NIHR | National Institute for Health and Care Research

Journals Library

Check for updates

Programme Grants for Applied Research

Volume 14 • Issue 6 • June 2026

ISSN 2050-4330

Rapid molecular diagnostics for pathogen identification in hospital-acquired and ventilator-associated pneumonia in critical care: INHALE research programme including RCT

Virve I Enne, Sarah-Jane F Stewart, Adam P Wagner, David Turner, Charlotte Russell, Juliet High, Susan Stirling, Julie A Barber, Robert Horne, David M Livermore and Vanya A Gant

DOI 10.3310/GJVG0801

NIHR | National Institute for Health and Care Research

Programme Grants for Applied Research

Check for updates

Extended Research Article

Rapid molecular diagnostics for pathogen identification in hospital-acquired and ventilator-associated pneumonia in critical care: INHALE research programme including RCT

Virve I Enne[1*] Sarah-Jane F Stewart[2] Adam P Wagner[3] David Turner[3] Charlotte Russell[4] Juliet High[4] Susan Stirling[4] Julie A Barber[5] Robert Horne[2] David M Livermore[3] and Vanya A Gant[6]

[1]Centre for Clinical Microbiology, University College London, London, UK
[2]School of Pharmacy, University College London, London, UK
[3]Norwich Medical School, University of East Anglia, Norwich, UK
[4]Norwich Clinical Trials Unit, University of East Anglia, Norwich, UK
[5]Department of Statistical Science, University College London, London, UK
[6]Department of Microbiology, University College London Hospitals, London, UK

[*]**Corresponding author** v.enne@ucl.ac.uk

Published June 2026
DOI: 10.3310/GJVG0801

This report should be referenced as follows:

Enne VI, Stewart SJF, Wagner AP, Turner D, Russell C, High J, *et al*. Rapid molecular diagnostics for pathogen identification in hospital-acquired and ventilator-associated pneumonia in critical care: INHALE research programme including RCT. *Programme Grants Appl Res* 2026;**14**(6). https://doi.org/10.3310/GJVG0801

Programme Grants for Applied Research

ISSN 2050-4330 (Online)

A list of Journals Library editors can be found on the NIHR Journals Library website

Programme Grants for Applied Research (PGfAR) was launched in 2013 and is indexed by Europe PMC, NCBI Bookshelf, DOAJ, Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and Scopus® (Elsevier, Amsterdam, Netherlands).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full PGfAR archive is freely available to view online at www.journalslibrary.nihr.ac.uk/pgfar.

Criteria for inclusion in the *Programme Grants for Applied Research* journal

Manuscripts are published in *Programme Grants for Applied Research* (PGfAR) if (1) they have resulted from work for the PGfAR programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Programme Grants for Applied Research programme

The Programme Grants for Applied Research (PGfAR) programme, part of the National Institute for Health and Care Research (NIHR), was established in 2006 to fund collaborative, multidisciplinary programmes of applied research to solve health and social care challenges. Findings are expected to provide evidence that lead to clear and identifiable patient benefits, in the relatively near future.

PGfAR is researcher led and does not specify topics for research; however, the research must be in an area of priority or need for the NHS and the social care sector of the Department of Health and Social Care, with particular emphasis on health and social care areas that cause significant burden, where other research funders may not be focused, or where insufficient funding is available.

The programme is managed by the NIHR Central Commissioning Facility (CCF) with strategic input from the Programme Director. For more information about the PGfAR programme please visit the website: https://www.nihr.ac.uk/explore-nihr/funding-programmes/programme-grants-for-applied-research.htm

This article

The research reported in this issue of the journal was funded by PGfAR as award number RP-PG-0514-20018. The contractual start date was in January 2016. The draft manuscript began editorial review in March 2024 and was accepted for publication in July 2025. As the funder, the PGfAR programme agreed the research questions and study designs in advance with the investigators. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The PGfAR editors and production house have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, CCF, PGfAR or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the PGfAR programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).

Abstract

Background: Intensive care unit patients are vulnerable to hospital-acquired and ventilator-associated pneumonias. Immediate antibiotic therapy is warranted. Because: (1) many different bacterial species can be responsible and (2) it takes at least 2 days for conventional microbiological investigation, empirical broad-spectrum agents are given. This creates two hazards. First, these may promote overgrowth of undesirable bacteria in the patient's gut. Second, the pneumonia may involve bacteria resistant to the antibiotic, precipitating failure. An alternative strategy – explored by the INHALE programme – is to use molecular tests to rapidly characterise the pathogen(s), facilitating early tailoring of antimicrobial therapy.

Selecting a molecular test to trial in hospital-acquired and ventilator-associated pneumonias: INHALE's work package 1 used routinely collected respiratory samples (n = 652) from intensive care units at 15 hospitals, comparing the organisms found by two multiplex polymerase chain reaction systems (FilmArray and Unyvero) with those from routine culture. The molecular tests found bacteria in more specimens (74.2–60.4% vs. 44.2%) and found them more quickly (70 minutes to 6 hours vs. > 2 days). Diagnostic accuracy performance was similar, but the FilmArray Pneumonia Panel was swifter, more convenient and better supported. Accordingly, it was carried forward to the work package 3 randomised controlled trial.

Defining the epidemiology and management of hospital-acquired and ventilator-associated pneumonias: Work package 2 reviewed patient-level data for hospital-acquired/ventilator-associated pneumonias at four intensive care units in England; 142 patients were considered, of whom only 46.5% received appropriate empirical therapy. The cure rate of pneumonia was 62.7%. Enterobacterales, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Haemophilus influenzae* predominate, corresponding with international literature. Compliance with local guidelines varied considerably among sites, as did the guidelines' recommendations.

Clinical trial of the effects of rapid microbiology on antibiotic stewardship and clinical cure: Intensive care unit hospital-acquired/ventilator-associated pneumonias patients about to receive new or changed antibiotics were randomised to: (1) a FilmArray Pneumonia Panel test, supported by an algorithm translating its outputs into treatment advice, or (2) 'standard-of-care', with empirical antibiotics based on the hospital's guidelines. Fourteen intensive care units participated, recruiting 545 adults and children over 2 years, with a 4-month-interruption owing to coronavirus disease discovered in 2019. Molecular tests were performed in intensive care unit, obviating transport delays. Two coprimary outcomes were considered. First, the proportion of patients on 'active and proportionate' antibiotics 24 hours after randomisation. This was substantially higher in the intervention arm (76.5% vs. 55.9%). Second, the proportion of patients with clinical cure of pneumonia 14 days post randomisation. This was marginally inferior in the intervention arm (56.4% vs. 64.7%), with the 95% confidence interval for the difference failing to exclude a preset 13% non-inferiority margin. Among secondary outcomes, there were slightly more deaths in the intervention arm, and slower improvement of clinical [sequential organ failure assessment and paediatric logistic organ dysfunction (PELOD)] scores, without statistical significance. Various interpretations are possible. Worse clinical outcomes may represent chance, given the borderline statistics. Alternatively, hospital pneumonia may, in its early stages, involve mixed bacteria, leading to a benefit from broad-spectrum therapy, which was more often given in the control arm.

Behavioural studies: INHALE work package 4 used mixed-method designs to examine prescribers' perceptions of the Pneumonia Panel and its use. Although most recognised the value of rapid results and the importance of antibiotic stewardship, Pneumonia Panel results had a limited impact on prescribing behaviour. Many clinicians were reluctant to avoid or stop initial broad-spectrum in response to test results. The decision to prescribe and maintain broad-spectrum antibiotics often represented an attempt to 'err on the side of caution' to protect the patient (and clinician), where the proximal need to protect was more imperative than the more distal threat of antibiotic resistance.

Costs and cost-effectiveness of rapid molecular microbiology for hospital-acquired and ventilator-associated pneumonias: The additional cost of the Pneumonia Panel (£198) represents a very small component of total intensive care unit costs and are typically below 2% of total costs per intensive care unit patient (base case). We found a reduction in total costs with patients in the intervention arm averaging £33,148, and patients in the control arm averaging £40,951. However, it remains unclear how this arises. There was evidence of the Pneumonia Panel being

cost-effective in terms of stewardship, but not for clinical cure; consequently, we cannot conclude an economic advantage for the Pneumonia Panel. However, this does not take account of the potential benefit of improved stewardship in terms of reduced antimicrobial resistance.

Limitations: The multiplex systems compared in work package 1 are subject to repeated updating, meaning that the better system might change with time. Both work package 1 and work package 3 were limited by the low prevalence of antibiotic resistance in England, precluding rigorous evaluation of resistance gene detection. Last, and critically, the coronavirus disease pandemic substantially changed the types of patients recruited.

Conclusions and future work: Overall, INHALE demonstrates the potential of molecular testing to swiftly detect pathogens in the respiratory secretions of intensive care unit pneumonia patients and shows that these data can influence prescribing. What remains elusive, needing further work, is translating the results into optimal therapy and improved clinical outcomes.

Trial registration (work package 3): This trial is registered as ISRCTN16483855.

Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research Programme (NIHR award ref.: RP-PG-0514-20018) and is published in full in *Programme Grants for Applied Research*; Vol. 14, No. 6. See the NIHR Funding and Awards website for further award information.

Contents

List of tables

List of figures

List of abbreviations

AMR	antimicrobial resistance
AMS	antimicrobial stewardship
BAL	bronchoalveolar lavage
BLC	Bayesian latent class
CCU	critical care unit
CT	computed tomography
DDD	defined daily dose
EMA	ecological momentary assessment
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GOSH	Great Ormond Street Hospital
HAP	hospital-acquired pneumonia
HRQoL	health-related quality of life
ICU	intensive care unit
ITT	intention to treat
IVD	in vitro diagnostic
LRTI	lower respiratory tract infection
NCF	necessity concerns framework
NCTU	Norwich Clinical Trials Unit
NNUH	Norfolk and Norwich University Hospital
NPV	negative predictive value
ONT	Oxford Nanopore Technologies
PCR	polymerase chain reaction
PELOD	paediatric logistic organ dysfunction
PPI	patient and public involvement
PPV	positive predictive value
PSC	Programme Steering Committee
pSOFA	paediatric sequential organ failure assessmentA
QALY	quality-adjusted life-year
QC	quality control
RCT	randomised controlled trial
REDCap	Research Electronic Data Capture
SOFA	sequential organ failure assessment
SOP	standard operating procedure
TMG	Trial Management Group
UCLH	University College London Hospital
VAP	ventilator-associated pneumonia
WP	work package

Plain language summary

Intensive care unit patients often develop pneumonia. The laboratory then takes several days to identify the type of bacteria responsible. Meantime, the doctor gives 'broad-spectrum' antibiotics to kill the most likely bacteria. This approach carries two risks:

- undesirable and antibiotic-resistant bacteria may overgrow in the gut
- second, the pneumonia may involve bacteria resistant to the antibiotic.

An alternative approach, explored by INHALE, is to use polymerase chain reaction (as in coronavirus disease testing) to rapidly identify the bacteria, guiding treatment.

We compared the bacteria found by two polymerase chain reaction systems with those found by microbiology labs across 15 intensive care units. Polymerase chain reaction was faster and found more bacteria. One polymerase chain reaction system, FilmArray, was better and was used for further research (randomised clinical trial), in 14 English intensive care units. Half of 545 patients received treatment guided by FilmArray. The other half had standard care, with broad-spectrum antibiotics until routine lab results were received.

More FilmArray patients (76.5% vs. 55.9%) received appropriate antibiotics within 24 hours, so helped lessen overprescribing of antibiotics, but, surprisingly, their clinical cure outcomes were slightly worse (56.7% cure vs. 64.5%). Other clinical outcomes tended to favour the control arm's patients, but differences were not statistically significant. We do not know what caused this difference. It may be chance, or it may indicate that intensive care unit pneumonias are more complex than supposed, with patients benefitting from an early broad-spectrum antibiotic.

We surveyed intensive care unit clinicians' views about these tests. Most welcomed their speed, but many were wary about stopping broad-spectrum antibiotics early. They were also torn between wanting to conserve antibiotics and wanting the 'best' for their patient, often prioritising the latter. Each test costs £198 per person, but the average total care cost per patient was lower (£33,148 vs. £40,951). The reason for this saving remains unclear.

Overall, INHALE showed the potential of polymerase chain reaction tests in intensive care unit pneumonias, and that the results could influence prescribing. How best to translate this into better patient outcomes remains unknown at present.

A poem summarising the study and written by the programme's patient and public involvement group, can be seen here: www.youtube.com/watch?v=7_2bqWIJzFE

Scientific summary

Background

Hospital-acquired and ventilator-associated pneumonias (HAP and VAP) affect one in five intensive care unit (ICU) patients and are responsible for significant excess morbidity, mortality and costs. They can be caused by a range of micro-organisms, including bacteria, viruses and fungi. Aetiological diagnosis is traditionally performed by bacteriological culture, taking 2–4 days. In the meantime, patients receive empirical broad-spectrum antibiotics, which is suboptimal as it frequently overtreats the pathogen present, driving antimicrobial resistance (AMR), or conversely, undertreats, potentially leading to worsened clinical outcomes. We investigated whether rapid molecular diagnostic methods would lead to improved treatment of HAP and VAP.

Objectives

The objectives of the programme were:

1. To define, across four different ICUs, the accuracy of three molecular diagnostic systems claiming to rapidly identify pathogens and their resistance genes in respiratory specimens from patients with HAP/VAP.
2. Based on (1) above, to select the best-performing test and to conduct a randomised controlled trial (RCT), comparing clinical outcomes and antibiotic utilisation in patients whose treatment is guided by the test versus those managed conventionally with empirical treatment refined by microbiological culture.
3. To measure clinicians' willingness to adopt molecular diagnostics and treat patients based on their results.
4. To determine whether the outcomes justify the cost.

Work package 1: clinical laboratory evaluation

Methods

Surplus lower respiratory samples were collected from patients with suspected HAP or VAP. Samples were tested on the BioFire FilmArray Pneumonia Panel and the Curetis Unyvero Pneumonia Panel and results compared to routine culture. Analysis was according to a predetermined statistical analysis plan using Stata® (StataCorp LP, College Station, TX, USA) and R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Six hundred and fifty-two eligible samples were collected from 15 sites between September 2016 and May 2018. Routine culture generated a result in a median time of 70.2 hours [interquartile range (IQR) 51.1–92.1 hours] and 44.2% of samples were positive for likely pathogens. Considerable site-to-site variation was observed, highlighting shortcomings of routine microbiology as a gold standard.

There were 631 eligible test results for the Unyvero, and 632 for the FilmArray. The overall positivity rate was 60.4% for Unyvero and 74.2% for FilmArray, considerably higher than for routine microbiology ($p < 0.0001$). The range of organisms detected by polymerase chain reaction (PCR) was as expected and broadly similar to routine microbiology.

