Clinical outcomes and economic costs projected for each vaccination strategy include IPD and all-cause CAP cases and attributable deaths, and costs of vaccination and medical treatment.

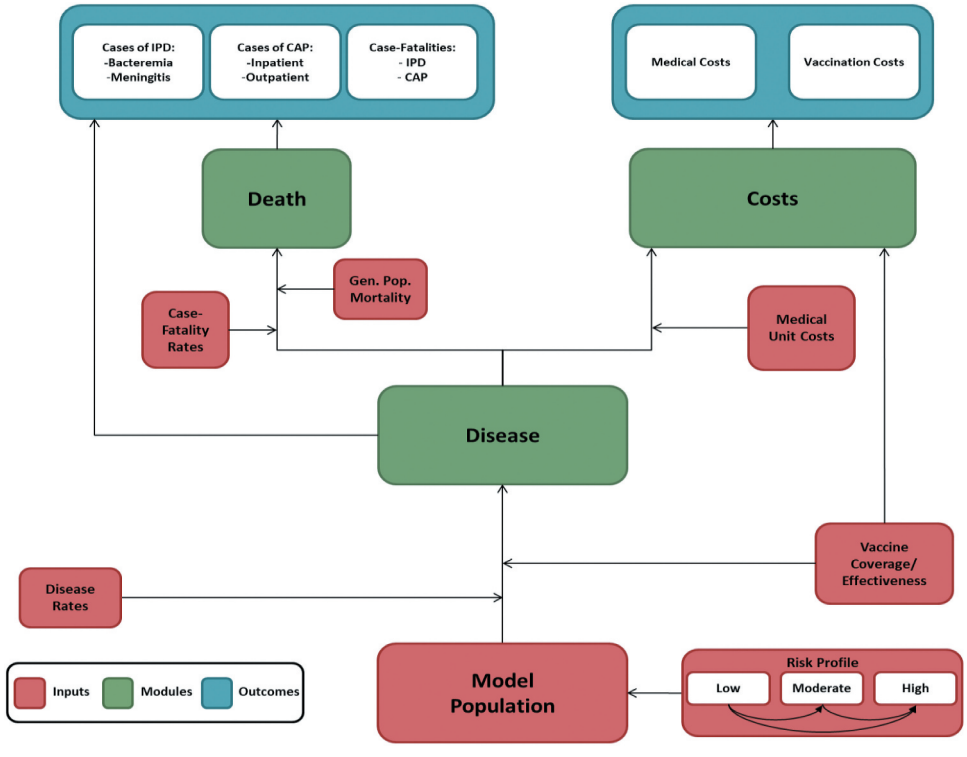


Figure 1. Model schematic.

2.2. Model parameter estimation

A summary of methods employed to estimate key model parameters is set forth below. A detailed description of methods employed to estimate all model parameters – including those employed in base case and scenario analyses – is provided in Supplementary Material, and corresponding parameter values are summarized in Table 1.

2.2.1. Population

The model population size (N = 15.6 M) and age distribution were based on the estimated English population in 2022, the year when PCV20 was approved for use among adults in the UK [25]. Persons in each age group were allocated into low-, moderate-, and high-risk subgroups based on published risk distributions [26].

2.2.2. Rates of IPD

Annual incidence of IPD was estimated by age (in one-year increments) and risk profile using recent age-specific disease rates [2,19], age-specific distributions by risk profile, and age-specific odds ratios (ORs) for IPD by risk profile [26]. IPD rates were apportioned between bacteremia and meningitis based on a recent prospective study [27].

2.2.3. Rates of all-cause CAP

Annual incidence of all-cause hospitalized CAP was estimated by age and risk profile using age-specific rates of radiologically confirmed pneumonia from a recent prospective study conducted in Bristol, UK [4], age-specific distributions by risk profile [26], and age-specific fully adjusted ORs for all-cause hospitalized CAP by risk profile [28]. All-cause outpatient CAP was not considered in base case analyses.

2.2.4. Vaccine uptake

Vaccine uptake was derived from the PPV23 Coverage Report for April 2019 to March 2020 [29]. Uptake was assumed to be the same in each year of the modeling horizon and for all vaccination strategies. Vaccine-eligible persons not vaccinated in year 1 of the modeling horizon were assumed to remain eligible for vaccination in subsequent years until vaccinated or the end of the modeling horizon.

2.2.5. Effectiveness of PCV20

Initial effectiveness of PCV20 against vaccine-type IPD (VT-IPD) and VT-CAP for low- and moderate-risk persons aged 18–99 years was based on data from CAPiTA [21,30]. Initial vaccine effectiveness (VE) against VT-IPD and VT-CAP for high-risk persons aged 18–99 years was assumed to be equal to 80% of corresponding values for low-/moderate-risk persons [31,32]. Initial VE-PCV20 was assumed to persist for 5 years, consistent with CAPiTA [21,33]. It was assumed that PCV20 effectiveness would be the same for serotypes covered by PCV13 and for the seven additional serotypes covered by PCV20 based on evidence of immune-bridging [22].

2.2.6. Effectiveness of PPV23

VE-PPV23 against VT-IPD for persons aged 18–99 years (by risk profile) was derived from a recent real-world effectiveness study conducted among UK adults [19]. VE-PPV23 against VT-CAP was assumed to be zero in base case analyses based on published sources, and consistent with base case assumptions employed in a number of economic studies and previous Joint Committee on Vaccination and Immunisation statements [34–50]. VE-PPV23 against VT-IPD was assumed to decline (linearly) to 76.2% of initial VE by year 5 [19].

2.2.7. Serotype coverage

Age-specific vaccine serotype coverage for PCV20 and PPV23 for IPD was based on prospectively collected surveillance data for 2016/2017 [2,19]. Vaccine serotype coverage for all-cause CAP was based on serotype coverage for pneumococcal CAP and the proportion of CAP due to pneumococcus in 2017/2018 [5]. Serotype coverage for pneumococcal CAP was assumed to be the same irrespective of age.

Herd effects for serotypes unique to 15-valent PCV (PCV15) and PCV20 (vs. PCV13) were assumed to begin 1 year after the corresponding pediatric immunization program is expected to be implemented (i.e. model years 3 and 4, respectively). Serotype coverage for PPV23 was also reduced to account for the impact of herd effects on serotypes common to PPV23 and PCV20. Reductions in serotype coverage due to herd effects from childhood vaccination were based on the observed impact of PCV13 on the five additional serotypes in PCV13 not in PCV7 (excluding serotype 3) [2]. Serotype replacement was assumed not to occur.

2.2.8. Costs

Costs of IPD (bacteremia, £4,542; meningitis, £5,600) and all-cause hospitalized CAP (£4,192) were derived based on average costs per finished consultant episode (FCE) from the 2019/2020 NHS reference costs [51] and the average number of FCEs per admission from the Hospital Episode Statistics for England [3]. Prices of PCV20 (£56.50) and PPV23 (£16.80) were based on the list value from the British National Formulary (2022) [52]. Vaccine administration cost (£10.06) was based on the General Practice Contract (2019) [53].

2.3. Analyses

2.3.1. Base case analyses

Clinical outcomes and economic costs were projected for the model population under PCV20 alone (hypothetical recommendation) and PPV23 (single dose, current recommendation). Analyses were conducted from the NHS perspective. Annual economic costs were considered in the context of the Department of Health and Social Care (DHSC) total budget of £129 billion in 2018 [54], of which approximately £6.45 billion (5%) and £397 million (0.3%) were spent on prevention and vaccines procurement, respectively [55,56].

2.3.2. Scenario analyses

Scenario analyses were conducted in which alternative input values were employed for key model parameters, including: rates of hospitalized CAP, costs of hospitalized CAP, rates of outpatient CAP, vaccine uptake, vaccine price, and VE-PPV23 vs. VT-CAP. Inputs employed in scenario/sensitivity analyses

Table 1. Base case model input values.

	Age and Risk Profile												
	18–49 Years		50–64 Years		65–74 Years			75–84 Years			85–99 Years		
	Moderate	High	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
No. of adults (in thousands)	1,254.6	449.5	1,784.1	1,315.7	3,392.3	1,220.8	963.3	1,970.8	1,005.5	818.2	626.0	456.0	379.1
Annual disease incidence (per 100,000)													
Bacteremia	18.7	42.0	17.6	48.9	4.8	18.8	62.3	8.1	21.9	94.7	15.0	40.5	175.4
Meningitis	2.1	4.7	1.7	4.8	0.3	1.1	3.6	0.3	0.7	3.0	0.1	0.3	1.5
All-cause hospitalized CAP	247.7	452.4	700.6	1,279.3	769.7	2,301.4	4,202.5	939.7	2,809.7	5,130.8	1,498.7	4,481.2	8,183.1
Annual mortality/case-fatality (per 100)													
General population	0.1	0.2	0.6	0.8	1.1	1.7	2.3	3.0	4.5	6.0	9.6	14.4	19.2
Bacteremia	6.0	7.2	12.8	15.4	14.0	17.5	21.0	22.0	27.5	33.0	32.3	40.3	48.4
Meningitis	6.0	7.2	12.8	15.4	14.0	17.5	21.0	22.0	27.5	33.0	32.3	40.3	48.4
All-cause hospitalized CAP	3.4	4.1	6.7	8.0	7.9	9.9	11.8	10.3	12.9	15.5	14.5	18.1	21.7
General population health-state utilities	0.7745	0.7346	0.7234	0.6852	0.9283	0.7308	0.7082	0.8921	0.6799	0.6607	0.8191	0.6038	0.5643
Vaccine uptake													
PCV20	8.1%	6.6%	8.1%	6.6%	4.3%	7.9%	8.4%	1.2%	1.5%	1.6%	1.3%	1.5%	1.5%
PPV23	8.1%	6.6%	8.1%	6.6%	4.3%	7.9%	8.4%	1.2%	1.5%	1.6%	1.3%	1.5%	1.5%
VE PCV vs. VT-IPD													
Year 1	81.5%	65.2%	79.2%	63.3%	75.0%	75.0%	60.0%	75.0%	75.0%	60.0%	75.0%	75.0%	60.0%
Year 5	81.5%	65.2%	79.2%	63.3%	75.0%	75.0%	60.0%	75.0%	75.0%	60.0%	75.0%	75.0%	60.0%
VE PCV vs. VT-CAP													
Year 1	55.6%	44.5%	51.3%	41.1%	45.0%	45.0%	36.0%	45.0%	45.0%	36.0%	45.0%	45.0%	36.0%
Year 5	55.6%	44.5%	51.3%	41.1%	45.0%	45.0%	36.0%	45.0%	45.0%	36.0%	45.0%	45.0%	36.0%
VE PPV23 vs. VT-IPD													
Year 1	32.7%	17.0%	32.4%	16.9%	55.9%	31.1%	16.2%	50.8%	28.2%	14.7%	37.6%	20.9%	10.9%
Year 5	24.9%	13.0%	24.7%	12.8%	42.6%	23.7%	12.3%	38.7%	21.5%	11.2%	28.7%	15.9%	8.3%

and corresponding methods of estimation are described in Supplementary Material.

3. Results

3.1. Base case analyses

During the five-year modeling horizon, use of PCV20 alone (in lieu of PPV23) would prevent 785 cases of IPD, 11,751 cases of hospitalized CAP, and 1,414 pneumococcal-related deaths, and would reduce medical care costs by £48.5 million (Table 2). Assuming current uptake levels, approximately 20% of the population would be vaccinated by year five, and total vaccination costs with PCV20 would increase by £107.2 million. The net budgetary impact to the NHS of replacing PPV23 with PCV20 would therefore be £58.7 million overall over the first 5 years of program implementation. Use of PCV20 in lieu of PPV23 would have the greatest budgetary impact in year 1, increasing the budget by £26.3 million, however, by year 5, budgetary impact of PCV20 use would decrease to £1.6 million (average annual budgetary impact, £11.7 million) (Figure 2).

Considering the average annual difference in costs of vaccine procurement, replacing PPV23 with PCV20 would cost an additional £21.4 million annually, representing a 0.02% increase in the DHSC total budget, a 0.33% increase in the budget allocated to prevention, and a 5.40% increase in that for vaccine procurement (Table 3). Considering total costs (i.e. medical care offsets, vaccine, and vaccine administration), the use of PCV20 instead of PPV23 would increase the annual total healthcare, prevention, and vaccines budgets by <0.01%, 0.18%, and 2.96%, respectively.

3.2. Scenario analyses

In scenario analyses, the five-year net budgetary impact of replacing PPV23 with PCV20 alone ranged from £45.7 to £159.6 million (Table 4; Supplement – Table S1). The budgetary impact was lowest in the scenario assuming annual uptake was 75% of base case values and was highest when assuming annual uptake of 75%. In analyses considering the burden of CAP treated in the outpatient setting, use of PCV20 prevented 5,232 general practitioner (GP) visits and is estimated to save £0.2 million in primary care costs. When CAP hospitalization costs were adjusted to include critical care admissions, PCV20 saved an additional £8.4 million (vs. base case), attributable to the prevention of approximately 611 intensive care admissions accounting for 6,722 critical care bed days.

4. Discussion

Findings from our analysis suggest replacing PPV23 with PCV20 alone for vaccination of all adults aged 65-99 years as well as adults aged 18–64 years with underlying conditions in England would considerably reduce the public health burden of pneumococcal disease at a modest additional cost to the NHS. Assuming future uptake of PCV20 would be consistent with current uptake of PPV23, use of PCV20 would prevent more than 12,500 hospitalizations and 1,400 pneumococcal-related deaths and would increase total costs (i.e. medical care and vaccination costs) by £58.7 million overall or £11.7 million annually (average) among vaccine-eligible adults in the first 5 years of program implementation. Procurement of PCV20 to replace PPV23 would therefore increase the annual pre-COVID -19 DHSC vaccines budget by 5.4% which corresponds to 0.02% of the annual total healthcare budget. However, taking into consideration cost offsets due to savings in medical care expenditures, the net annual increase to the DHSC vaccines budget would be 2.96% and the net annual increase to the healthcare budget would be <0.01%.

Findings from scenario analysis considering CAP treated by GPs show that use of PCV20 would prevent over 5,000 additional cases of clinically diagnosed CAP treated in the primary care setting. Although the associated cost savings are relatively low, the reduction in cases would free up GP resources – which are known to be in increasingly short supply in the NHS – to treat other patients [57]. The scenario analysis considering critical care costs also suggests use of PCV20 would reduce costs of pneumonia-related care by an additional £8.4 million by preventing approximately 6,700 CAP-related critical care bed-days in the first 5 years of program implementation, further alleviating pressure on the NHS.

While we believe that the scenario analysis including both outpatient CAP and costs of critical care for CAP may be the most accurate estimate of potential savings in medical care costs with use of PCV20 presented herein, real total savings to the NHS may still be underestimated in this scenario because clinical outcomes and costs associated with clinically suspected pneumonia treated in primary care and IPD requiring critical care and ventilation have not been included. Recent estimates suggest that rates of clinically suspected pneumonia are approximately nine times higher than rates of clinically diagnosed pneumonia employed in scenario analyses considering outpatient CAP [58]. Therefore, assuming that some cases of clinically suspected pneumonia are indeed vaccine-preventable, the impact of PCV20 use may be even greater than in analyses presented herein. Moreover, given that IPD is a more severe manifestation of pneumococcal disease than CAP and that the 2018/19 British Thoracic Society pneumonia national audit reported that 5% of hospitalized CAP patients required intensive or critical care, it is likely that a greater proportion of IPD patients require intensive care, which would further increase the potential cost savings with use of PCV20 [6]. Additional research is needed on clinical outcomes and costs associated with clinically suspected pneumonia treated in primary care and IPD requiring critical care and ventilation so that these outcomes may be included in future budget impact analyses.

Our base case analysis employed PCV20 uptake rates consistent with current PPV23 uptake (approximately 4.9% annually), however, uptake may be higher in the years immediately after program implementation, especially if program launch is accompanied by strong public health messaging. We therefore conducted a sensitivity analysis in which we assumed vaccine uptake was 25% higher than in the base case values (i.e. 6.1% annual uptake resulting in >500,000 additional persons vaccinated). Although cumulative overall costs (£70.6 million) increased for PCV20 (vs. PPV23), the

Table 2. Budgetary impact of PCV20 vs. PPV23 among at-risk persons aged 18–64 years and all persons aged 65-99 years in England – base case analysis.