Polymerase chain reaction assay sensitivity was > 95% for most target bacteria, with negative predictive values (NPVs) > 98%. Specificity and positive predictive values (PPVs) were lower, due to the PCR tests detecting more organisms per sample and finding more positive samples than routine microbiology. To address the problem of culture representing a poor gold standard, performance parameters were also obtained using Bayesian latent class (BLC) analyses. This showed routine microbiology was the least sensitive technique. Sensitivity values for the PCR tests remained high; specificity and PPV values for both PCR tests increased.

The tests were evaluated for their other characteristics such as speed, size and useability. A final decision-making meeting was held with all stakeholders. The FilmArray Pneumonia Panel was chosen for progression to the randomised controlled trial in work package (WP) 3.

Work package 2: epidemiology of the units

Methods

This work took place at four ICUs participating in WP1. There were two components: (1) collection of patient-level data and (2) collection of unit-level data.

Individual participants needed to have an eligible sample included in WP1, in addition to providing consent or assent to participate. Data were collected for up to 21 days after enrolment. The data were used to determine whether antibiotics prescribed were appropriate and proportionate against pathogens found by either PCR and/or culture. Data were analysed according to a predefined analysis plan using Stata and R. In addition to patient-level data, unit-level prescribing and microbiology data were collected from the participating ICUs using hospital information systems. Data were acquired for a period of 15 months, from October 2016 to December 2017.

Results

One hundred and forty-two participants were recruited. The majority were male (65.5%) with a median age of 57.9 years, 24.6% were children. Fifty-two and one-tenth per cent had VAP and the remainder had HAP. The majority (86%) had received an antibiotic prior to enrolment and over half of prescriptions were broad-spectrum agents. For their episode of HAP or VAP, 51.4% received empirical treatment within the ambit of local guidelines, 32.4% received non-guideline empirical therapy and the remainder received non-empirical therapy based on a susceptibility result. Commonly used regimens were piperacillin/tazobactam ± an aminoglycoside, coamoxiclav, ceftazidime or ciprofloxacin + teicoplanin. At day 21, 62.7% of patients were considered cured of pneumonia when using the cure definition in the WP2 protocol, increasing to 74.6% when the WP3 definition was used. Overall mortality at 21 days was 18.3%.

All three methods show a slightly higher cure rate when treatment was judged appropriate as opposed to inappropriate. For routine microbiology, cure rates were reasonably similar across all stewardship categories. However, in the case of PCR, cure rates were noticeably lower when inactive treatment for a positive result was given, at just (17/35) 48.6% compared with (71/103) 68.9% among those with an appropriate treatment based on FilmArray results ($\chi^2 = 4.69$, $p = 0.03$) and (20/37) 54.1% vs. (65/99) 65.7% based on Unyvero results ($\chi^2 = 1.55$, $p = 0.21$).

At the unit level, adults had a HAP/VAP rate of almost double that of children, with the rate 22.9 cases/1000 bed-days at University College London Hospital (UCLH) ICU. In terms of microbiology, there were discrepancies in the positivity rate of samples, with UCLH having a ~35% positivity rate compared to ~65% at Cromwell and ~80% at Great Ormond Street Hospital (GOSH). The epidemiology of HAP/VAP was as expected at Norfolk and Norwich University Hospital (NNUH) and UCLH, but at the Cromwell there was a radically different epidemiology, dominated by *Pseudomonas aeruginosa* and Enterobacterales but with a substantial proportion (14%) of *Acinetobacter baumannii*. At GOSH, traditionally community-acquired organisms, *Haemophilus influenzae* and *Moraxella catarrhalis*, were frequently isolated from lower respiratory tract infection (LRTI) samples. Antibiotic prescribing also differed between the units.

Work package 3: randomised controlled trial

Methods

We ran a pragmatic, multicentre, open-label, parallel-group, RCT to investigate clinical, safety and cost-effectiveness of the Pneumonia Panel test plus trial based prescribing algorithm versus standard care across 14 ICUs. Those who received an antibiotic to treat new or worsening HAP or VAP and provided consent or assent were eligible to participate. Participants randomised to the treatment arm received a Pneumonia Panel test performed at the point of

care, alongside an optional treatment algorithm designed to encourage good antibiotic stewardship. Primary outcomes were equivalence of clinical cure of pneumonia at day 14 and improvement in antibiotic stewardship at 24 hours.

Clinical cure rate was initially assumed at 70% with a non-inferiority margin of 13%, but cure rate was lowered to 55% following the inclusion of coronavirus disease discovered in 2019 (COVID-19) patients. This sample size required at least 528 participants to achieve 91% power with a significance level still at 5% and was inflated to 552 to allow for 5% attrition. Analyses were based on intention to treat (ITT) and followed a predefined statistical analysis plan using Stata version 17.

Results

Five hundred and fifty-four participants were recruited, of which 92 were children; primary outcomes were available for 531. Median age for adults was 61 years, and 7.5 months for children. At randomisation, 33.6% had COVID-19 infection. Time to result post randomisation was 1.7 [standard deviation (SD) 0.8 hour] for the Pneumonia Panel compared to 110 (SD 116.2 hours) in the control arm.

Intention-to-treat analysis for the coprimary stewardship outcome at 24 hours after randomisation showed that 205/268 (76.5%) intervention arm participants were receiving active and proportionate antibiotics by 24 hours, versus 147/263 (55.9%) in the control arm [estimated difference after accounting for site 21%, 95% confidence interval (CI) 13% to 28%, $p < 0.001$]. One hundred and fifty-two of 268 (56.7%) intervention arm participants had clinical cure of pneumonia at 14 days, versus 171/265 (64.5%) control patients. The estimated difference, after accounting for site, was −6% with 95% confidence limits of −15% to 2%. These values overlap the non-inferiority margin of 13%, meaning that non-inferiority was not established.

Analyses of secondary outcomes supported the primary stewardship results, with improvements consistently apparent for the intervention arm. We saw a 28-day mortality of 31.3% in the intervention arm and 28.2% in the control arm, a non-significant difference. No significant differences between arms were observed for ICU length of stay, ventilator-free days, incidence of septic shock or occurrence of secondary pneumonia.

Work package 4: behavioural study

Methods

Work package 4 used mixed methods across four separate but related studies examining prescribers perceptions of (1) antibiotic prescribing in ICU, (2) the application of molecular diagnostic techniques and (3) their prescribing behaviour in response to Pneumonia Panel results. Study 1 used focus groups and interviews to explore ICU clinician perceptions of antibiotic prescribing using two fictitious vignettes of patients with HAP/VAP. Data were analysed using thematic analysis, applying the Necessity Concerns Framework (NCF). Study 2 used data collected through Study 1, focusing in more detail on clinicians' beliefs about rapid molecular diagnostic technology 'in principle', and its potential role in prescribing. Study 3 used qualitative methods to explore clinicians' perceptions of using the Pneumonia Panel in practice. Study 4 used ecological momentary assessments (EMA) to examine whether Pneumonia results influenced individual prescribing decisions for specific patients, and to elicit the clinicians' beliefs that influenced each decision.

Results

The overarching findings from Studies 1 and 2 provided novel insights into the psychology of prescribing. When asked about the risks of broad-spectrum antibiotics, few clinicians focused on the potential toxic effects of broad-spectrum antibiotics to individual patients. The major concern about using broad-spectrum antibiotics was perceived to be increasing AMR, which clinicians were aware of and concerned about. However, this concern was juxta-positioned against a more immediate and profound concern about the patient in front of them. Therefore, a prescription and continuation of broad-spectrum antibiotics was an attempt to '*err on the side of caution*' in protecting the patient (and clinician) from the adverse consequences of not prescribing, over-riding concerns about AMR. The immediate necessity to protect fuelled the necessity to prescribe, over-riding more distal concerns about AMR. Study 3 found clinicians' perceptions about using the 'Pneumonia Panel' to treat HAP/VAP patients were nuanced. Although many perceived the value of these tests for supporting antibiotic decision-making and local antimicrobial stewardship (AMS), many harboured concerns about their application in practice (e.g. false negatives/positives). Quantitative data from Study

4 highlighted that hospital guidelines are one of the most influential factors for antibiotic decision-making; however clinicians' confidence in, and adherence to them, was low (24.9% of decisions were not consistent with local hospital guidelines). Clinicians also reported low confidence in, and adherence to, the WP3 prescribing algorithm (67.6% of decisions were not consistent with the algorithm).

Work package 5: health-economic analysis

Methods

Health-economic data relating to cost of ICU stay were collected for individual participants of WP2, to enable calculation of the costs associated with hospital stays for HAP or VAP. In parallel with WP1, we estimated the cost-per-test for the two PCR diagnostics being evaluated.

A review of health-economic models used in previous studies investigating costs of HAP and VAP was conducted. Clinician interviews were performed and a clinical pathway developed. These components were used to develop a bespoke health-economic model of HAP and VAP for this study.

Health-economic analyses were conducted alongside WP3 following a predefined health-economic analysis plan. We calculated the additional cost per additional person on active and proportionate antimicrobial therapy within 24 hours of clinical diagnosis ('stewardship') as well as the additional cost per additional clinical cure of pneumonia at 14 days post randomisation ('cure'). Costs were obtained from hospital finance departments and represented hospital income. We also used NHS reference costs. Costs were in 2020–1 Great British pounds, apart from early work to estimate cost of test used in WP1 and WP2 which were in 2018–9 Great British pounds.

Results

Work alongside WP2 estimated that mean costs for a hospital stay for an adult with HAP or VAP was £42,136. The cost of the Pneumonia Panel was calculated as £189, and this was revised to £198 during WP3. The length of ICU stay was the largest component of cost. In WP3, total costs for the control arm were £40,951 compared to £33,148 for the intervention arm, a difference of £7802 (95% CI −15,696 to 92). For economic evaluation of stewardship and clinical cure, we found estimates of difference in cost for the intervention arm compared to the control arm of −£7373 and −£7147, respectively. For these economic analyses, lower costs for the intervention arm persisted for all sub-analyses, including separate costs for survivors and those that died. Cost-effectiveness of the Pneumonia Panel was demonstrated for antibiotic stewardship but not for clinical cure.

Conclusions

Rapid molecular diagnosis of the aetiology of HAP and VAP was faster and more sensitive than standard care culture. PCR tests revealed additional pathogens which were not reported by culture, possibly due to reasons of lack of standardisation in interpretation and reporting. The Pneumonia Panel was chosen for further progression to the RCT and placed at the point of care within participating ICUs. This strategy increased uptake of the test and recruitment to the trial. The Pneumonia Panel intervention was successful in improving AMS by 21% in absolute terms. This was despite reservations expressed by clinicians regarding de-escalation of antibiotics for seriously ill patients. The intervention was also associated with a cost saving linked to reduced costs for the ICU stay, although the drivers of this are not yet clear.

However, equivalence of clinical cure was not demonstrated. Other clinical outcomes such as mortality and sequential organ failure assessment (SOFA) did not demonstrate significant differences but tracked with clinical cure. It is not currently clear whether the failure to demonstrate clinical cure is related to a small but real effect, another explanation or pure chance. This must be established to confirm the safety of the intervention. Our behavioural work suggests that to realise the potential for molecular diagnostic technologies to improve AMS, we need to employ a 'technology plus' approach that acknowledges the challenges that clinicians face when applying technological solutions to the care of individual patients.

Future work

Future work should focus on whether or not use of the intervention to improve AMS leads to worse clinical outcomes. Such a finding could have broad reaching implications if true and must therefore be investigated further. Work is already underway to carry out a deeper analysis of the existing trial participants and their data. Should these analyses prove inconclusive the next step would be a follow-on trial focusing particularly on clinical outcomes. Future work should also involve the design and development of behavioural materials and interventions to support clinicians with antibiotic decision-making. Another area of interest is the use of broader diagnostic techniques such as metagenomics, which provide a complete overview of the lung microbiome as opposed to focusing on specific pathogens.

Trial registration

This trial is registered as ISRCTN16483855.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research Programme (NIHR award ref.: RP-PG-0514-20018) and is published in full in *Programme Grants for Applied Research*; Vol. 14, No. 6. See the NIHR Funding and Awards website for further award information.

Synopsis

Background

Hospital-acquired and ventilator-associated pneumonias (HAP/VAP) are the most frequent reason for prescribing antibiotics in the intensive care unit (ICU). Antibiotic treatment for these patients must begin at clinical diagnosis, whereas culture and susceptibility of the causative bacteria take 48–72 hours. This leads to a hazard that patients are undertreated if they have an unusually resistant pathogen, not covered by the empirical antibiotics given. More often, patients with broadly susceptible bacteria are given broad-spectrum antibiotics, exerting selection pressure for resistance for no discernible gain.

Many assert that the key to improvement lies in swifter microbiological investigation, using molecular methods to seek pathogens and resistance genes in respiratory secretions without culture, thereby delivering results in hours rather than days. Thus far, however, there is scant real-world evidence that such methods cost-effectively deliver better stewardship or better clinical outcomes, let alone whether their results – which are not comprehensive – will readily be trusted by either ICU physicians or microbiologists. The INHALE programme aimed to address all these aspects, exploring the utility, performance and acceptability of molecular microbiology for HAP/VAP in practice.

Objectives

The original objectives of the programme are listed below.

1. To define, across four different ICUs, the accuracy of three molecular diagnostic systems claiming to rapidly identify pathogens and their resistance genes in respiratory specimens from patients with HAP and VAP.
2. Based on (1) above, to select the best-performing test and to conduct a randomised controlled trial (RCT), comparing clinical outcomes and antibiotic utilisation in patients whose treatment is guided by the test *versus* those managed conventionally with empirical treatment refined by microbiological culture.
3. To measure clinicians' willingness to adopt molecular diagnostics and treat patients based on their results.
4. To determine whether the outcomes justify the cost.

The programme is structured into five work packages (WPs). In WP1, addressing objective 1, we compared the agreement of multiple molecular microbiological tests for HAP/VAP with conventional microbiology and each other. In WP2, we reviewed the current microbiology, antibiotic treatment and outcomes of HAP/VAP in order to inform the design of the RCT and aid selection of the molecular test, addressing objectives 1 and 2. In WP3, we took the best-performing test from WP1 and ran a RCT comparing stewardship and clinical outcomes for (a) patients whose treatment was managed using this diagnostic and (b) those managed conventionally, with empirical therapy adapted once laboratory results became available, addressing objective 2. In WP4, we explored the views of ICU physicians and microbiologists apropos molecular testing in general, and the preferred test in particular, before and during the RCT, addressing objective 3. Lastly, in WP5, we reviewed the cost-effectiveness of the tests employed in WPs 1 and 3, addressing objective 4.

The programme was divided into two phases, with phase I comprising WP1, WP2 and pre-trial components of WP4 and WP5. Phase II encompassed WP3 and during trial components of WP4 and WP5 (*Figure 1*).

Changes to the programme

The programme's core objectives have remained the same throughout it is lifetime. Some changes were made, either to overcome obstacles or to improve the programme's design. The duration of the programme was also extended, from an initial 5–7.5 years. This was due to effects of the coronavirus disease discovered in 2019 (COVID-19) pandemic and some aspects of the research taking longer than anticipated.

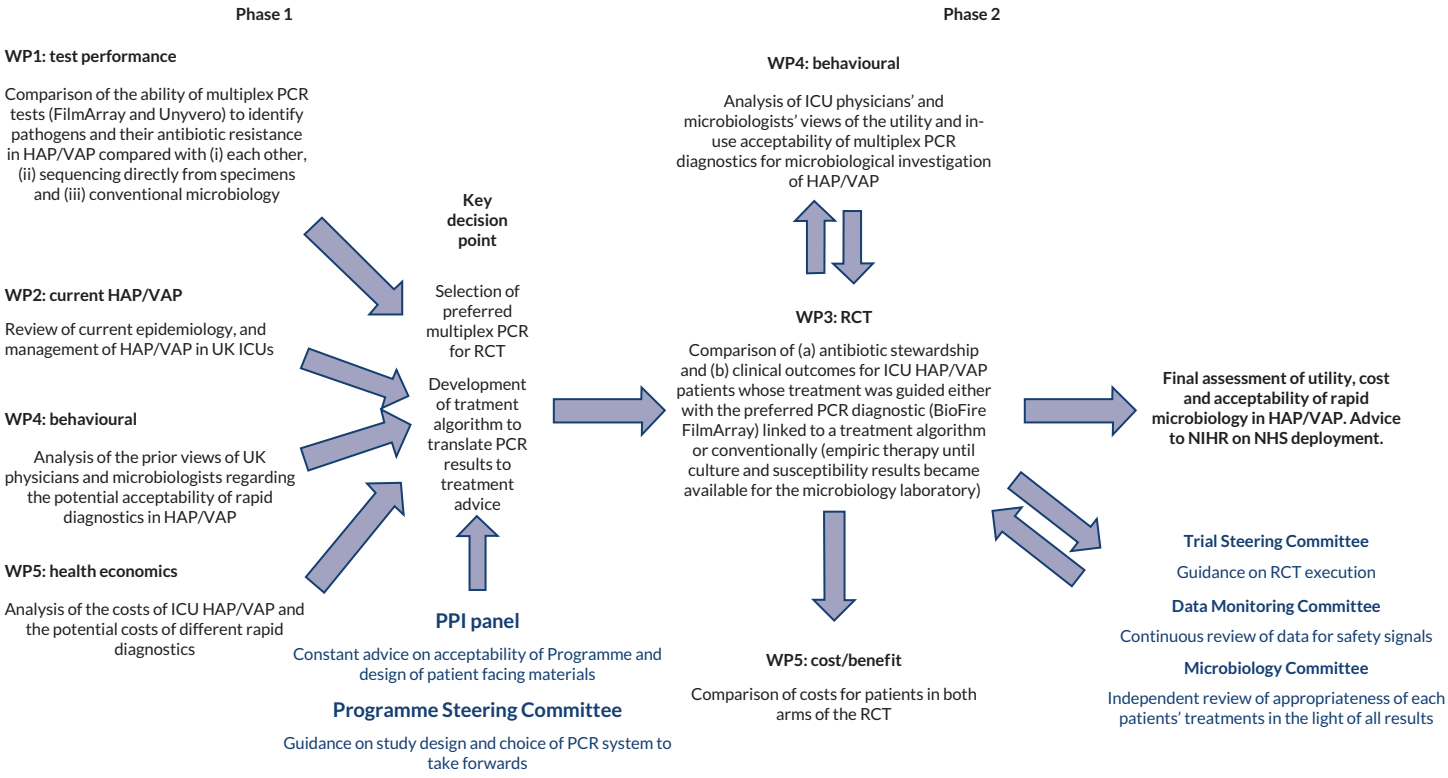


FIGURE 1 INHALE programme structure. NIHR, National Institute for Health and Care Research; PCR, polymerase chain reaction; PPI, patient and public involvement.

Work package 1

- The original programme planned to conduct a head-to-head comparison of three molecular tests for pneumonia. However, the Novodiag platform was not ready on time.
- To replace Novodiag, we carried out an evaluation of nanopore metagenomic sequencing. This technology had a lot to offer, but its deployment to treat patients in real time would have been premature and hence it was not considered for final progression to the RCT.
- It became clear early in WP1 that recruitment was too slow from the original four planned sites. We therefore expanded the number of recruiting sites to 15. We also allowed inclusion of frozen samples.
- A more refined statistical analysis plan, incorporating Bayesian latent class (BLC) modelling and concordance analysis, was developed to more closely reflect the nature of the data. This allowed the sample size for WP1 to be reduced from the original 868 to between 500 and 700 samples.

Work package 2

- Data collection methodology was changed, and consent was sought from participants to allow more detailed patient-level data to be collected.

Work package 3

- Instruments were placed directly in participating ICUs at the point of care rather than the laboratory. Pre-trial evidence suggested this would lead to faster turnaround-time and better uptake.
- Given lower than expected recruitment in WP1, the number of sites for WP3 was increased.
- Disruption caused by the COVID-19 pandemic forced the trial to stop recruiting in March 2020. Sites were gradually reopened from July 2020 onwards, and formally included eligible COVID-19 patients after that date.

- COVID-19 patients had worse clinical cure rates than other participants and, as a result, it was necessary to increase the trial sample size from 466 to 552 (including 5% attrition).
- While recruitment to the main trial was paused, we launched an observational COVID-19 substudy at five sites during which the Pneumonia Panel was used to diagnose secondary infections and aid patient management.

Work package 4

- The planned pre-trial methodology was replaced with a vignette-based interview method. This allowed more detailed understanding of clinicians' decision-making in relation to antibiotic prescribing.
- Methodology for task 4.4 was changed from short interviews to short 'EMA' questionnaires, supplemented with in-depth interviews, to achieve higher completion rates. During the COVID-19 pandemic, WP4 ran a substudy looking at prescriber attitudes to antimicrobial stewardship (AMS) and rapid diagnostic in COVID-19 patients.

Work package 5

No changes.

Work package 1: clinical laboratory evaluation

Introduction

Bacteriology culture of sputum, bronchoalveolar lavage (BAL) or endotracheal tube aspirate is considered the gold standard for microbiological diagnosis of pneumonia. Culture is far from an ideal diagnostic method. It is slow, typically requiring at least 48–72 hours to be performed, often longer due to process delays. Meanwhile, patients are treated with empirical broad-spectrum antibiotics. Culture is an insensitive method and fails to identify a pneumonia pathogen in as many as 50% of cases.[2,3] Several faster and more sensitive molecular tests have recently been developed to address this issue.

Aims of work package 1

To compare the performance of three different molecular tests for the microbiological diagnosis of HAP and VAP with routine microbiological culture. We prospectively evaluated the BioFire FilmArray Pneumonia Panel, Curetis Unvyero Pneumonia panel and Oxford Nanopore Technologies (ONT) MinION nanopore metagenomic sequencing. Nanopore sequencing was introduced mid-way through the WP, when withdrawal of the originally planned Novodiag test was confirmed. We evaluated analytical performance, ease of use, user acceptability and suitability for deployment into a routine setting.

Methods

Routine lower respiratory samples (sputum, tracheal aspirates, endotracheal tube exudates and BALs) were included if they had sufficient volume (> 400 µl) and were from patients within a participating ICU, hospitalised for ≥ 48 hours and about to receive a new or change of antibiotic to treat a suspected lower respiratory tract infection (LRTI). Samples were eligible if collected within 12 hours of antibiotic initiation. Sample and relevant patient details were collected.

Clinical samples were evaluated within 72 hours of collection using the BioFire FilmArray Pneumonia Panel and the Curetis Unyvero pneumonia panel (see *Appendix 1*, *Table 19*), following the manufacturers' standard operating procedures (SOPs), or frozen within 72 hours and tested later. A proportion of specimens had MinION nanopore metagenomics sequencing performed within 7 days of collection using a bespoke processing protocol developed during a sub-project of this programme.[4] The specimens were tested at two sample processing sites: University College London and the University of East Anglia; supplementary reference tests were also undertaken.

A bespoke database was developed in Research Electronic Data Capture (REDCap).

Analyses were carried out using Stata® (v 15) (StataCorp LP, College Station, TX, USA) and R (v 3.5 or above) (The R Foundation for Statistical Computing, Vienna, Austria), and followed a predefined, detailed statistical plan. Diagnostic performance was estimated for each polymerase chain reaction (PCR) target, taking routine microbiology results as the gold standard. Estimates were also calculated using BLC models[5,6] incorporating results from both PCR tests, and routine microbiology.

Results

Recruitment for INHALE WP1 took place between 14 September 2016 and 31 May 2018, with 652 eligible samples collected across 15 participating sites. The majority, 60.1%, were from VAP patients, while 39.9% came from those with HAP. Routine culture generated a result in a median time of 70.2 hours [interquartile range (IQR) 51.1–92.1 hours] and was positive for likely pathogens in 44.2% of samples. However, there was considerable site-to-site variation, with positivity for likely pathogens ranging from 29.5% to 85.7% across sites (*Figure 2*). This variation was much less pronounced by PCR. This demonstrates lack of standardisation in either (1) clinical diagnosis of HAP/VAP or (2) in the interpretation of respiratory culture across the UK, or both. It also highlights the unreliability of routine microbiology as a gold standard.

Routine culture isolated expected pathogens, with the most common organisms isolated being *Staphylococcus aureus*, *Pseudomonas aeruginosa* and Enterobacterales (*Figure 3*). Rates of antimicrobial resistance (AMR) among these key pathogens were relatively high. Virology results were as expected but only 17.3% of samples had routine virology performed.

There were 631 eligible test results for the Unyvero, and 632 for the FilmArray. The overall positivity rate was 60.4% for Unyvero and 74.2% for FilmArray, considerably higher than for routine microbiology (chi-squared test: $p < 0.0001$). Most samples had multiple organisms detected by PCR. The principal species detected by PCR and their relative prevalence were similar to routine microbiology (*Figure 4*). Among viruses detected by the FilmArray, rhinovirus was the most prominent ($n = 55$), followed by influenza A ($n = 29$) and B ($n = 25$).

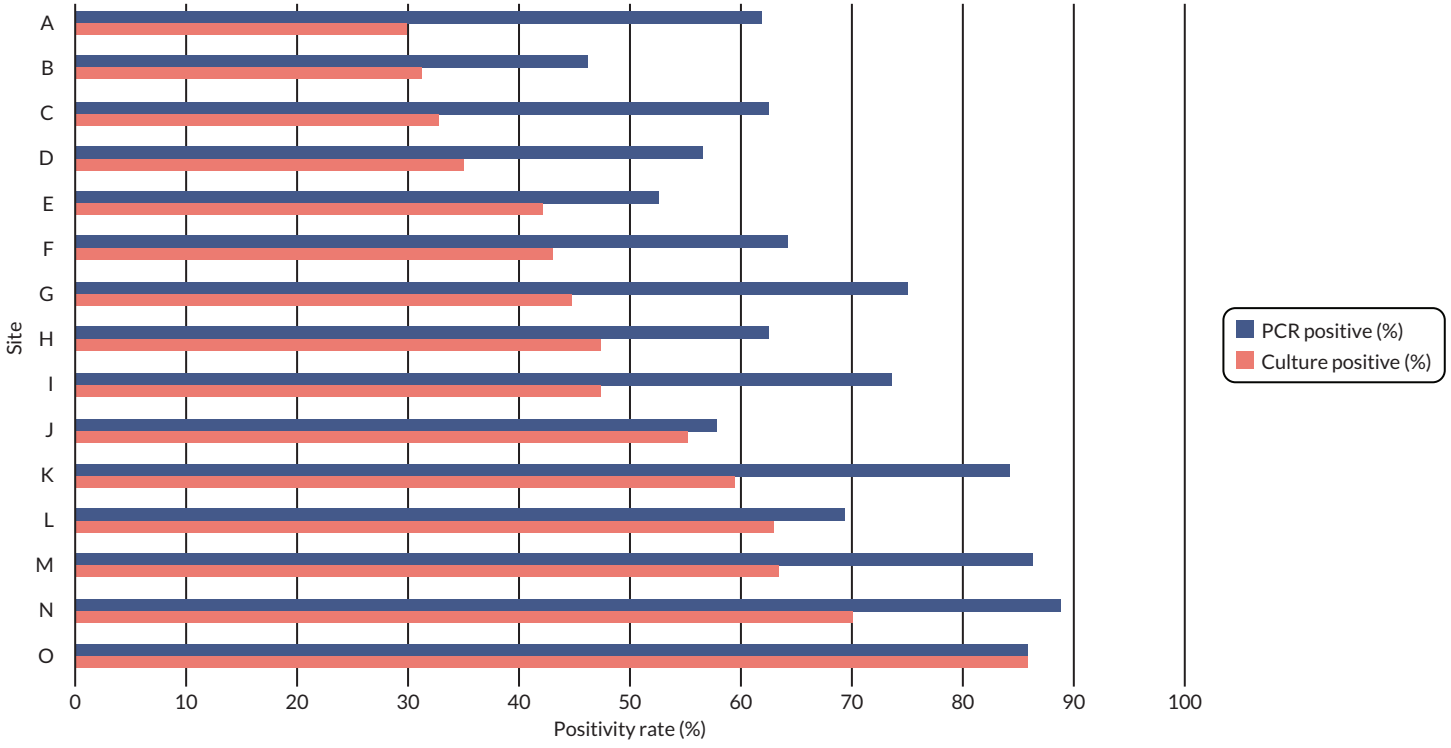


FIGURE 2 Sample pathogen positivity (%) by site using PCR vs. culture.