	Year 1			Year 2			Year 3			Year 4			Year 5			Cumulative		
	PPV23	PCV20	Difference	PPV23	PCV20	Difference	PPV23	PCV20	Difference	PPV23	PCV20	Difference	PPV23	PCV20	Difference	PPV23	PCV20	Difference
Epidemiology																		
No. of Cases																		
IPD	4,833	4,773	-61	4,840	4,720	-120	4,870	4,688	-181	4,806	4,568	-238	4,118	3,933	-184	23,467	22,682	-785
All-cause hospitalized CAP	293,863	292,980	-883	296,148	294,430	-1,718	297,702	295,189	-2,513	298,705	295,402	-3,302	290,039	286,704	-3,335	1,476,457	1,464,705	-11,751
No. Disease-Related Deaths																		
IPD	1,258	1,247	-11	1,283	1,260	-23	1,313	1,278	-35	1,311	1,264	-46	1,152	1,114	-38	6,317	6,164	-153
All-cause CAP	38,255	38,165	-90	38,992	38,813	-179	39,637	39,370	-267	40,206	39,849	-357	39,487	39,118	-368	196,576	195,315	-1,261
Costs (in millions)																		
Medical Care	£1,254.1	£1,250.1	-£4.0	£1,220.9	£1,213.5	-£7.5	£1,185.9	£1,175.2	-£10.6	£1,149.3	£1,135.8	-£13.5	£1,076.0	£1,063.1	-£12.9	£5,886.2	£5,837.7	-£48.5
IPD	£22.2	£21.9	-£0.3	£21.5	£20.9	-£0.5	£20.9	£20.1	-£0.8	£19.9	£18.9	-£1.0	£16.5	£15.7	-£0.7	£100.9	£97.6	-£3.3
All-cause hospitalized CAP	£1,231.9	£1,228.2	-£3.7	£1,199.5	£1,192.5	-£7.0	£1,165.0	£1,155.2	-£9.8	£1,129.4	£1,116.9	-£12.5	£1,059.5	£1,047.4	-£12.2	£5,785.3	£5,740.1	-£45.2
Vaccination																		
Vaccine	£12.8	£43.1	£30.3	£10.5	£35.2	£24.8	£8.6	£29.0	£20.4	£7.3	£24.4	£17.1	£6.2	£20.7	£14.5	£45.3	£152.5	£107.2
Administration	£7.7	£7.7	£0.0	£6.3	£6.3	£0.0	£5.2	£5.2	£0.0	£4.3	£4.3	£0.0	£3.7	£3.7	£0.0	£27.2	£27.2	£0.0
Subtotal	£20.5	£50.8	£30.3	£16.8	£41.5	£24.8	£13.8	£34.2	£20.4	£11.6	£28.8	£17.1	£9.8	£24.4	£14.5	£72.5	£179.7	£107.2
Total	£1,274.6	£1,300.9	£26.3	£1,237.7	£1,255.0	£17.3	£1,199.7	£1,209.4	£9.8	£1,160.9	£1,164.6	£3.7	£1,085.8	£1,087.5	£1.6	£5,958.7	£6,017.3	£58.7
Cost per person	£81.52	£83.20	£1.68	£82.04	£83.18	£1.14	£82.55	£83.22	£0.67	£83.09	£83.35	£0.26	£80.98	£81.10	£0.12	£444.40	£448.74	£4.35
Number of persons	15,635,909	15,635,909	0	15,087,048	15,087,144	96	14,532,068	14,532,351	283	13,972,124	13,972,679	556	13,408,360	13,409,270	910	13,408,360	13,409,270	910
Cumulative percent of persons vaccinated	4.9%	4.9%	0.0%	9.2%	9.2%	0.0%	13.2%	13.2%	0.0%	16.9%	16.9%	0.0%	20.3%	20.3%	0.0%	20.3%	20.3%	0.0%

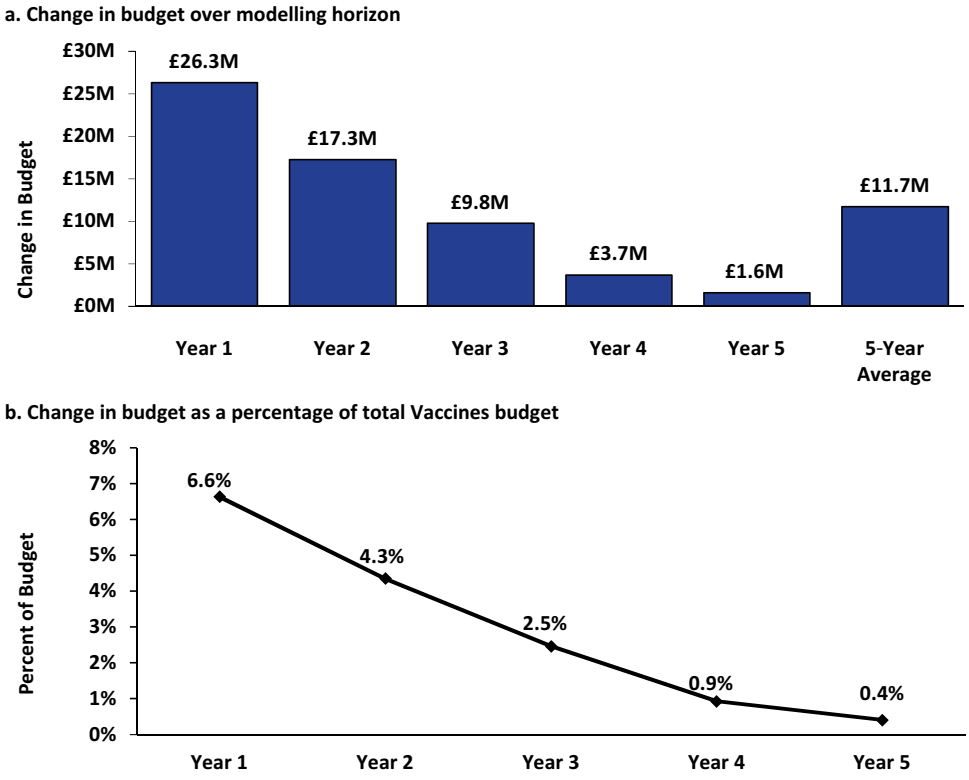


Figure 2. Impact on budget over first 5 years of PCV20 (vs. PPV23).

Table 3. Impact of adult vaccination programs on DHSC annual budgets for Vaccines, Prevention, and Healthcare*.

	Average Annual** Budget Impact, in millions	Percentage of Budget		
		Vaccines	Prevention	Healthcare
Vaccination costs only				
PPV23	£9.1	2.28%	0.14%	0.01%
PCV20	£30.5	7.68%	0.47%	0.02%
Difference	£21.4	5.40%	0.33%	0.02%
Total costs				
PPV23	£14.2	3.57%	0.22%	0.01%
PCV20	£25.9	6.52%	0.40%	0.02%
Difference	£11.7	2.96%	0.18%	0.01%

*Based on 2018 budgets for vaccination (£397 million), prevention (£6.45 billion), and healthcare (£129 billion)
**Annual 5-year average
DHSC: Department of Health and Social Care

higher uptake resulted in 15,388 fewer hospitalizations, 1,740 fewer deaths, and lower medical care costs (by £59.5 M) compared with use of PPV23. In an alternative scenario, we assumed annual pneumococcal vaccine uptake was 75% (both vaccines), consistent with the WHO coverage target for seasonal influenza vaccines [59] and UK targets for seasonal influenza/pneumococcal co-vaccination [60]. In this scenario, use of PCV20 (vs. PPV23) would reduce nine times more cases and save 11 times more lives than the base case analysis.

This analysis conservatively estimates the public health and budget impact of adult vaccination with PCV20, as the anticipated herd effects from a future childhood PCV15 and/or PCV20 program were considered. A proportion of the reduction in the burden of pneumococcal disease among adults is therefore assumed to be indirectly addressed by infant vaccination; however, higher-valent PCVs have not yet received regulatory approval for use among children and there is no guarantee that infant programs will be implemented. Moreover, while reductions in IPD attributable to vaccine serotypes following the introduction of PCV13 in children are the best available approximation of future reductions in disease attributable to PCV20 serotypes, the true herd effects from future pediatric use of higher valent PCVs are unknown in terms of their magnitude, timing, and impact on individual serotypes. The impact of herd effects on model outcomes is heavily dependent on the accuracy of starting serotype coverage data employed in the model. In light of recent studies showing that IPD serotype distributions have changed little since the 2016/17 season [15,61], we employed IPD data collected during 2016/17 and CAP data collected during 2017/18 because it is the most recent local data available with sufficient granularity (i.e. reported at the level of individual serotypes). The extent to which CAP serotype coverage may have changed since 2017/18 is uncertain but is unlikely to differ substantially from IPD.

Serotype replacement may also occur following widespread use of higher valent PCVs in England, however, given the complexity of serotype replacement among pneumococci and the challenges in predicting serotype replacement based on historic data, it has not been included in these analyses, thus its potential impact on model results is unknown. In addition, prices for vaccines provided by the NHS are subject

Table 4. Budgetary impact of PCV20 vs. PPV23 among at-risk persons aged 18–64 years and all persons aged 65-99 years in England – sensitivity analyses.

	5-Year Cumulative Differences*											
	75% of Base Case Uptake	125% of Base Case Uptake	75% Annual Uptake	100% Annual Uptake	Hospitalized CAPfrom Pick et al. 2020	200% Hospitalized CAP from Pick et al. 2020	Inclusion of Outpatient CAP	Inpatient Costs Adjusted for CC	Inclusion of Outpatient CAP & Inpatient Costs Adjusted for CC	10% Vaccine Price Reduction	VE-PPV23 vs. VT-CAP from Lawrence et al	Inpatient CAP Cost from Campling et al
Epidemiology												
No. of Cases												
IPD	-599	-963	-6,509	-7,030	-789	-787	-785	-785	-785	-785	-785	-785
All-cause CAP												
Hospitalized	-8,976	-14,425	-107,131	-114,945	-2,914	-5,807	-11,751	-11,751	-11,751	-11,751	-8,753	-11,751
Requiring outpatient care only	–	–	–	–	–	–	-5,232	–	-5,232	–	–	–
No. Disease-Related Deaths												
IPD	-116	-188	-1,728	-1,862	-154	-154	-153	-153	-153	-153	-153	-153
All-cause CAP	-961	-1,551	-13,898	-14,888	-321	-638	-1,261	-1,261	-1,261	-1,261	-998	-1,261
Costs (in millions)												
Medical Care	-£37.0	-£59.5	-£446.9	-£481.7	-£14.5	-£25.7	-£48.7	-£56.9	-£57.1	-£48.5	-£36.8	-£45.4
IPD	-£2.5	-£4.1	-£27.9	-£30.3	-£3.3	-£3.3	-£3.3	-£3.3	-£3.3	-£3.3	-£3.3	-£3.3
All-cause CAP												
Hospitalized	-£34.5	-£55.5	-£419.0	-£451.4	-£11.2	-£22.3	-£45.2	-£53.6	-£53.6	-£45.2	-£33.5	-£42.1
Requiring outpatient care only	–	–	–	–	–	–	-£0.2	–	-£0.2	–	–	–
Vaccination												
Vaccine	£82.7	£130.2	£606.5	£620.7	£107.4	£107.3	£107.2	£107.2	£107.2	£96.4	£107.2	£107.2
Administration	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0
Subtotal	£82.7	£130.2	£606.5	£620.7	£107.4	£107.3	£107.2	£107.2	£107.2	£96.4	£107.2	£107.2
Total	£45.7	£70.6	£159.6	£139.0	£92.8	£81.6	£58.5	£50.2	£50.0	£48.0	£70.4	£61.8
Cost per person	£3.38	£5.23	£11.53	£9.97	£6.87	£6.05	£4.33	£3.71	£3.70	£3.55	£5.22	£4.58

*Net incremental difference for PCV20 vs. PPV23

to tender and net prices are confidential, thus prices of PCV20 and PPV23 may be overestimated in the analyses described herein.

Because the most recent data on incidence of pneumonia in the UK is reported for all-cause CAP, there may be some cases of bacteremic CAP which have been double counted in our model (i.e. because they are also accounted in IPD incidence rates). While the extent of double-counting is unknown, the impact on model results is believed to be minimal. The results from our scenario analysis employing incidence of all-cause CAP requiring hospitalization from Pick et al. suggest that even if CAP incidence rates were 70–80% lower (vs. base case) [5], total budget impact would be 1.6 times higher than in the base case. We also conducted a scenario analysis in which PPV23 was assumed to provide some protection against VT-CAP based on point estimates from the recent study by Lawrence et al. [17]. Although disease reduction with PCV20 (vs. PPV23) was smaller in this analysis than in the base case, the budget impact remained relatively modest (1.2x base case).

Budgetary impact analyses are a useful tool for estimating the short-term costs of implementing novel interventions. However, limiting outcomes to a 5-year modeling horizon obscures the full benefit and value for money of a future PCV20 program for adults given that PCV20 is expected to provide protection for a minimum of 5 years based on the durability of protection observed in CAPiTA with PCV13 [21,33]. The short-term nature of BIA also precludes the inclusion of long-term consequences of pneumococcal disease such as exacerbations of underlying comorbidities, elevated risks of mortality, and development of antimicrobial resistance, all of which may be costly [62–64].

5. Conclusions

Our findings suggest that replacing PPV23 with PCV20 in the adult pneumococcal vaccination program in England would considerably reduce the public health burden of pneumococcal disease among all adults aged 65-99 years and adults aged 18–64 years with underlying conditions and would have minimal budgetary impact. Compared with current recommendations for adult pneumococcal disease prevention, implementation of a PCV20 program for adults would potentially reduce strain on the healthcare system by avoiding hospitalizations and freeing up critical care beds and GP resources, which is particularly important in the era of COVID-19.

Authors' contributions

Authorship was designated based on guidelines promulgated by the International Committee of Medical Journal Editors (2004). All persons who met criteria for authorship were listed as authors on the title page. The contribution of each of these persons to this study is as follows: (1) conception and design (all authors), acquisition of data (AA, DM, AV, TM), analysis or interpretation of data (all authors); and (2) preparation of manuscript (all authors), critical review of manuscript (all authors). All authors have read and approved the final version of the manuscript.

The study sponsor, Pfizer Inc., reviewed the study research plan and study manuscript; data management, processing, and analyses were conducted by Policy Analysis Inc. (PAI). All final analytic decisions and the decision to submit for publication were made solely by study investigators.

Funding

This study was funded by Pfizer Inc.

Declaration of interest

The research described here and manuscript development was supported by Pfizer Inc. T Mugwagwa, R Sato, A Vyse, J Campling, G Ellsbury, and are employees and shareholders of Pfizer; no other relationships or activities that could appear to have influenced the submitted work. M Slack has received personal fees from GSK, Pfizer, Merck, AstraZeneca and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards (outside the scope of the submitted work). M Slack has also worked as a contractor for Pfizer and received remuneration from Pfizer. M Atwood, A Averin, and D Weyckerare employees of PAI, which received financial support from Pfizer Inc. for this study (including manuscript preparation). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

A reviewer on this manuscript has disclosed that their institute has received research funding from Sanofi, GSK and Pfizer. All reviewers on this manuscript have received an honorarium for their review work. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose.

ORCID

Tendai Mugwagwa http://orcid.org/0000-0001-7515-8548
Ahuva Averin http://orcid.org/0000-0002-4490-7021
Reiko Sato http://orcid.org/0000-0003-2785-7103
Andrew Vyse http://orcid.org/0000-0002-0339-7491
James Campling http://orcid.org/0000-0002-6886-8565
Derek Weycker http://orcid.org/0000-0002-5405-2215
Mary Slack http://orcid.org/0000-0001-5119-4085
Gillian Ellsbury http://orcid.org/0000-0002-6855-4080
Diana Mendes http://orcid.org/0000-0002-1672-4906

References

1. Chalmers J, Campling J, Ellsbury G, et al. Community-acquired pneumonia in the United Kingdom: a call to action. Pneumonia. 2017;9(1):15.
2. Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. Lancet Infect Dis. 2018;18(4):441–451.
3. NHS Digital. Hospital admitted patient care activity 2019-20. 2020.
4. Hyams C, Begier E, Gonzalez MG, et al. Incidence of acute lower respiratory tract disease hospitalisations, including pneumonia, among adults in Bristol, UK, 2019, estimated using both a prospective and retrospective methodology. BMJ Open. 2022;12(6):e057464.
5. Pick H, Daniel P, Rodrigo C, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. Thorax. 2020;75(1):38–49.
6. Lim WS, and Lawrence H. National audit report: adult community-acquired pneumonia audit 2018-2019. Brit Thoracic Soc. 2019;10(4):1–13 .