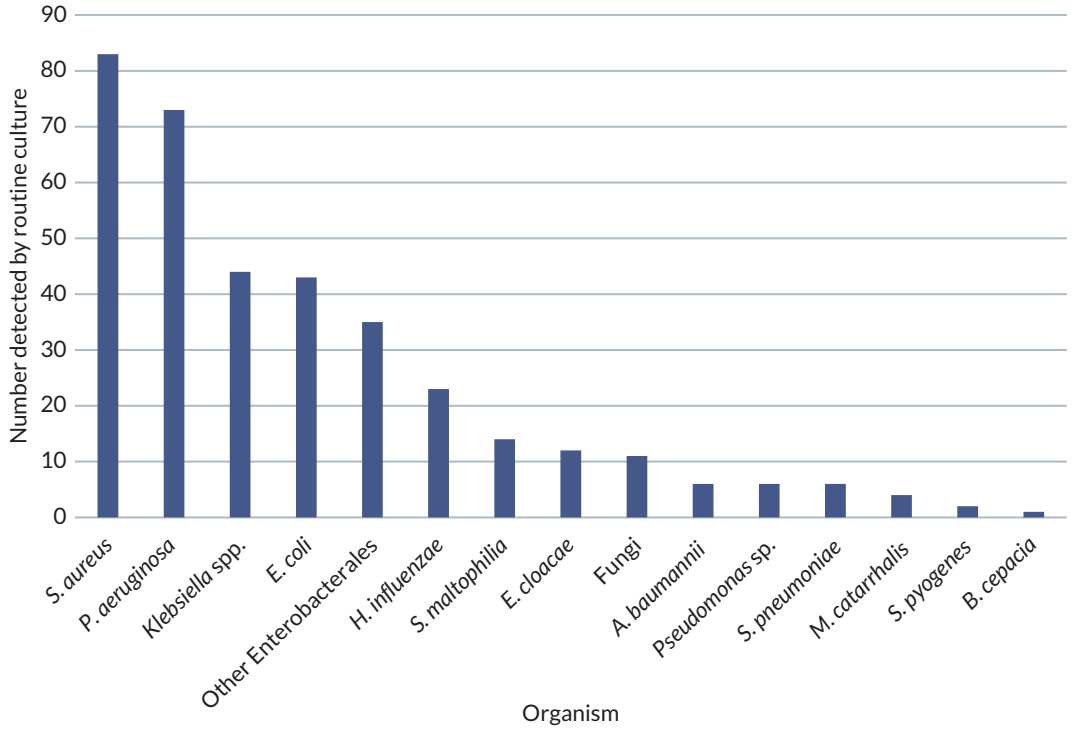


FIGURE 3 Frequency of bacterial pathogens isolated from WP1 samples by routine culture. Reproduced with permission from Enne *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

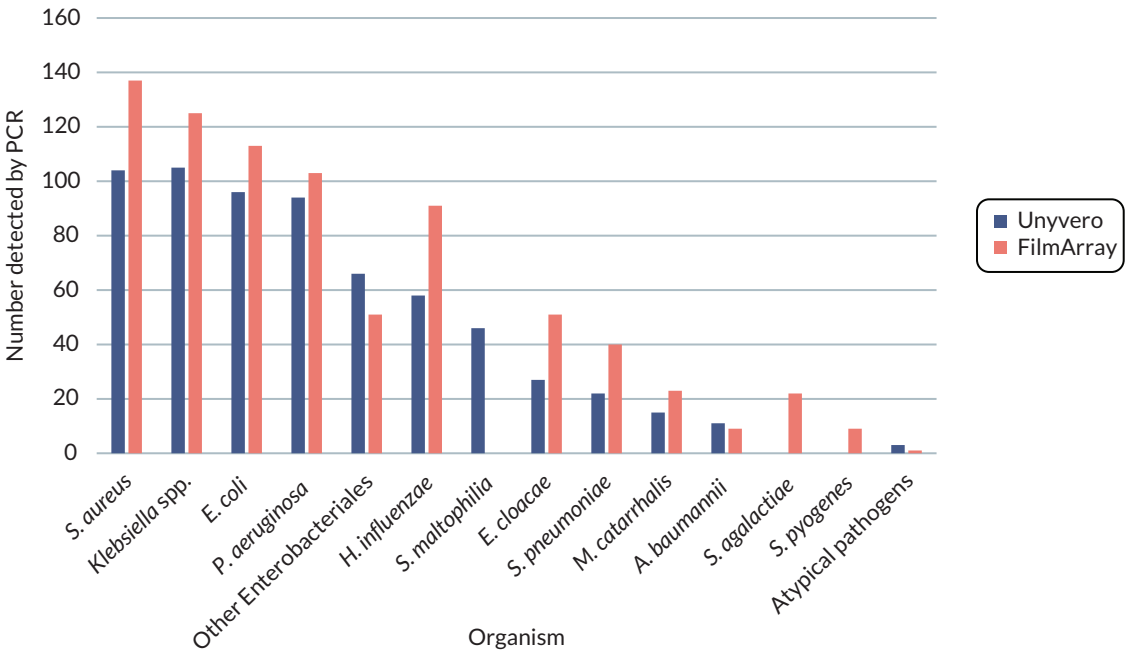


FIGURE 4 Frequency of pathogens in WP1 samples detected by the PCR tests. Reproduced with permission from Enne *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

Polymerase chain reaction assay sensitivity was > 95% for most targets, with negative predictive values (NPVs) > 98% (*Table 1*). Specificity and positive predictive values (PPVs) were lower, due to PCR tests detecting more organisms per sample and finding more positive samples than routine microbiology. Often, both PCRs found the *same* organism as each other when routine microbiology failed to record any organism, casting doubt on routine microbiology as a gold standard.[3]

We performed a range of analyses to accommodate for the observation that routine microbiology culture is an imperfect 'gold standard'. A concordance analysis was carried out to measure agreement between culture and PCR tests. Most results were either fully or partially concordant. Major discordance, where PCR failed to detect a cultured pathogen, was rare at 4.6% for Unyvero and 1.8% for FilmArray.

To address the problem of culture representing a poor gold standard, performance parameters were also obtained using BLC analyses.[5,6] This method accounts for all available results and makes no presumptions about one particular test being the reference. BLC analysis showed routine microbiology was the least sensitive technique, with sensitivity values for individual pathogens ranging from 27.1% to 68.7% (*Table 2*). In contrast, sensitivity values for the PCR tests remained high; FilmArray sensitivity ranged from 89.4% to 99.3% versus 83.9% to 96.9% (except *Klebsiella aerogenes*, 48.4%) for Unyvero. Specificity and PPV values for both PCR tests increased substantially compared with the values calculated using routine microbiology as a gold standard.[3]

TABLE 1 Pathogen-specific performance of PCR tests as compared with routine microbiology as the gold standard

	Unyvero				FilmArray			
Organism	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Acinetobacter baumannii complex	100.0	99.0	45.5	100.0	100.0	99.5	66.7	100.0
Citrobacter freundii	100.0	98.7	11.1	100.0	N/A	N/A	N/A	N/A
Enterobacter cloacae	100.0	97.5	44.4	100.0	91.7	93.4	21.6	99.8
Escherichia coli	87.8	89.4	37.5	99.0	97.6	87.5	36.3	99.8
Haemophilus influenzae	100.0	93.7	36.2	100.0	95.2	88.1	22.0	99.8
Klebsiella aerogenes	50.0	99.5	50.0	99.5	100.0	99.2	54.5	100.0
Klebsiella oxytoca	90.9	95.0	25.0	99.8	100.0	95.2	27.5	100.0
Klebsiella pneumoniae	83.3	94.2	37.0	99.3	92.0	91.4	31.1	99.6
Moraxella catarrhalis	100.0	98.2	26.7	100.0	100.0	96.9	17.4	100.0
Morganella morganii	100.0	98.3	9.1	100.0	N/A	N/A	N/A	N/A
P. aeruginosa	95.3	93.9	64.9	99.4	98.5	93.1	63.1	99.8
S. aureus	87.2	93.2	65.4	98.0	96.2	88.9	56.2	98.2
Streptococcus agalactiae	N/A	N/A	N/A	N/A	ND	96.5	0.0	100.0
Stenotrophomonas maltophilia	92.9	94.4	28.3	99.8	N/A	N/A	N/A	N/A
Serratia marcescens	77.8	98.3	41.2	99.7	100.0	98.2	45.0	100.0
Streptococcus pneumoniae	100.0	97.3	27.3	100.0	100.0	94.5	15.0	100.0
Streptococcus pyogenes	N/A	N/A	N/A	N/A	100.0	98.9	22.0	100.0

N/A, not applicable; organism not on test. ND, not determined because routine microbiology detected no positives.

Source

Reproduced with permission from Enne *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The table includes minor additions and formatting changes to the original text.

TABLE 2 Pathogen-specific performance of routine microbiology and PCR tests estimated using BLC models

	Routine microbiology				Unyvero				FilmArray			
Organism	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Acinetobacter baumannii complex	57.5	99.9	87.4	99.4	92.6	99.5	70.9	99.0	89.4	99.9	91.3	99.8
Enterobacter cloacae	42.9	99.9	94.6	97.2	94.9	99.9	97.2	99.8	94.2	96.4	56.1	99.7
Escherichia coli	38.8	99.7	96.1	88.5	89.6	99.7	98.6	97.8	98.9	98.7	94.2	99.8
Haemophilus influenzae	36.3	99.9	96.8	93.5	96.9	99.7	97.1	99.7	95.3	93.8	62.4	99.5
K. aerogenes	68.7	99.9	88.9	99.6	48.4	99.6	62.1	99.3	89.8	99.4	67.8	99.9
Klebsiella oxytoca	30.2	99.9	94.3	95.5	92.7	99.2	88.7	99.5	95.2	99.7	95.9	99.7
Klebsiella pneumoniae	37.8	99.5	89.3	93.5	88.9	99.8	97.6	98.8	98.1	97.7	82.2	99.8
Moraxella catarrhalis	27.6	99.9	86.7	98.0	89.0	99.9	95.5	99.7	95.7	98.9	71.4	99.9
P. aeruginosa	64.7	99.7	97.3	93.9	95.8	99.9	99.2	99.2	99.2	99.3	96.6	99.9
S. aureus	65.2	99.2	95.2	92.5	91.1	99.8	99.3	98.0	99.3	95.6	83.9	99.8
Serratia marcescens	48.4	99.9	92.9	98.4	83.9	99.9	95.7	99.5	96.1	99.8	94.2	99.9
Streptococcus pneumoniae	27.1	99.9	90.0	97.0	90.8	99.9	96.7	99.6	97.1	97.1	57.9	99.9

Note
Only organisms on both PCR panels are included.

Source
Reproduced with permission from Enne *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The table includes minor additions and formatting changes to the original text.

Due to the withdrawal of the Novodiag PCR test, resources were diverted to developing and evaluating a different method – nanopore metagenomic sequencing.[4] This method can generate a result in approximately 6 hours directly from a respiratory sample. It was used to evaluate a subset of 336 WP1 samples, 238 of which met quality control (QC) parameters. The distribution of organisms detected was similar to culture, with a sample positivity rate of 77%, slightly higher than that obtained by PCR. In terms of performance, overall sensitivity was 87.6% compared to culture, while specificity was 40.2%. We noted significant site-specific variation in sensitivity, ranging from 70% to 100%.

The final component of WP1 was the overall evaluation of the platforms and the choice of a suitable test for progression to WP3. We used criteria based on performance, user-friendliness and cost (see *Appendix 2*). Because all three molecular tests are much more sensitive than routine culture, it was further decided to add a concordance-based analysis alongside traditional sensitivity and specificity calculations of results compared with classical culture-based testing. Test platforms had to meet two essential criteria to be considered for progression for WP3. These were:

1. **Implementability**. The machine must be sufficiently developed to allow routine use in the NHS. The hands-on time required to process samples must be < 45 minutes and the machine must be usable by an operator with skill levels expected of a Biomedical Scientist Band 5 or lower. The test must have/or be close to obtaining CE-marking as an in vitro diagnostic (IVD) assay.
2. **Concordance.** Major discordance, that is failures by the test to find pathogen(s) detected by routine microbiology, must account for < 5% of all tests performed.

Tests that passed the 2 essential criteria where then scored against 10 'Desirable Criteria', scoring a total of 150 (see *Appendix 2*, *Table 20*). In addition to diagnostic performance, we also considered factors important for implementation in NHS settings. Some criteria were assessed based on known characteristics of the machines while the ease of use and quality of customer service were assessed using user questionnaires. The study's health economists calculated the cost-per-test, taking into account equipment purchase cost, delivery cost and staff costs. The scale was weighted towards accurate detection of pathogens, with implementation-based criteria given a lower weighting. A meeting was held to review the data and decide the platform to progress to WP3.

Nanopore metagenomic sequencing was judged to have failed against the essential criterion of implementability. The test has great potential due to the breadth of pathogens it can detect and the wealth of information generated. Nevertheless, the hands-on time and necessary skill required for processing made it unsuitable for an NHS diagnostic laboratory at the time, although improvements to the pipeline have since been made.

Both the FilmArray and Unyvero diagnostic platforms met the two essential criteria and were then scored against predefined and agreed 'desirable criteria' as outlined in *Appendix 2*. FilmArray scored 105 points versus 68 for Unyvero (*Table 3*). Unyvero was more concordant with routine microbiology, but FilmArray had better sensitivity; Unyvero had a broader target panel but more failed tests. FilmArray performed better on characteristics relating to implementation, ease of use, turnaround time and user experience. Accordingly, we progressed the FilmArray Pneumonia Panel for the INHALE WP3 RCT.[1]

Discussion and conclusions

Both PCR tests, the Unyvero and the FilmArray, were considerably faster than routine microbiology and detected more organisms, highlighting the known poor sensitivity of routine microbiology in pneumonia.[2,3] Notably, PCR tests tended to detect the *same* additional organisms in a given sample, implying these additional detections were '*real*'. This finding was corroborated by the fact that we were able to culture additional organisms using a comprehensive culture method. A limitation is that, unlike the molecular tests, routine microbiology was decentralised, performed across 11 different hospital laboratories, receiving specimens from the 15 ICUs.

To analyse test performance, we initially took routine microbiology as a gold standard. Only half of PCR results were fully concordant with routine microbiology, with the remaining partial concordances and minor discordances mostly reflecting additional organisms detected by PCR. Per-pathogen sensitivity performance was consistently good. Sensitivity and specificity values are similar to those reported by others for the two PCR tests.[7–10]

We adopted BLC analysis to overcome the limitations of routine microbiology culture.[5] Using BLC, (1) the sensitivity of routine microbiology was estimated to be extremely poor and (2) the specificity and PPV of the PCR tests were

TABLE 3 Scores allocated to PCR tests based on scoring system designed to evaluate overall performance, ease of use and implementability

	Machine score			
	Curetis Unyvero Pneumonia Panel		BioFire FilmArray Pneumonia Panel	
Criterion	Value	Score	Value	Score
Overall concordance (maximum 45 points)	74.8%	20	71.3%	16
Sensitivity for detection of common pathogens (maximum 20 points)	Three targets with better performance	6	Seven targets with better performance	14
Breadth of panel (maximum 15 points)	244 unique detections	15	191 unique detections	12
Time to result (maximum 15 points)	270 minutes	7	75 minutes	14
Cost-per-test (maximum 15 points)[a]	+++	10	++	15
Failure rate (maximum 15 points)	9.1%[b]	0	1.9%	11
Footprint (maximum 5 points)	7.4 sq. ft	1	3.2 sq. ft	5
Customer service (maximum 5 points)	–	3	–	4
Consumable logistics (maximum 5 points)[c]	–	0	–	5
Ease of use (maximum 10 points)	–	6	–	9
Total (maximum 150)	**–**	**68**	**–**	**105**

a Costs in the range of £150–300/test depending on local purchase conditions. Includes estimates of cost of instrument purchase and operator time.
b Includes both total and partial failures.
c Comprised of one point each for space required for storage, storage temperature, delivery cost, delivery timescales and shelf life.

Source
Reproduced with permission from Enne *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The table includes minor additions and formatting changes to the original text.

considerably higher than those calculated using routine microbiology as the 'gold' standard. This suggests that both PCR tests were superior to routine microbiology, and that the latter should perhaps not be considered a gold standard technique. A caveat is that it is perhaps predictable that two similar PCR tests (albeit with different primers and detection methods) should agree better with each other than with a dissimilar culture-based method.[1] A potential limitation is that PCR may detect residual nucleic acids from dead organisms, although our comprehensive culture data refute this. It should be noted that all patients in this study were severely ill, clinically diagnosed with respiratory infection and received antibiotic treatment; it therefore seems more reasonable to consider an organism found by any one method as potentially significant. The run times of the machines are measured in hours rather than the days required for culture. Total turnaround time for PCR could not be measured here because the tests were run retrospectively. However, we established that the median transport time of samples from the ICU to the laboratory was 6 hours. If the advantages of speed are to be realised, the machine must be placed in, or near to, the ICU. The decision of whether to adopt a rapid diagnostic into routine clinical practice will depend not only on its performance but also on the practicalities. Here, we evaluated potential for implementation, finding the FilmArray faster, smaller and easier to use then the Unyvero. Accordingly, we have taken the FilmArray Pneumonia Panel forward into INHALE's RCT described in WP3.

Work package 2: epidemiology of the units

Introduction

Intensive care unit patients are a complex and heterogeneous group of individuals in whom antimicrobial use is high. They are prone to healthcare-associated infections and can succumb to HAP or VAP, defined as pneumonia developing

48 hours after hospitalisation or ventilation, respectively. Clinical scoring systems such as sequential organ failure assessment (SOFA) for adults and paediatric logistic organ dysfunction (PELOD) for children can be used to measure their condition and prognosis. The rate of HAP and VAP among ICU patients is considerable, varying between 5% and 40% of patients, depending on the setting.[11] The attributable mortality of VAP in ICU is high, at 13% on average but is considerably higher in certain subgroups such as surgical patients or those with high severity scores on admission.[12] Treatment is generally with broad-spectrum antibiotics but with some variation depending on local resistance epidemiology and practises. The additional cost of HAP and VAP infections is considerable and has been estimated at around $40,000 per hospital stay.[13]

We conducted a detailed survey of HAP and VAP patients which enabled us to have better understanding of local bacterial epidemiology and prescribing practises.

Aims of work package 2

1. Define baseline HAP and VAP rates, and proportions of clinically diagnosed HAP/VAP patients with a pathogen identified by microbiology.
2. Determine and compare pathogen aetiology and resistance prevalence rates in HAP/VAP.
3. Review overall antibiotic resistance rates in each ICU. Review antimicrobial prescribing in the four ICUs.
4. Review clinical cure rates for HAP/VAP in relation to microbiological results (if any) and empirical antibiotics.
5. Therefore:
    i. Inform selection of the molecular test to progress to WP3.
6. Aid design of the step-up/step-down treatment algorithm for WP3. Collect patient-specific clinical data and scores of disease progression and severity; these will be used to assess any need for stratification of patients in WP3 and to formulate secondary outcomes. Key scores for which data will be collected are: SOFA score[14] and PELOD-2 score.[15]
7. Inform the descriptive health-economic analysis (WP5).

The overarching aim of this WP is to gather data for protocol development, outcome definition and the power calculation for the randomised trial performed in WP3.

Methods

Work package 2 took place at BUPA Cromwell, Great Ormond Street Hospital (GOSH), Norfolk and Norwich University Hospital (NNUH) and University College London Hospital (UCLH).

A protocol was prepared to define data collection and consent procedures. Eligible participants were inpatients within one of the four participating ICUs and had to be included in WP1. Additionally, they needed to provide consent for data collection, assent was given by parents or guardians in the case of child participants and relatives or a consultee in the case of those lacking capacity to consent.

Data were collected for up to 21 days after enrolment. Data included reason for admission, type of pneumonia, demographics, prior hospital stays, clinical scores (SOFA and PELOD-2), ventilation need, mortality, cure of pneumonia and antibiotic prescriptions during the study period and 15 days before enrolment. Additionally, a phone call was made to participants at the end of the study to establish their current health, current need for antibiotics and general practitioner use. The EuroQol-5 Dimensions, five-level version (EQ-5D-5L) quality-of-life questionnaire was performed during the phone call.

A bespoke REDCap database was made to aid data collection, which was primarily performed by research nurses from medical records. Core study staff checked data and determined whether antibiotics prescribed were appropriate and proportionate against pathogens found by routine microbiology or PCR (Unyvero or FilmArray). Five stewardship categories were defined for both routine microbiology and PCR results: (1) active and proportionate therapy, (2) active and disproportionate therapy, (3) inactive therapy, (4) negative result, therapy compliant with hospital guidelines and (5) negative result, therapy not compliant with hospital guidelines. These classifications were further aggregated to overall appropriate (active and proportionate and guideline compliant) and inappropriate (active and disproportionate, inactive and guideline non-compliant).

Unit-level data on antimicrobial prescribing and AMR were collected from hospital information systems. Prescribing data were extracted from pharmacy records, whereas microbiology data were obtained from Laboratory Information Management systems. Rates of HAP/VAP were estimated from WP1 screening logs. Denominators to calculate incidence rates were extracted from hospital bed-management records. We also reviewed each unit's empirical prescribing policies for HAP/HAP. Data were acquired for a period of 15 months from October 2016 to December 2017.

Data were analysed according to a predefined analysis plan using Stata (v 15) and R (v 3.5 or above). Descriptive summary statistics for participants were generated. Relationships between outcomes and appropriateness of treatment (described as two groups: appropriate or not) were investigated using multiple regression models adjusting for gender, age, site, antimicrobial therapy in the 15 days before enrolment and type of pneumonia and Pediatric Index of Mortality/Acute Physiologic Assessment and Chronic Health Evaluation score. Summary descriptions were generated for unit-level data.

Results

Patient-level data

One hundred and forty-two patients were recruited between 12 December 2016 and 29 May 2018. The numbers recruited per site were as follows: Cromwell (7), GOSH (35), NNUH (39) and UCLH (61).

Table 4 shows the baseline demographics of the WP2 population. The majority were male (65.5%); 75.4% were adults and the remainder were children. Adults had a median age of 65.1 years, while children had a median age of 1.0 years. The most common comorbidities were cardiovascular conditions, solid tumours and diabetes. The median length of hospitalisation prior to enrolment was 8.7 days, with a median time in ICU of 5.0 days; 52.1% had VAP and the remainder had HAP. Mean adult SOFA score at randomisation was 6.2, suggesting moderate severity of illness. Most participants had received antibiotics (for any condition) in the 15 days prior to enrolment (*Table 5*). The antimicrobials prescribed range from those commonly used as first-line agents such as amoxicillin–clavulanate, to those used in surgical prophylaxis (metronidazole) to broad-spectrum agents generally reserved for the seriously ill (piperacillin-tazobactam and meropenem).

TABLE 4 Baseline demographics of patients in WP2 (*n* = 142)

Demographics	Frequency (%)
Male	93 (65.5%)
Adults (18 + years)	107 (75.4%)
Age in adults (years)	
Mean (SD)	63.3 (14.7)
Median (IQR)	65.1 (54.2–74.5)
Children (all < 18 years)	35 (24.7%)
Age in children (years)	
Mean (SD)	2.7 (4.5)
Median (IQR)	1.0 (0.3–2.0)
Comorbidities (adults) (some had more than one)	
Cardiovascular	44 (41.1%)
Cancer – haematological	13 (12.1%)
Cancer – solid tumour	24 (22.4%)

continued

TABLE 4 Baseline demographics of patients in WP2 (*n* = 142) (*continued*)

Demographics	Frequency (%)
Chronic kidney disease/renal failure	15 (14.0%)
Chronic obstructive pulmonary disease	14 (13.1%)
Chronic liver disease/cirrhosis	7 (6.5%)
Diabetes	25 (23.4%)
Immunocompromised	11 (10.3%
Other	58 (54.2%)
Comorbidities (children) (some had more than one)	
Congenital cardiac malformation (excluding patent ductus arteriosus, secundum atrial septal defect)	16 (45.7%)
Chromosomal abnormality	5 (14.3%)
Chronic lung disease	7 (20.0%)
Inherited metabolic disease	3 (8.6%)
Immunocompromised	1 (2.9%)
Severe neurodevelopmental delay	3 (8.6%)
Other	11 (31.4%)
ICU admission	
Reason	
Medical	99 (69.7%)
Surgical	40 (28.2%)
Trauma	1 (0.7%)
Other admission	2 (1.4%)
Previous hospital admission within 3 months	61 (43.0%) denominator includes 21 unknowns
Previous ICU admission within 3 months	26 (19.0%) denominator includes 24 unknowns
Time in hospital since enrolment (days)	
Median (IQR)	8.7 (4.1–17.8)
Time in ICU since enrolment (days)	
Median (IQR)	5.0 (2.0–9.0)
Pneumonia and ventilation	
Type	
HAP	68 (47.9%)
VAP	74 (52.1%)
Ventilated: invasive	103 (72.5%)
Duration of ventilation (days)	
Media (IQR)	11.6 (5.4–24.9)

TABLE 4 Baseline demographics of patients in WP2 (*n* = 142) (*continued*)

Demographics	Frequency (%)
Clinical scores	
APACHE II score at ICU admission (adults, n = 101) [range: 0 (good)–55 (poor)]	
Mean	23.1 (7.9)
Median (IQR)	23.0 (19.0–27.0)
SOFA score in adults at randomisation (n = 100) [range 0 (good)–24 (poor)]	
Mean	6.2
Median (IQR)	6.0 (4.0–8.0)
PIM3 at ICU admission (children, n = 34) (probability of death: 0–1.0)	
Mean	0.25
Median (IQR)	0.10 (0.02–0.41)
PELOD-2 score in children at randomisation (n = 19) [range: 0 (good)–33 (poor)]	
Mean	6.9
Median (IQR)	8.0 (4.0–8.5)

SD, standard deviation.

Note
Numbers are frequency (%) unless otherwise stated.

TABLE 5 Antimicrobials prescribed in the 15 days prior to randomisation (some patients received more than one)

Antimicrobials	Number of participants receiving antimicrobial (%) (*n* = 142)
Any antimicrobial	122 (85.9)
Broad-spectrum antimicrobial	78 (54.9)
Narrow spectrum antimicrobial	44 (31.0)
Aminoglycosides	28 (19.7)
Amoxicillin–clavulanate	42 (29.6)
Cefuroxime	22 (15.5)
Ciprofloxacin	15 (10.6)
Carbapenems	15 (10.6)
Glycopeptides	29 (20.4)
Metronidazole	31 (21.8)
Piperacillin/tazobactam	39 (27.5)

Among the 142 patients, 73 (51.4%) received empirical treatment within the ambit of local guidelines, 46 (32.4%) received non-guideline empirical therapy and 23 received non-empirical therapy based on a susceptibility result. Commonly used regimens were piperacillin/tazobactam ± an aminoglycoside, coamoxiclav, ceftazidime or ciprofloxacin + teicoplanin.

Table 6 shows that when judged by either PCR result, more participants were considered to be receiving inappropriate treatment than when judged by routine microbiology. When considering routine microbiology results, 53.5% of therapy was inappropriate, compared to *circa* 60% for PCR. Furthermore, inactive therapy accounted for 14.1% of cases when judged by culture compared to 25–27% for PCR. This is explained by the finding that PCR tests found a pathogen more often than culture. This WP was observational and hence treating clinicians were not aware of the PCR results.

At day 21, 62.7% of patients were considered cured of pneumonia when using the definition in the WP2 protocol. This increased to 74.6% when the WP3 definition was used. The main difference between the two was that in WP2 any death was considered not cured, whereas in WP3 pneumonia was considered cured in those that died providing pneumonia did not contribute to the death. In the remaining analyses, the WP2 definition was used. Overall mortality at 21 days was 18%. *Figure 5* shows mean SOFA score over 21 days. Overall mean scores reduced over the 21-day period for those at NNUH and UCLH from an average of 6 to close to 4. In contrast, at the Cromwell, the mean score remained around 6.5 after 21 days. The association between clinical cure and average daily clinical score was investigated. Mean SOFA score over 21 days was 4.86 for those who were cured, compared to 6.20 for those who were not. This association was significant when examined using a regression model adjusting for confounders [odds ratio (OR) 0.63, 95% confidence interval (CI) 0.45 to 0.85, $p = 0.002$, $N = 99$]. However, in an equivalent analysis, a significant association was not identified in the smaller sample of children: mean PELOD-2 6.1 for those who were cured compared to 6.19 in those who were not; OR 0.96, 95% CI 0.64 to 1.47, $p = 0.85$, $N = 24$.

Table 7 shows cure rates per stewardship category. Overall, all three diagnostic methods show a slightly higher cure rate when treatment was judged appropriate as opposed to inappropriate. For routine microbiology, cure rates are reasonably similar across all five stewardship categories. However, in the case of PCR, cure rates are noticeable lower than for culture when inactive treatment for a positive result is given, at just 48.6% for FilmArray and 54.1% for Unyvero. This was significant for FilmArray ($\chi^2 = 6.02$, $p < 0.05$) but not Unyvero. A logistic regression analysis was used to investigate the relationship between clinical cure and appropriate versus inappropriate categories adjusting for confounders. This demonstrated that there was no statistically significant association between appropriateness of treatment and outcome for all three diagnostic methods (routine microbiology: OR 1.23, 95% CI 0.57 to 2.60; FilmArray: OR 1.51, 95% CI 0.69 to 3.38; Unyvero: OR 1.40, 95% CI 0.63 to 3.21).