7. Ostermann H, Garau J, Medina J, et al. Resource use by patients hospitalized with community-acquired pneumonia in Europe: analysis of the REACH study. BMC Pulm Med. 2014;14(1):36.
8. Dixon J, Warburton W. NHS funding in England: money's too tight to mention. BMJ. 2016;354:i4204.
9. Mahase E. NHS gets £5.9bn funding boost in autumn budget to tackle waiting lists in England. BMJ. 2021;375:n2637.
10. Mahase E. Winter pressure: RSV, flu, and covid-19 could push NHS to breaking point, report warns. BMJ. 2021;374:n1802.
11. Scobie S. Snowed under: understanding the effects of winter on the NHS. London: Nuffield Trust; 2018.
12. Brueggemann AB, Jansen van Rensburg MJ, Shaw D, et al. Changes in the incidence of invasive disease due to Streptococcus pneumoniae, Haemophilus influenzae, and *Neisseria meningitidis* during the COVID-19 pandemic in 26 countries and territories in the invasive respiratory infection surveillance initiative: a prospective analysis of surveillance data. Lancet Digital Health. 2021;3(6):e360–e370.
13. UK Health Security Agency. Pneumococcal disease: cases caused by strains covered by Prevenar 13 vaccine. 2022.
14. UK Health Security Agency. Pneumococcal disease infections caused by serotypes not in Prevenar 13 vaccine. 2022.
15. Amin-Chowdhury Z, Aiano F, Mensah A, et al. Impact of the coronavirus disease 2019 (COVID-19) pandemic on invasive pneumococcal disease and risk of pneumococcal coinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): prospective National Cohort study, England. Clinl Infect Dis. 2020;72(5):e65–e75.
16. Mitsi E, Reiné J, Urban BC, et al. Streptococcus pneumoniae colonization associates with impaired adaptive immune responses against SARS-CoV-2. J Clin Invest. 2022;132(7). DOI:10.1172/JCI157124.
17. Lawrence H, Pick H, Baskaran V, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: a case-control test-negative design study. PLoS Med. 2020;17(10):e1003326.
18. Andrews NJ, Waight PA, George RC, et al. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine. 2012;30(48):6802–6808.
19. Djennad A, Ramsay ME, Pebody R, et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine and changes in invasive pneumococcal disease incidence from 2000 to 2017 in those aged 65 and over in England and Wales. EClinicalMedicine. 2018;6:42–50.
20. Joint Committee on Vaccination and Immunisation. Interim JCVI statement on adult pneumococcal vaccination in the UK. 2015.
21. Bonten MJM, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372(12):1114–1125.
22. Essink B, Sabharwal C, Cannon K, et al. Pivotal Phase 3 randomized clinical trial of the safety, tolerability, and immunogenicity of 20-valent pneumococcal conjugate vaccine in adults aged ≥18 years. Clinl Infect Dis. 2021. DOI:10.1093/cid/ciab990.
23. McLaughlin JM, Jiang Q, Isturiz RE, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine against hospitalization for community-acquired pneumonia in older US adults: a test-negative design. Clinl Infect Dis. 2018;67(10):1498–1506.
24. Theilacker C, Fletcher MA, Jodar L, et al. PCV13 vaccination of adults against pneumococcal disease: what we have learned from the community-acquired pneumonia immunization trial in adults (CAPiTA). Microorganisms. 2022;10(1):127.
25. Office for National Statistics (UK). 2018-based National Population Projections. 2019.
26. van Hoek AJ, Andrews N, Waight PA, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012;65(1):17–24.
27. Amin-Chowdhury Z, Collins S, Sheppard C, et al. Characteristics of invasive pneumococcal disease caused by emerging serotypes after the introduction of the 13-valent pneumococcal conjugate vaccine in England: a prospective observational Cohort Study, 2014–2018. Clinl Infect Dis. 2020;71(8):e235–e243.
28. Campling J, Jones D, Chalmers JD, et al. The impact of certain underlying comorbidities on the risk of developing hospitalised pneumonia in England. Pneumonia. 2019;11(1):4.
29. UK Health Security Agency. Pneumococcal polysaccharide vaccine (PPV) coverage report, England, april 2019 to march 2020. Health Protection Report Volume 15, Number 19. 2020.
30. Mangen MJ, Rozenbaum MH, Huijts SM, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J. 2015;46(5):1407–1416.
31. Klugman KP, Madhi SA, Huebner RE, et al. A Trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003;349(14):1341–1348.
32. French N, Gordon SB, Mwalukomo T, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. N Engl J Med. 2010;362(9):812–822.
33. Patterson S, Webber C, Patton M, et al. A post hoc assessment of duration of protection in CAPiTA (community acquired pneumonia immunization trial in adults). Trials Vaccinol. 2016;5:92–96.
34. Boccalini S, Bechini A, Levi M, et al. Cost-effectiveness of new adult pneumococcal vaccination strategies in Italy. Hum Vaccin Immunother. 2013;9(3):699–706.
35. Cho B-H, Stoecker C, Link-Gelles R, et al. Cost-effectiveness of administering 13-valent pneumococcal conjugate vaccine in addition to 23-valent pneumococcal polysaccharide vaccine to adults with immunocompromising conditions. Vaccine. 2013;31(50):6011–6021.
36. Fry AM, Zell ER, Schuchat A, et al. Comparing potential benefits of new pneumococcal vaccines with the current polysaccharide vaccine in the elderly. Vaccine. 2002;21(3):303–311.
37. Heo JY, Seo YB, Choi WS, et al. Cost-effectiveness of pneumococcal vaccination strategies for the elderly in Korea. PLOS ONE. 2017;12(5):e0177342.
38. S-I H, Kondo M, Okubo I. Economic evaluation of immunisation programme of 23-valent pneumococcal polysaccharide vaccine and the inclusion of 13-valent pneumococcal conjugate vaccine in the list for single-dose subsidy to the elderly in Japan. PLOS ONE. 2015;10(10):e0139140.
39. Johnstone J, Marrie TJ, Eurich DT, et al. Effect of pneumococcal vaccination in hospitalized adults with community-acquired pneumonia. Arch Internal Med. 2007;167(18):1938–1943.
40. Örtqvist Å, Hedlund J, Burman L-Å, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Lancet. 1998;351(9100):399–403.
41. Sisk JE, Whang W, Butler JC, et al. Cost-effectiveness of vaccination against invasive pneumococcal disease among people 50 through 64 years of age: role of comorbid conditions and race. Ann Intern Med. 2003;138(12):960–968.
42. Smith KJ, Wateska AR, Nowalk MP, et al. Modeling of cost effectiveness of pneumococcal conjugate vaccination strategies in U.S. Older adults. Am J Prev Med. 2013;44(4):373–381.
43. Stoecker C, Kim L, Gierke R, et al. Incremental cost-Effectiveness of 13-valent pneumococcal conjugate vaccine for adults age 50 years and older in the United States. J Gen Intern Med. 2016;31(8):901–908.
44. Stoecker C, Kobayashi M, Matanock A, et al. Cost-effectiveness of continuing pneumococcal conjugate vaccination at age 65 in the context of indirect effects from the childhood immunization program. Vaccine. 2020;38(7):1770–1777.
45. Moberley S, Holden J, Tatham DP, et al. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;1. DOI:10.1002/14651858.CD000422.pub3.
46. Evers SMAA, Ament AJHA, Colombo GL, et al. Cost-effectiveness of pneumococcal vaccination for prevention of invasive pneumococcal disease in the elderly: an update for 10 Western European countries. Eur J Clin Microbiol Infect Dis. 2007;26(8):531–540.
47. Kuhlmann A, Theidel U, Pletz MW, et al. Potential cost-effectiveness and benefit-cost ratios of adult pneumococcal vaccination in Germany. Health Econ Rev. 2012;2(1):4.