Regression analyses were used to investigate the effect of appropriateness of antimicrobial therapy on mortality and mean SOFA or PELOD-2 score over the 21-day study period. No association between these clinical outcomes and appropriateness of therapy was identified by any diagnostic method.

Unit-level data

This WP collected unit-level prescribing and microbiology data from the participating ICUs. Obtaining data proved to be more difficult than anticipated as statistics on antimicrobial prescribing and microbiology results are not routinely collated by the hospitals.

TABLE 6 Classification of HAP/VAP therapy of participants according to diagnostic result

Classification	Routine microbiology (*n* = 142)	FilmArray (*n* = 138)	Unyvero (*n* = 136)
Positive, active and proportionate	20 (14.1%)	30 (21.7%)	27 (19.9%)
Positive, active and disproportionate	16 (11.3%)	26 (18.8%)	20 (14.7)
Positive, inactive	20 (14.1%)	35 (25.4%)	37 (27.2%)
Negative, guideline compliant	46 (32.4%)	25 (18.1%)	26 (19.1%)
Negative, guideline non-compliant	40 (28.1%)	22 (15.9%)	26 (19.1%)
Total appropriate	66 (46.5%)	55 (39.9%)	53 (39.0%)
Total inappropriate	76 (53.5%)	83 (60.1%)	83 (61.0%)

Note
Appropriate = active and proportionate and guideline compliant. Inappropriate = active and disproportionate, inactive and guideline non-compliant.

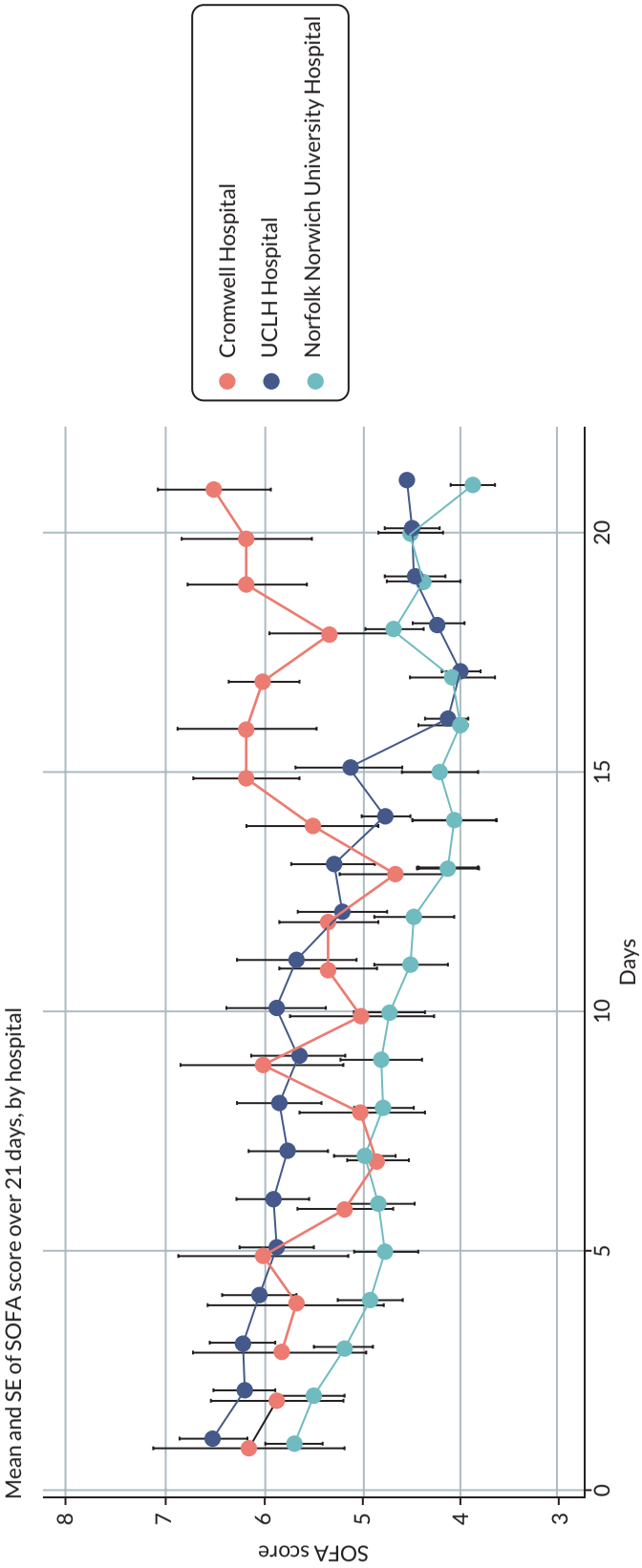


FIGURE 5 Mean SOFA score among adult WP2 participants from enrolment to day 21 (n = 101). SE, standard error.

TABLE 7 Cure rate among WP2 participants according to appropriateness of treatment

Classification	Routine microbiology (*n* = 142)	FilmArray (*n* = 138)	Unyvero (*n* = 136)
Positive, active and proportionate	12/20 (60.0%)	21/30 (70.0%)	18/27 (66.7%)
Positive, active and disproportionate	9/16 (56.3%)	19/26 (73.1%)	13/20 (65.0%)
Positive, inactive	13/20 (65.0%)	17/35 (48.6%)	20/37 (54.1%)
Negative, guideline compliant	31/46 (67.4%)	17/25 (68.0%)	17/26 (65.4%)
Negative, guideline non-compliant	24/40 (60.0%)	14/22 (63.6%)	17/26 (65.4%)
Total appropriate	43/66 (65.2%)	38/55 (69.1%)	35/53 (66.0%)
Total inappropriate	46/76 (60.5%)	50/83 (60.2%)	50/83 (60.2%)

Only two sites, UCLH and GOSH, had provided sufficient data to enable an estimate of the HAP/VAP incidence rate. At GOSH, the rate was 12.6 cases of HAP/VAP per 1000 bed-days, whereas, in the adult population at UCLH, it was almost double, 22.9 cases/1000 bed-days. UCLH ICU collected around 130 lower respiratory samples per quarter, compared to 180 at NNUH, a smaller unit. Cromwell collected 30, in keeping with its small bed numbers and data were unavailable for GOSH. There were discrepancies in the positivity rate of samples, with UCLH having a ~35% positivity rate compared to ~65% at Cromwell and ~80% at GOSH.

Figure 6 shows the distribution of organisms identified from positive respiratory samples. The NNUH and UCLH have the expected epidemiology for HAP/VAP, with sizeable proportions of *S. aureus*, Enterobacteriaceae and *P. aeruginosa*, while *Acinetobacter baumannii* accounted for < 2% of isolates. The Cromwell, with a patient population including a high proportion of previously hospitalised transfers from abroad, had a radically different epidemiology, dominated by *P. aeruginosa* and Enterobacteriaceae but with a substantial proportion (14%) of *A. baumannii*, and only tiny numbers of *S. aureus*. At GOSH, Enterobacteriaceae and *S. aureus* were common, but *P. aeruginosa* accounted for a much lower proportion of isolates than at other sites. In contrast, the traditionally community-acquired organisms, *Haemophilus influenzae* and *Moraxella catarrhalis*, were frequently isolated from LRTI samples at GOSH. These differences suggest a

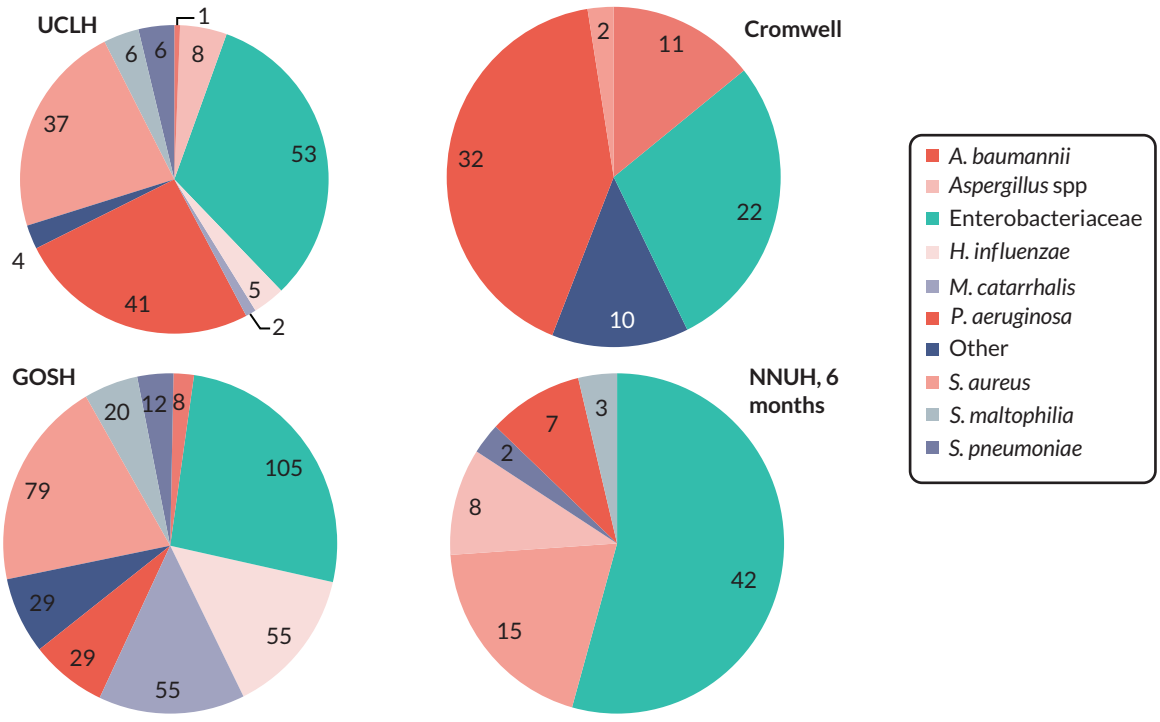


FIGURE 6 Pathogen epidemiology of ICU HAP and VAP at GOSH, NNUH, BUPA Cromwell and UCLH. Note: NNUH data relate to 6 months only, for winter 2016–7.

different aetiology of infections at GOSH, likely due at least in part to their paediatric patient population and a larger number of direct community admissions.

Figure 7 shows unit-level antimicrobial prescribing for all conditions. Prescribing tracked with epidemiological differences: the NNUH substantially used piperacillin/tazobactam as well as penicillins and aminoglycosides, UCLH – now unusually – was a heavy user of cephalosporins, while the Cromwell used carbapenems and colistin heavily, reflecting (1) high rates of beta-lactam resistance in Enterobacteriaceae and (2) the considerable numbers of carbapenem-resistant non-fermenters (*P. aeruginosa* and *A. baumannii*). Many of the latter organisms are from long-stay patients receiving prolonged therapy; thus, a small number of patients accounted for much of the unusually large colistin usage. At GOSH (*Figure 8*), the most commonly used antimicrobials were aminoglycosides, piperacillin/tazobactam and penicillins with comparatively less cephalosporin and carbapenem use.

Discussion and conclusions

Individual patient-level data collected from 142 patients enabled a better understanding of HAP/VAP patients ahead of protocol design for WP3. It was also useful for trialling collection of relatively complex data and enabled teething problems to be resolved. Prior use of antimicrobials in this group was high, and concerningly many had already received broad-spectrum and last-resort antimicrobial therapy.

When the appropriateness of empirical HAP/VAP therapy was compared to pathogen detection, a number of concerning findings were made. Only 46.5% of participants were receiving appropriate empirical therapy when judged against culture and 14% were predicted to have received inactive therapy. These figures worsened when judged against PCR, finding only ~39% receiving appropriate therapy and 25–27% receiving inactive therapy. Furthermore, those receiving inactive treatment by PCR also had lower cure rates. This may be a reflection of the greater sensitivity of PCR methods and suggests additional organisms observed using these tests are clinically significant and should be treated. However, such findings were not significant in a regression analysis, with the small sample size a likely contributory factor.

Unit-level data revealed considerable heterogeneity among different UK ICUs. Antimicrobial prescribing practices differed markedly between the units included. Similarly, there were notable differences in pathogen epidemiology. Differences in positivity rates of respiratory cultures were also noted here and in WP1 and allude to different processing practices at participating laboratories. These observations highlight the need for multicentre studies to ensure this diversity is captured.

Learnings from WP2 were incorporated into WP3 protocols.

Work package 3: randomised controlled clinical trial with internal pilot

Introduction

It is acknowledged that ICUs are the 'incubators of antibiotic resistance' – in that they concentrate those patients in need of antibiotics, who coincidentally also are at greatest risk of developing hospital-acquired infections. HAP and VAP are by far the most common infections in this context. Accordingly, the use of broad-spectrum antibiotics is particularly prevalent, prompting both the emergence of AMR and its spread in this cohort of acutely vulnerable patients. We leveraged learning from WP1 and WP2 to inform the design and execution of a RCT investigating the potential for rapid diagnostics to provide

1. superior antibiotic stewardship; and
2. at least equivalent clinical outcomes.

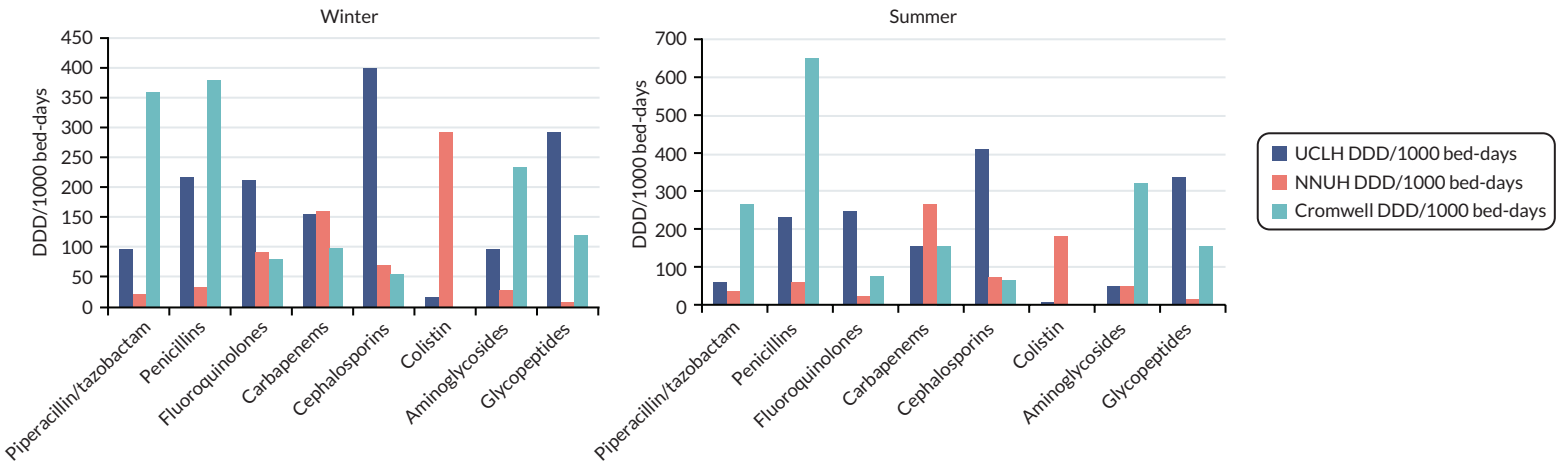


FIGURE 7 Adult antimicrobial prescribing in defined daily doses (DDDs)/1000 bed-days, ICU patients January–March 17 and October–December 17 ('Winter') and April–September 17 ('Summer').

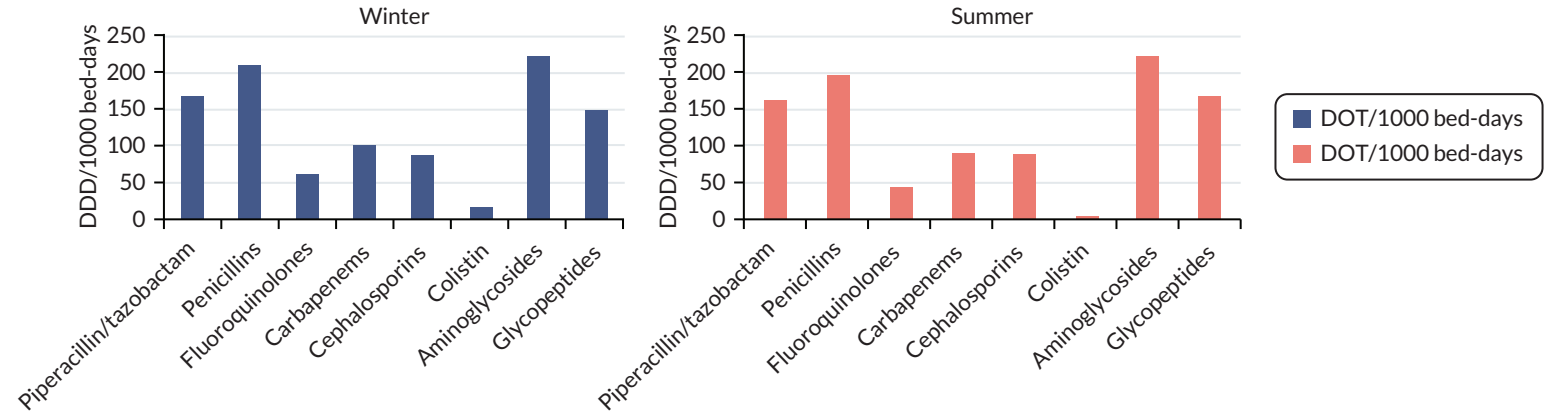


FIGURE 8 Children's antimicrobial prescribing in days of therapy (DOTs)/1000 bed-days, ICU patients January–March 17 and October–December 17 ('Winter') and April–September 17 ('Summer').

The trial was 'pragmatic' – defined by broad recruitment criteria to reflect the 'real life' elements of antimicrobial prescribing across UK ICUs. The FilmArray Pneumonia Panel diagnostic chosen in WP1 was placed at the point of care in participating ICUs to shorten time to result and improve clinical engagement. The diagnostic result was provided alongside an optional prescribing algorithm designed to promote good AMS.

Methods

Abbreviated methodology is described below and is extracted from the published protocol paper by High *et al.*[17]

Registration

The trial was registered with the following number: ISRCTN16483855 on 15 July 2019.

Design

A pragmatic, multicentre, open-label, parallel-group, RCT to investigate clinical, safety and cost-effectiveness of the FilmArray Pneumonia Panel test plus trial-based prescribing algorithm versus standard care, with the aim of showing non-inferiority in participant outcomes and superiority in AMS.

Inclusion and exclusion criteria

Patients were eligible if the following criteria were met:

1. About to receive an antimicrobial to treat a suspected lower respiratory infection (LRTI – including suspected HAP/VAP) for the first time, or a change in existing antimicrobial for LRTI because of deteriorating clinical condition. Inpatients in a participating ICU/critical care unit (CCU).
2. Hospitalised for > 48 hours.
3. Sufficient volume of airway specimen obtained for routine testing at site plus 200 µl for the FilmArray test.

Setting

The trial took place in 11 adult and 3 paediatric ICUs/CCUs across England. The group mainly consisted of NHS hospitals but included one private (adult) hospital.

Consent

Consent followed a retrospective process, due to the urgent need to treat ICU pneumonia promptly. Patients or their consultees were approached for consent as soon as possible after randomisation. For children (aged 15 years or under), the parent(s) or guardian were approached to give consent for their child to participate.

Randomisation and blinding

Participants were allocated in a 1 : 1 ratio to receive either standard care or the trial intervention, together with treatment as usual, using REDCap, a web-based randomisation system. Allocation was blocked (using blocks of randomly varying block length) and stratified by site.

Group assignment was concealed from all team members before randomisation, but subsequently the trial was open label to all except Stewardship Committee assessors.

Procedures

Patients in each group had a lower respiratory tract specimen collected before randomisation. For patients in the intervention group, part of the sample was run, as swiftly as possible, using the Pneumonia Panel performed in the ICU by a trained member of the clinical team. The ICU care team were provided with the results and a localised antimicrobial prescribing algorithm (see *Appendix 3*) translating the test's results to prescribing advice. For control patients, a portion of sample was frozen at −20 °C or below within 24 hours, and batched frozen samples from control patients were shipped to one of two central laboratories and tested on the Pneumonia Panel, but results were not provided to clinical teams. All samples underwent standard-of-care culture microbiological culture.

Outcomes

Coprimary outcomes

1. Non-inferiority in clinical cure of pneumonia at 14 days post randomisation.

Cure of pneumonia defined as: absence of (1) death where the pneumonia was considered causative or at least contributory, (2) septic shock (except when associated with a documented non-respiratory infection) and (3) relapse of the pneumonia. Relapse is defined as an infectious pulmonary event, associated with clinical and radiological signs of HAP or VAP, or a worsening of two points of the baseline multiple organ dysfunction score (SOFA or PELOD-2) or (4) other evidence that the original pneumonia is not cured.

2. Improvement in AMS at 24 hours post randomisation. Defined as:

Participants on active and proportionate antimicrobial therapy within 24 hours of clinical diagnosis, where active therapy is defined as receiving an antimicrobial active against the organism(s) in vitro and proportionate as defined in the prescribing algorithm specific to that site.

Secondary outcomes

1. ICU/CCU length of stay – time from randomisation to discharge from ICU/CCU
2. Number of ventilator-free days over 21 days post randomisation (VAP participants only surviving 21 days post randomisation)
3. Mortality – death from any cause within 28 days of randomisation
4. Incidence of septic shock – within 21 days of randomisation
5. Change in SOFA (ΔSOFA) score from randomisation to 7 days post randomisation (adults)
6. Change in PELOD-2 (ΔPELOD-2) score from randomisation to 7 days post randomisation (children)
7. Change in paediatric SOFA (pSOFA) (ΔpSOFA) score from randomisation to 7 days post randomisation (children)
8. Proportion of participants on antibiotics active/inactive against the pathogen(s) found at 24 and 72 hours from randomisation
9. Proportion of participants on proportionate/disproportionate antibiotics in relation to pathogen(s) found at 72 hours from randomisation
10. Proportion of participants on narrow-spectrum antimicrobials at 24 and 72 hours from randomisation
11. Proportion of participants with specific adverse events associated with antibiotics within 21 days from randomisation
12. Proportion of participants that contract a secondary pneumonia within 21 days from randomisation
13. Total antibiotic usage in defined daily doses (DDDs) at 21 days post randomisation (all conditions)
14. In patient-stay-related costs.

For each patient, a Stewardship Committee reviewed whether treatment was active and proportionate at 24 and 72 hours post randomisation in the light of *all* microbiological data from culture and molecular testing. The terms of reference can be found in the appendix (see *Appendix 4*).

Sample size and statistical analysis

Data for the first 100 patients from WP2 provided estimates for the initial sample size calculation. For the non-inferiority outcome, the clinical cure rate observed in WP2 (using WP3 definition) was 72.4%, and initial power calculation assumed a cure rate of 70%. Since including COVID-19 patients in the trial, cure rate of pneumonia decreased. The sample size calculation was updated to reflect a new assumed cure rate of 55% and defining a non-inferiority limit of 13%, required at least 528 participants to achieve 91% power (chosen to maintain 90% power for the coprimary analyses) with a significance level still at 5%.

From WP2 data we found, under standard care, that 53% of patients received antibiotics that were both appropriate and proportionate at 24 hours. A clinically important improvement rate of 20% was agreed (to 73%). With the sample

size of 528 participants required for the non-inferiority outcome, such a difference would be detected with 99% power at a 5% significance level. To allow for 5% attrition, the final sample size was agreed at 552 participants.

Analyses were based on ITT (all participants were analysed according to the group to which they were randomised, irrespective of the treatment received). and followed a predefined statistical analysis plan using Stata version 17 (StataCorp. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC; 2021). The detailed statistical analysis plan for WP3 is publicly available at https://norwichcrtu.uea.ac.uk/ctudocs_public/inhale/Analysis%20plan%20v1.0%20-%20INHALE%2022-02-2022.pdf

Protocol change: COVID-19

Due to the COVID-19 pandemic, the trial was halted in March 2020 and resumed in July 2020 with a protocol change to include participants known to have COVID-19, provided they met all other criteria. The updated sample size calculations were based on an assumption of around 30% of the final sample size being patients with COVID-19.

During the period the main trial was halted, an observational substudy, allowing use of the Pneumonia Panel in the clinical management of COVID-19 patients with suspected secondary bacterial infections was conducted at five trial sites. Data were collected around pathogens identified and antimicrobial prescribing.

Results

Recruitment

The first patient was randomised on 5 July 2019 and all sites were open by the end of the year. The COVID-19 pandemic forced the trial to halt recruitment on 16 March 2020, with 185 participants having been recruited. Recruitment resumed from July 2020, and was completed on 18 August 2021, some 6 weeks ahead of schedule.

Trial results

We recruited 554 patients, with primary outcomes calculable in 531, which included 92 children. Median age for adults was 61 years, and 7.5 months for children. At randomisation, 33.6% had COVID-19 infection (*Table 8* and *Figure 9*).

Time to result post randomisation was 36 times quicker in the intervention arm, at 1.7 hours [standard deviation (SD) 0.8] compared to 110 hours (SD 116.2) in the control arm.

TABLE 8 Baseline patient characteristics[2]

	Intervention (*n* = 276)	Standard of care (*n* = 269)
Demographics		
Male	184 (66.7%)	189 (70.3%)
Adults (18 + years)	228 (82.6%)	225 (83.6%)
Age in adults (years)	58.2 (16.2) [60 (47–71)]	59.4 (15.0) [61 (52–70)]
Children (all < 18 years)	48 (17.4%)	44 (16.4%)
Children (< 2 years)	34 (12.3%)	31 (11.5%)
Age in children (years)	2.6 (4.2) [0.5 (0.1–2.4)]	2.8 (4.4) [0.7 (0.2–3.2)]
Age in children (months)	31.6 (50.5) [5.5 (1.5–29)]	33.2 (53.0) [8.5 (2.5–38)]

continued

TABLE 8 Baseline patient characteristics (*continued*)

	Intervention (*n* = 276)	Standard of care (*n* = 269)
Ethnicity		
White British	147 (53.3%)	147 (54.7%)
White other	29 (10.5%)	35 (13.0%)
Indian, Pakistani or Bangladeshi	17 (6.2%)	15 (5.6%)
Asian other	19 (6.9%)	13 (4.8%)
Black Caribbean	1 (0.4%)	3 (1.1%)
Black African	5 (1.8%)	2 (0.7%)
Black other	12 (4.4%)	10 (3.7%)
Mixed race	4 (1.4%)	10 (3.7%)
Any other	6 (2.2%)	14 (5.2%)
Not stated	36 (13.0%)	20 (7.4%)
Comorbidities		
SARS-CoV-2 infection at randomisation[a]	93 (33.7%)	90 (33.5%)
Missing/unknown SARS-CoV-2 infection at randomisation[a]	25 (9.1%)	24 (8.9%)
Bloodstream infection in 7 days prior to randomisation	7 (2.5%)	18 (6.7%)
Missing	1 (0.4%)	1 (0.4%)
Abdominal	30 (10.9%)	26 (9.7%)
Cardiovascular	126 (45.7%)	128 (47.6%)
Cancer – haematological	11 (4.0%)	12 (4.5%)
Cancer – solid tumour	35 (12.7%)	28 (10.4%)
Chronic kidney disease/renal failure	15 (5.4%)	15 (5.6%)
Chronic lung disease	58 (21.0%)	52 (19.3%)
Chronic liver disease/cirrhosis	8 (2.9%)	17 (6.3%)
Congenital cardiac malformation (excluding PDA, secundum ASD)	17 (6.2%)	20 (7.4%)
Congenital, other	12 (4.3%)	11 (4.1%)
Chronic obstructive pulmonary disease	29 (10.5%)	22 (8.2%)
Diabetes	55 (19.9%)	56 (20.8%)
Immunocompromised	14 (5.1%)	13 (4.8%)
Mental health	26 (9.4%)	29 (10.8%)
Neurological	21 (7.6%)	19 (7.1%)
Postoperative	63 (22.8%)	57 (21.2%)
Rheumatological	19 (6.9%)	21 (7.8%)
ICU admission type		
Medical	194 (70.3%)	190 (70.6%)
Surgical	59 (21.4%)	52 (19.3%)

TABLE 8 Baseline patient characteristics (*continued*)

	Intervention (*n* = 276)	Standard of care (*n* = 269)
Trauma	16 (5.8%)	20 (7.4%)
Other	7 (2.5%)	7 (2.6%)
Elective admission	18 (6.5%)	18 (6.7%)
From emergency department	86 (31.2%)	77 (28.6%)
From elsewhere in hospital	112 (40.6%)	111 (41.3%)
From another hospital	60 (21.7%)	63 (23.4%)
Type of pneumonia		
HAP	84 (30.4%)	87 (32.4%)
VAP	191 (69.2%)	182 (67.7%)
Data missing	1 (0.4%)	0
Ventilation status at randomisation		
Not ventilated	31 (11.2%)	33 (12.3%)
Ventilated: non-invasive	10 (3.6%)	7 (2.6%)
Ventilated: invasive	234 (84.8%)	228 (84.8%)
Data missing	1 (0.4%)	1 (0.4%)
LRT sample type		
Endotracheal tube exudate	185 (67.0%)	183 (68.0%)
BAL	43 (15.6%)	36 (13.4%)
Non-directed BAL	4 (1.5%)	8 (3.0%)
Sputum	37 (13.4%)	33 (12.3%)
Other	7 (2.5%)	9 (3.4%)
Received antimicrobials for any indication in 7 days prior to randomisation	255 (92.4%)	245 (91.2%)
APACHE II score at ICU admission (adults) [range: 0 (good)–55 (poor)]	24.6 (9.3) [25 (16.5–31)] (*n* = 204)	23.5 (7.9) [24 (17–29)] (*n* = 199)
SOFA score in adults at randomisation (*n* = 454)[b]	6.8 (3.0) (*n* = 228)	7.1 (3.0) (*n* = 226)
PIM3 at ICU admission (children) (probability of death: 0–1.0)	0.11 (0.19) [0.05 (0.03–0.11)] (*n* = 48)	0.11 (0.13) [0.06 (0.02–0.15)] (*n* = 43)
pSOFA score in children at randomisation (*n* = 91)[b]	4.7 (2.3) (*n* = 48)	4.9 (1.9) (*n* = 43)
PELOD-2 score in children at randomisation (*n* = 91)[b]	5.1 (1.9) (*n* = 48)	6.0 (2.3) (*n* = 43)

ASD, atrial septal defect; PDA, patent ductus arteriosus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

a The method for determining SARS-CoV-2 status depended on time of randomisation. Routine ICU SARS-CoV-2 screening data were collected for all patients after 2 July 2020. Prior to 16 March 2020, the study did not formally recruit COVID-19 patients, but we recognised that there may have been unknown cases of SARS-CoV-2 in early 2020. Accordingly, available frozen samples were retrospectively tested for SARS-CoV-2 by PCR but did not recover any positives among 55 samples. We have assumed all those recruited prior to 1 January 2020 were SARS-CoV-2 negative. Those recruited between 1 January 2020 and 16 March 2020 where no sample was available for testing have been treated as unknowns.

b Score on day 1 for those patients randomised on day 1, and day 2 for those patients randomised on day 2. Missing values imputed with mean values.