48. Simberkoff MS, Cross AP, Al-Ibrahim M, et al. Efficacy of pneumococcal vaccine in high-risk patients. N Engl J Med. 1986;315(21):1318–1327.
49. Smith KJ, Zimmerman RK, Lin CJ, et al. Alternative strategies for adult pneumococcal polysaccharide vaccination: a cost-effectiveness analysis. Vaccine. 2008;26(11):1420–1431.
50. Joint Committee on Vaccination and Immunisation. Minutes of the meeting on 07 october 2015.
51. Department of Health. NHS reference costs 2019 to 2020. 2021.
52. Joint Formulary Committee. British National Formulary. 2022.
53. NHS England. Directed enhanced service specification: seasonal influenza and pneumococcal polysaccharide vaccination program 2019/20. 2019.
54. The King's Fund. Budget. 2018.
55. Department of Health and Social Care. Prevention is better than cure: our vision to help you live well for longer. 2018.
56. Department of Health and Social Care. Annual Reports and Accounts: 2018-2019. 2019.
57. Majeed A. Shortage of general practitioners in the NHS. BMJ. 2017;358:j3191.
58. Sun X, Douiri A, Gulliford M. Pneumonia incidence trends in UK primary care from 2002 to 2017: population-based cohort study. Epidemiol Infect. 2019;147:e263.
59. WHO: seasonal vaccination policies and coverage in the European Region [Internet]. Managing seasonal vaccination policies and coverage in the European Region. Denmark: World Health Organization Regional Office for Europe. 2022 Cited 2021 Dec 29. Available from: https://www.who.int/europe/activities/managing-seasonal-vaccination-policies-and-coverage-in-the-european-region
60. Public Health England. Seasonal influenza vaccine uptake in GP patients: winter season 2020 to 2021. 2021.
61. Amin-Chowdhury Z, Bertran M, Sheppard CL, et al. Does the rise in seasonal respiratory viruses foreshadow the return of invasive pneumococcal disease this winter? Lancet Respir Med. 2022;10(1):e1–e2.
62. Campling J, Jones D, Chalmers J, et al. Clinical and financial burden of hospitalised community-acquired pneumonia in patients with selected underlying comorbidities in England. BMJ Open Respir Res. 2020;7(1):e000703.
63. Hughes GJ, Wright LB, Chapman KE, et al. Serotype-specific differences in short- and longer-term mortality following invasive pneumococcal disease. Epidemiol Infect. 2016;144(12):2654–2669.
64. Myint PK, Hawkins KR, Clark AB, et al. Long-term mortality of hospitalized pneumonia in the EPIC-Norfolk cohort. Epidemiol Infect. 2016;144(4):803–809.

Appendix 2 – Supplementary Material

A2.1 Full Presentation from the British Thoracic Society Winter Meeting

Establishing the true incidence of hospitalised community acquired pneumonia (CAP) in the UK: a Hospital Episode Statistics (HES) analysis

James Campling – Senior Medical Affairs Adviser, Pfizer UK Ltd

BTS Winter Meeting 6th December, London

Date of Prep: Dec 2017 PP-PNA-GBR-0266

Disclosures

Full time employee of Pfizer Ltd, UK

Background

- Consideration of immunisation programmes relies on accurate incidence data of the diseases of interest
- Public Health England (PHE) and the Joint Committee on Vaccination and Immunisation (JCVI) use these data to make decisions on vaccination policy
- In November 2015, the JCVI made the following recommendation:

"PCV13 should continue to be offered to those risk groups previously identified as being at particularly high risk of, and high mortality from, IPD, but should not be offered more widely to other risk-groups or older adults"[1]*

- A key driver for this decision was the presumed low incidence of vaccine preventable disease[2]

*PCV13: Pneumococcal polysaccharide conjugate vaccine (13-valent adsorbed) 1. Joint Committee on Vaccination and Immunisation. Interim JCVI statement on adult pneumococcal vaccination in the UK. Available from https://www.gov.uk/government/publications/jcvi-interim-statement-on-adult-pneumococcal-vaccination. Accessed November 2017. 2. van Hoek AJ, Miller E Plos One 2016 11(2) e0149540.doi:10.1371/journal.pone.0149540

Ready for Life

Introduction

- PHE's national pneumococcal surveillance programme captures the majority of cases of IPD in England[1]
- However, the incidence of CAP treated in the community (rarely radiologically confirmed) and the incidence of hospitalised CAP is poorly understood because:
  - Lack of a diagnostic test to differentiate CAP from other lower respiratory tract infections
  - Lack of a surveillance programme
  - No prospective study designed with this specific end point in mind[2]
- A single-centre study conducted in Nottingham* was set up to evaluate trends in pneumococcal serotypes causing hospitalised CAP. **This study was not designed to determine incidence[2]**
- Comparative data from across the developed world suggests the incidence of hospitalised CAP is underestimated in the UK[2–7]
- The HES database[8] is a comprehensive database detailing all admissions, outpatient appointments and A&E attendances at NHS hospitals in England
  - It is routinely used for healthcare analyses by researchers, national bodies and regulators (e.g. NICE)

*Prof. Wei Shen Lim, Dr. Priya Daniel, Dr. Cham Rodrigo, Dr. Tom Bewick, Dr. Norman Fry, Dr. Carmen Sheppard, Prof. Mary Slack. †Average for date range. ‡Based on population average across data range. §Based on THIN data, which are generated from a 5% representation of the UK population. **Based on percentages of ONS estimate of UK population in 2015 (65.1 million).

BLF, British Lung Foundation; CAP, community acquired pneumonia; HCAP, hospital community acquired pneumonia; HES, Hospital Episode Statistics; IC, in children; IPD, invasive pneumococcal disease; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; ONS, Office for National Statistics; PHE, Public Health England; THIN, The Health Improvement Network.

1. Public Health England. Pneumococcal disease: guidance, data and analysis. Available from: https://www.gov.uk/government/collections/pneumococcaldisease-guidance-data-and-analysis [Accessed November 2017]. 2. Rodrigo C et al. ERJ 2015; 45(6):1632-41 3. Said MA et al. PLoS One. 2013;8:e60273. 4. Hospital Episode Statistics (HES) data. 2016. Reused with the permission of NHS digital. All rights reserved. 5. British Lung Foundation. Pneumonia statistics. Available from: https://statistics.blf.org.uk/pneumonia [Accessed July 2017]. 6. NICE. Pneumonia in adults: diagnosis and management. CG1919. Available from: https://www.nice.org.uk/guidance/cg191 [Accessed July 2017]. 7. NHS Choices. Pneumonia. Available from: http://www.nhs.uk/conditions/Pneumonia/Pages/Introduction.aspx [Accessed July 2017]. 8. NHS Digital. Available from: http://content.digital.nhs.uk/hes. [Accessed November 2017].

Ready for Life

Introduction

Pfizer Vaccines

- PHE's nationa

Varying incidence rates of all-cause and hospitalised all-cause CAP reported in the UK

Reference	CAP incidence rate per 100,000	Date range
Rodrigo et al. (2015)	Hospitalised all-cause CAP: 79.9 Hospitalised pneumococcal CAP: 23.4	2008–2013 (Nottingham, UK)
HES 2016	Hospitalised all-cause CAP: 232†,‡	2008–2012 (UK)
British Lung Foundation	Hospitalised all-cause CAP: 336.3‡,§	2004–2012
NICE	All-cause CAP: 326–650**	Annually (UK)
NHS Choices	All-cause CAP: 800	2016 (UK)

hospitals in England

- It is routinely used for healthcare analyses by researchers, national bodies and regulators (e.g. NICE)

*Prof. Wei Shen Lim, Dr. Priya Daniel, Dr. Cham Rodrigo, *** Dr. Tom Bewick, Dr. Norman Fry, Dr. Carmen Sheppard, Prof. Mary Slack. †Average for date range. ‡Based on population average across data range. §Based on THIN data, which are generated from a 5% representation of the UK population. **Based on percentages of ONS estimate of UK population in 2015 (65.1 million).

BLF, British Lung Foundation; CAP, community acquired pneumonia; HCAP, hospital community acquired pneumonia; HES, Hospital Episode Statistics; IC, in children; IPD, invasive pneumococcal disease; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; ONS, Office for National Statistics; PHE, Public Health England; THIN, The Health Improvement Network.

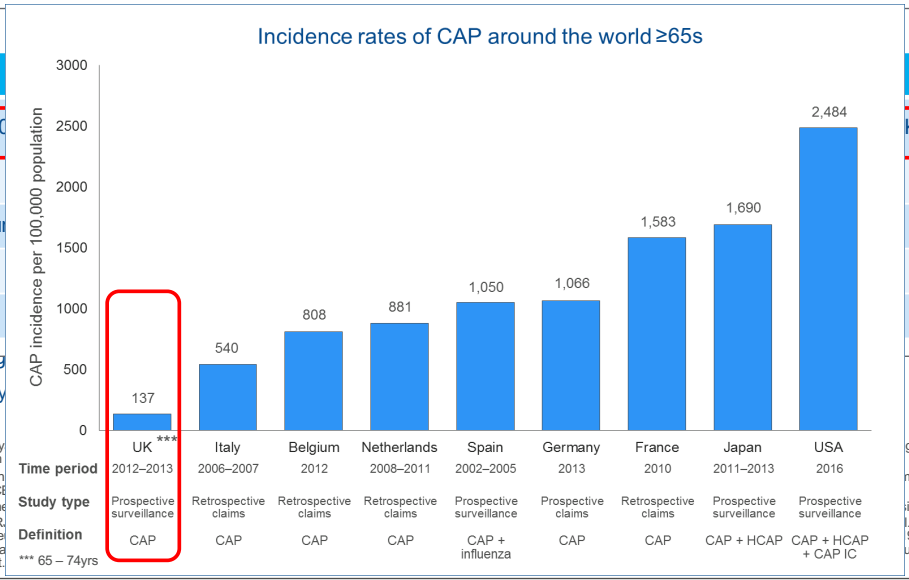
1. Public Health England. Pneumococcal disease: guidance, data and analysis. Available from: https://www.gov.uk/government/collections/pneumococcaldisease-guidance-data-and-analysis [Accessed November 2017]. 2. Rodrigo C et al. ERJ 2015; 45(6):1632-41 3. Said MA et al. PLoS One. 2013;8:e60273. 4. Hospital Episode Statistics (HES) data. 2016. Reused with the permission of NHS digital. All rights reserved. 5. British Lung Foundation. Pneumonia statistics. Available from: https://statistics.blf.org.uk/pneumonia [Accessed July 2017]. 6. NICE. Pneumonia in adults: diagnosis and management. CG1919. Available from: https://www.nice.org.uk/guidance/cg191 [Accessed July 2017]. 7. NHS Choices. Pneumonia. Available from: http://www.nhs.uk/conditions/Pneumonia/Pages/Introduction.aspx [Accessed July 2017]. 8. NHS Digital. Available from: http://content.digital.nhs.uk/hes data. [Accessed November 2017].

Ready for Life

Introduction

Pfizer Vaccines

Incidence rates of CAP around the world ≥65s



- It is routinely

*Prof. Wei Shen Lim, Dr. Priy ge across data range.
§Based on THIN data, which
BLF, British Lung Foundation nococcal disease; NHS,
National Health Service; NICE
1. Public Health England. Pne is [Accessed November
2017]. 2. Rodrigo C et al. ER l. All rights reserved. 5.
British Lung Foundation. Pne 919. Available from:
https://www.nice.org.uk/guida uly 2017]. 8. NHS Digital.
Available from: http://content.

Ready for Life

Methodology

- We compared the actual number of hospitalised CAP admissions reported to the HES database in Nottingham with published data by Rodrigo et. al over a 5 year period
- Comparison of datasets:

HES data[1]*	Nottingham Study[2]
Age ≥ 18 years	Age ≥ 16 years
April 2008 – March 2013	September 2008 – August 2013
All cause pneumonia (J12–J18†) including CAP, HAP & VAP including codes in both the primary and secondary position	All cause community acquired pneumonia (CAP) – as per study protocol

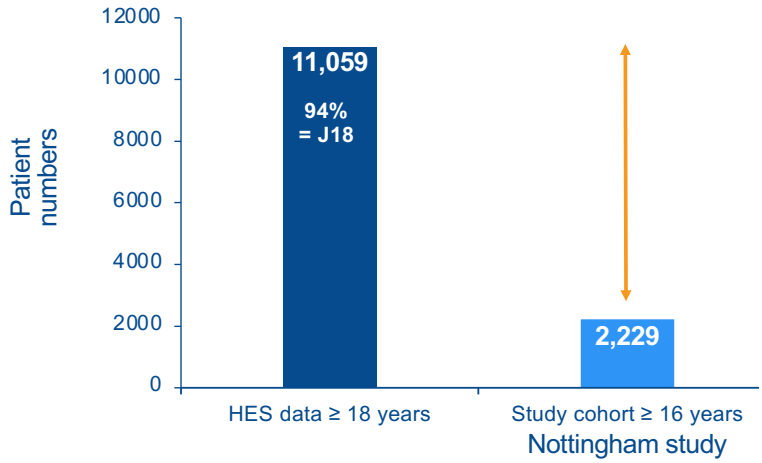
*HES data: refers to patients with more than 1 diagnosis. †J12 = viral pneumonia; J13 = pneumococcal pneumonia; J14 = *Haemophilus influenzae* pneumonia; J15 = due to other bacteria; J17 = elsewhere classified; J18 = unspecified. J12-J18 coded in any diagnostic field.
CAP, community acquired pneumonia; HAP, hospital acquired pneumonia, VAP, ventilator acquired pneumonia.
1. NHS Digital. Available from: http://content.digital.nhs.uk/hesdata. Accessed November 2017. 2. Rodrigo et al. Eur Respir J 2015;45(6):1632–41.

Nottingham Study Methodology

Study Population	Consecutive adults admitted to Nottingham University Hospitals NHS Trust with CAP.
Inclusion Criteria	Adults (patients aged ≥ 16 years) with symptoms suggestive of lower respiratory tract infection with new infiltrates on CXR consistent with pneumonia, and treated for CAP.
Exclusion criteria	Post-obstruction pneumonia due to lung cancer, active TB, discharged from hospital within 10 days and adults with aspiration pneumonia.
Enrolment	All eligible patients seen by a research investigator within 36 hours of admission to confirm study eligibility and obtain informed consent.

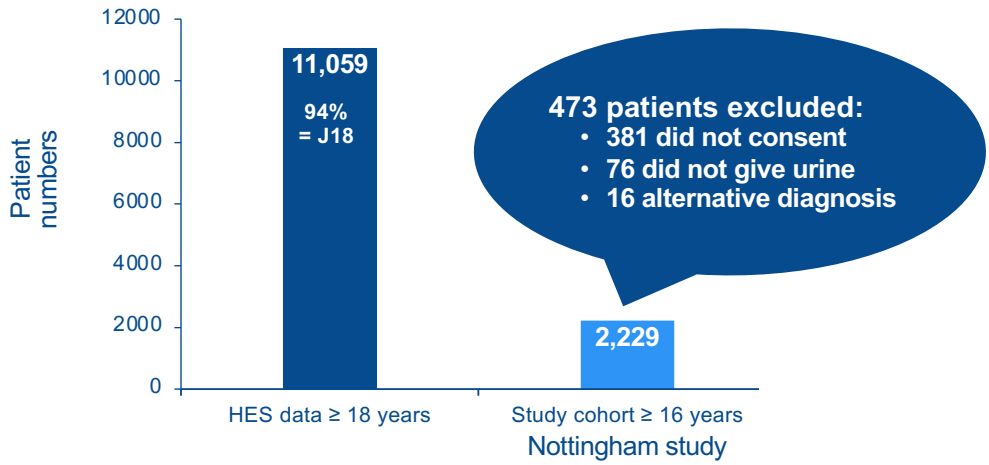
CAP, community acquired pneumonia; CXR, chest x-ray; TB, tuberculosis.
Rodrigo C et al. ERJ 2015;45(6):1632–41.

Results: Patients with Hospitalised CAP in Nottingham 2008–2013



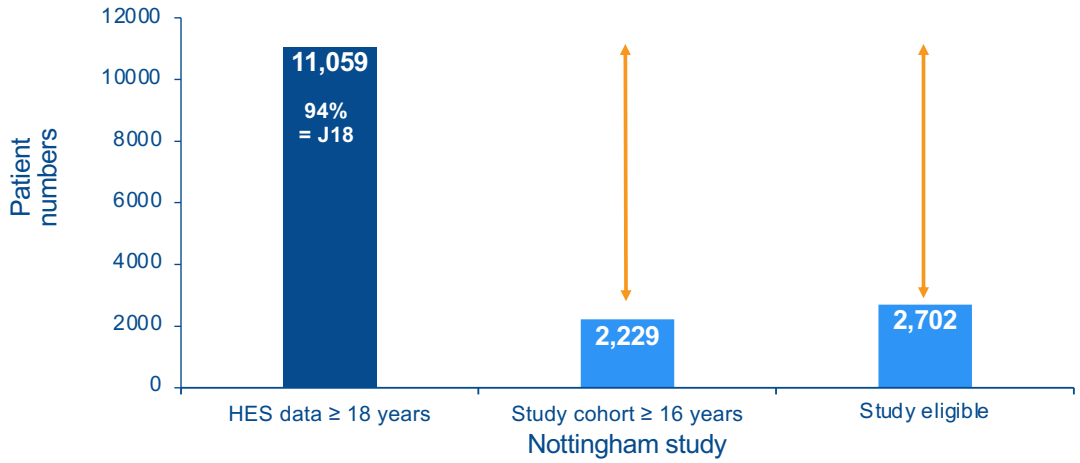
Rodrigo C et al. ERJ 2015; 45(6):1632-41
Primary J Code analysis of HES conducted by Harvey Walsh for Pfizer on Nottingham City and Queen's Medical Centre hospitals, 2016

Results: Patients with Hospitalised CAP in Nottingham 2008–2013



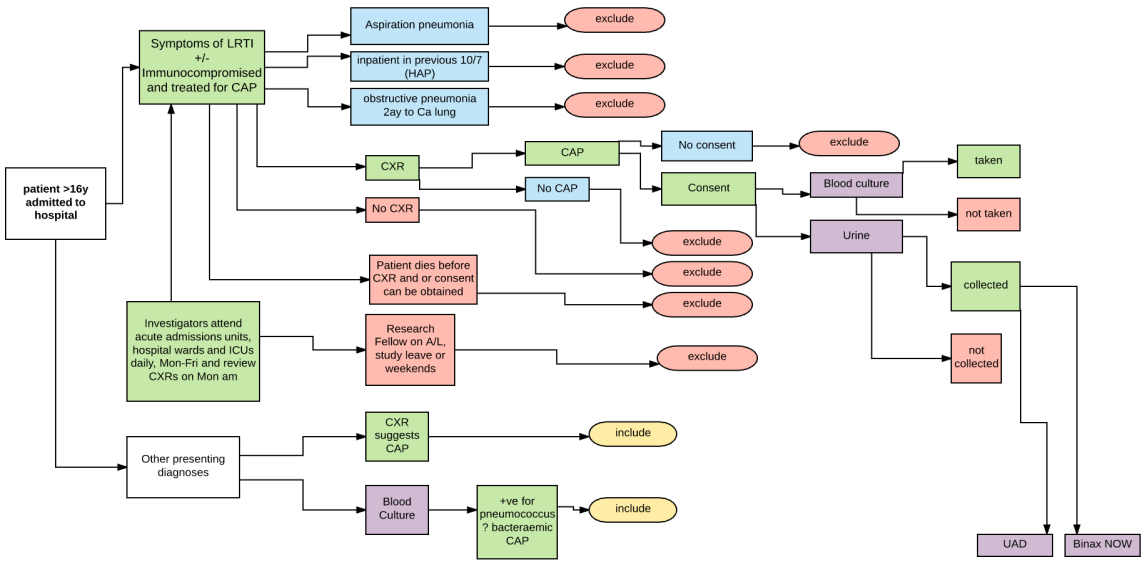
Rodrigo C et al. ERJ 2015; 45(6):1632-41
Primary J Code analysis of HES conducted by Harvey Walsh for Pfizer on Nottingham City and Queen's Medical Centre hospitals, 2016

Results: Patients with Hospitalised CAP in Nottingham 2008–2013



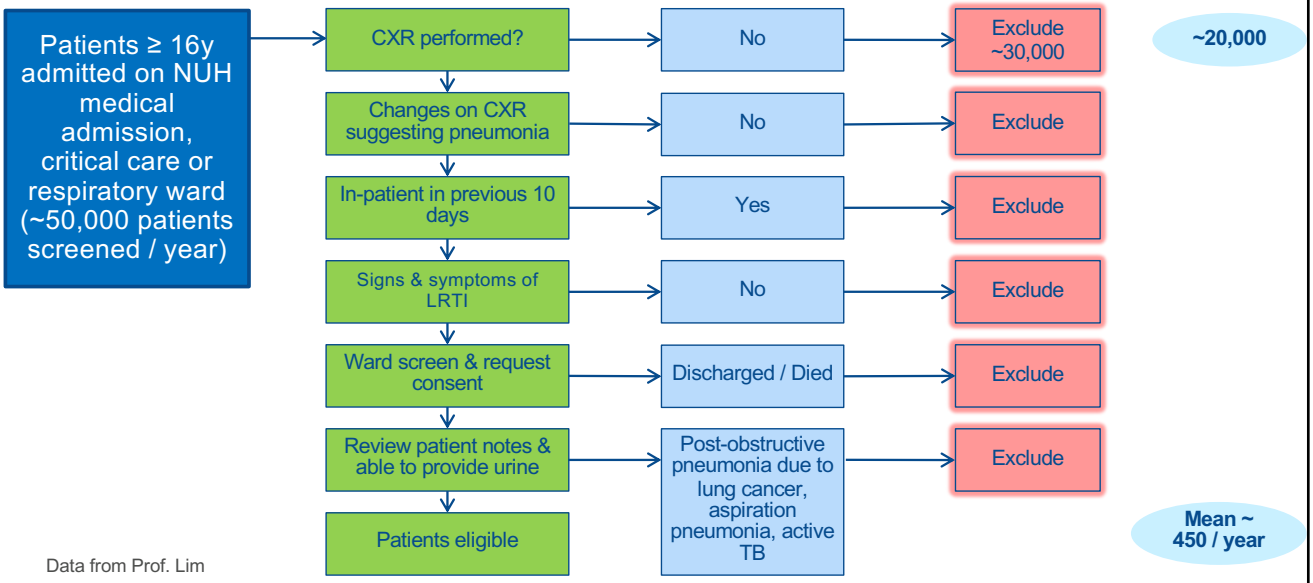
Rodrigo C et al. ERJ 2015; 45(6):1632-41
Primary J Code analysis of HES conducted by Harvey Walsh for Pfizer on Nottingham City and Queen's Medical Centre hospitals, 2016

Nottingham Study – patient journey



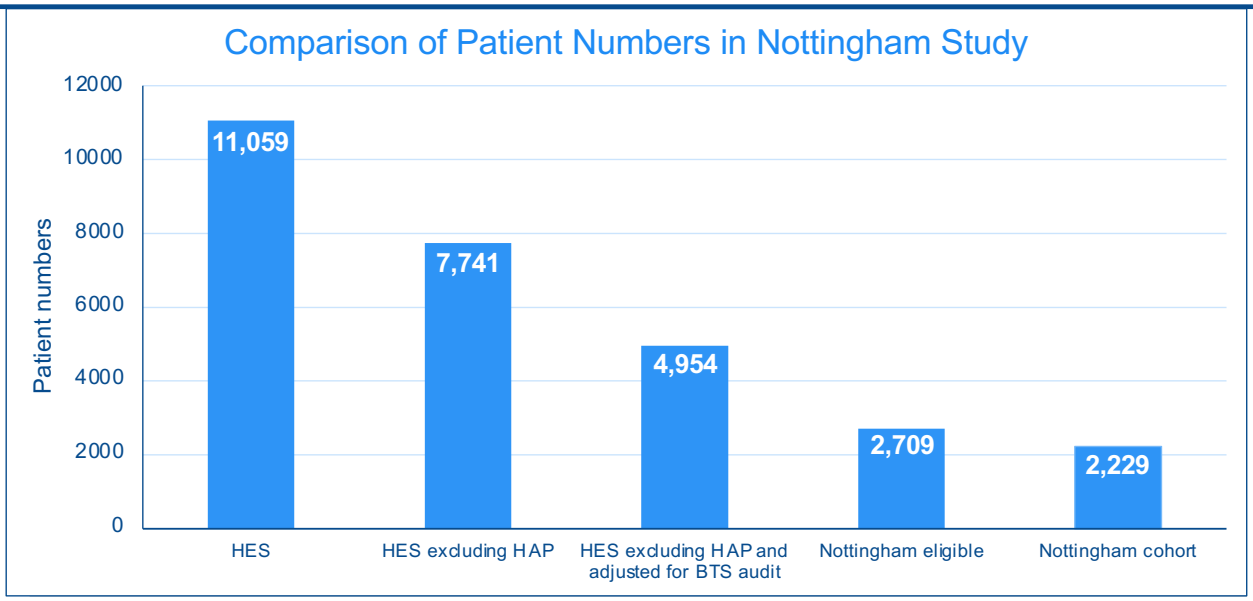
Data from Rodrigo et al ERJ, 2015; 45: 1524

Nottingham Study Enrolment Pathway



Data from Prof. Lim

HES Considerations & Comparison with BTS Audit



Conclusion

- Better diagnostic tools are required
- New data accurately showing the true incidence of CAP are needed
- HES is a powerful tool to interrogate Big Data
- The discrepancy between results from the Nottingham study and this analysis of HES data needs to be investigated further
- This analysis of HES data indicates that the number of hospitalised CAP cases identified in the Nottingham study was substantially lower than reported in HES which is also in agreement with the BTS audit
- More accurate data on the incidence of CAP would assist the policy makers in reaching recommendations on adult immunisation

Acknowledgements

Pfizer Ltd

- Dr. Harish Madhava
- Dr. Carole Czudek
- Dr. Gillian Ellsbury
- Dr. Andrew Vyse
- Dr. Dylan Jones
- Prof. Mary Slack (Consultant)

Nottingham NHS Trust

- Prof. Wei Shen Lim
- Dr. Hannah Lawrence

Harvey Walsh Ltd

- Sue Beecroft