Note

Data are *n* (%), mean (SD) or [median (IQR)].

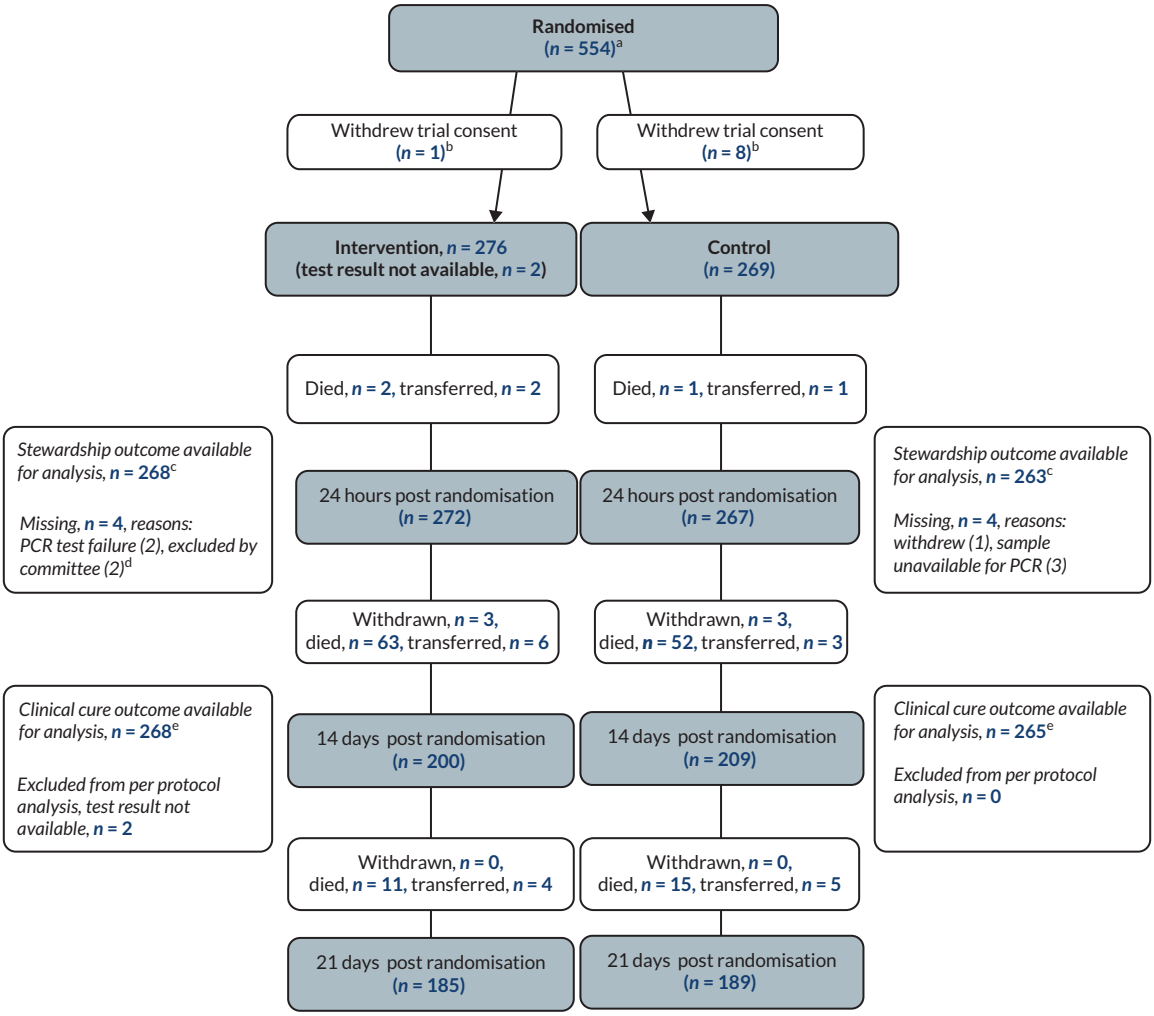


FIGURE 9 Study profile. Shaded boxes indicate numbers still being followed up. a Four additional patients (one intervention, three control) were randomised but later found to be ineligible. These four are excluded from numbers in the figure. b These withdrawals represent nine participants who were initially randomised but subsequently withdrew consent to all aspects of the trial including use of any of their data. Data for these patients were removed prior to analysis. c Death does not impede 24-hour stewardship outcome from being determined unless the participant died before 24 hours. d Two further participants were excluded by stewardship committee due to ineligibility, one was clearly moribund at recruitment and the other was a case of neonatal sepsis with no signs of pneumonia. e Death at any time does not impede 14-day clinical cure outcome from being determined. Clinical cure was also available for some patients who were transferred to another hospital (***n* = 3** intervention, ***n* = 3** control).

Intention-to-treat analysis for the coprimary superiority (stewardship) outcome at 24 hours after randomisation showed that 205/268 (76.5%) intervention arm participants were receiving active and proportionate antibiotics 24 hours after randomisation, as adjudged by the Stewardship Committee, versus 147/263 (55.9%) in the control arm [estimated difference after accounting for site 21%, 95% CI 13% to 28% (OR 2.57, 95% CI 1.77 to 3.73), $p < 0.001$].[16] Importantly, 8.6% of patients in the intervention group were considered to be on inactive antibiotics at 24 hours, as opposed to 22.4% – a threefold difference (*Table 9*).

One hundred and fifty-two of 268 (56.7%) intervention arm participants had clinical cure of pneumonia at 14 days, versus 171/265 (64.5%) control patients. The estimated difference, after accounting for site, was −6% with 95% confidence limits of −15% to 2%. These values overlap the non-inferiority margin of 13%, meaning that non-inferiority was not established.[16] Adjusting for age, baseline SOFA/pSOFA, COVID status and bloodstream infection in the 7 days preceding randomisation slightly reduced the estimated difference and CI [estimated difference −5% (95% CI −12% to 3%)], with the lower limit now falling just within the non-inferiority region (*Table 10*).

TABLE 9 Antimicrobial stewardship-related primary and secondary outcomes

	Intervention	Standard of care	Treatment effect estimates (intervention vs. standard of care)[a]	
	n/N (%)	*n/N* (%)	Difference in proportions (95% CI)	Odds ratio (95% CI)
Active and proportionate antibiotics at 24 hours (n = 531)				
	205/268 (76.5%)	147/263 (55.9%)	0.21 (0.13 to 0.28) $p < 0.001$	2.57 (1.77 to 3.73)
Active antibiotics at 24 hours (n = 531)				
	245/268 (91.4%)	204/263 (77.6%)	0.13 (0.07 to 0.20)	3.12 (1.86 to 5.25)
Active and proportionate antibiotics at 72 hours (n = 516)				
	185/252 (73.4%)	150/255 (58.8%)	0.15 (0.07 to 0.23)	1.95 (1.34 to 2.85)
Active antibiotics at 72 hours (n = 516)				
	230/252 (91.3%)	208/255 (81.6%)	0.10 (0.04 to 0.16)	2.36 (1.38 to 4.06)
Patients on narrow-spectrum antimicrobials at 24 hours (n = 539)				
	47/272 (17.3%)	44/267 (16.5%)	0.005 (−0.06 to 0.07)	1.06 (0.67 to 1.68)
Patients on narrow-spectrum antimicrobials at 72 hours (n = 516)				
	74/257 (28.8%)	61/259 (23.6%)	0.05 (−0.02 to 0.13)	1.32 (0.88 to 1.97)
DDD of antibiotics administered in ICU, up to 21 days (n = 526)				
	Mean (SD) [median (IQR)]		Difference in means (95% CI)	
DDD/day in ICU	1.2 (1.1) [1.0 (0.5–1.7)] *n* = 264	1.3 (1.3) [1.0 (0.5–1.6)] *n* = 262	−0.08 (−0.26 to 0.11)	

a Difference in proportions from mixed-effects binomial generalised linear model with identify link, using a random effect for study site (Stata command *gllamm*). ORs from mixed-effects logistic regression models with a random effect for site (Stata command *melogit*).

TABLE 10 Primary and secondary clinical outcomes

	Intervention	Standard of care	Treatment effect estimates (intervention vs. standard of care)[a]	
	n/N (%)	*n/N* (%)	Difference in proportions (95% CI)	Odds ratio/hazard ratio (95% CI)
Clinical cure at 14 days				
'Intention to treat' analysis	152/268 (56.7%)	171/265 (64.5%)	−0.06 (−0.15 to 0.02)	OR 0.68 (0.47 to 0.98)
'Per protocol' analysis	150/266 (56.4%)	171/265 (64.7%)	−0.06 (−0.15 to 0.02)	OR 0.68 (0.47 to 0.98)
All-cause mortality at 28 days (n = 538)				
	85/272 (31.3%)	75/266 (28.2%)	0.05 (−0.01 to 0.11)	HR 1.18 (0.87 to 1.61)
Septic shock within 21 days of randomisation (n = 519)				
	37/262 (14.1%)	31/257 (12.1%)	0.03 (−0.01 to 0.07)	1.23 (0.72 to 2.10)
Antibiotic-induced diarrhoea within 21 days of randomisation (n = 520)				
	26/263 (9.9%)	14/257 (5.5%)	0.04 (0.001 to 0.09)[b]	1.95 (0.97 to 3.93)
Secondary pneumonia within 21 days of randomisation (n = 519)				
	25/263 (9.5%)	31/256 (12.1%)	−0.03 (−0.08 to 0.03)[b]	0.76 (0.43 to 1.23)

continued

TABLE 10 Primary and secondary clinical outcomes (*continued*)

	Intervention	Standard of care	Treatment effect estimates (intervention vs. standard of care)[a]	
	n/*N* (%)	*n*/*N* (%)	Difference in proportions (95% CI)	Odds ratio/hazard ratio (95% CI)
ICU length of stay, days (up to 28 days)				
	Median (IQR)			
All patients (*n* = 539)	11 (6–25) (*n* = 274)	13 (6–26) (*n* = 265)	–	HR[c] 0.95 (0.82 to 1.10)
Patients surviving to 28 days (*n* = 393)	14 (7–28) (*n* = 196)	14 (7–28) (*n* = 197)	–	–
Patients not surviving to day 28 (*n* = 146)	7 (4–12) (*n* = 78)	10 (5–15.5) (*n* = 68)	–	–
Ventilator-free days (up to day 21)				
	Median (IQR)			
All patients (*n* = 517)	2 (0–16) (*n* = 261)	2 (0–16.5) (*n* = 265)	–	OR 0.98 (0.72 to 1.35)
Patients surviving to day 21 (*n* = 371)	11 (1–18) (*n* = 184)	9 (1–18) (*n* = 187)	–	OR 1.10 (0.77 to 1.58)

HR, hazard ratio or sub-hazard ratio; –, not calculated.
a From generalised linear mixed models with a random effect for study site or Cox model with gamma distributed shared frailty for site (Stata command *stcox*), as appropriate.
b Due to small numbers, analyses did not account for site and CIs were obtained using the method of Agresti and Caffo.[18]
c Sub-hazard ratio from Cox competing risks model for time until discharge (length of stay) and death (Stata command: *stcrreg*).

Analyses of secondary outcomes supported the primary stewardship results, with improvements consistently apparent for the intervention arm. More intervention arm participants had active and proportionate antibiotics at 72 hours and more received active antibiotics (irrespective of proportionality) at 24 and 72 hours, with differences relative to the control arm being statistically significant. Only 16.9% of patients received narrow-spectrum antibiotics at 24 hours, with no significant differences between arms. There were no differences in antibiotic consumption between the two arms as measured by DDD. There was a tendency for control arm participants to receive more broad-spectrum antimicrobials, principally aminoglycosides, carbapenems and piperacillin–tazobactam, whereas intervention arm participants received more narrow-spectrum drugs, although this did not reach significance. Antibiotic-associated diarrhoea was more frequent in the intervention arm, occurring in 26/263 (9.9%) patients, versus 14/257 (5.5%) in the control arm [estimated difference after accounting for site 6% (95% CI 4% to 9%)] (see *Tables 9* and *10*).

Twenty-eight-day mortality was 31.3% in the intervention arm and 28.2% in the standard-of-care arm. A Kaplan–Meier plot (*Figure 10*) shows higher risk of death for the intervention group, but this was not significant in a Cox regression analysis. No significant differences between arms were observed for ICU length of stay, ventilator-free days, incidence of septic shock or occurrence of secondary pneumonia. Trends in organ dysfunction over time were measured in both adults and children. We found no significant differences in the degree of reduction of these scores in either adults or children or between trial arms. No severe or unexpected adverse events were reported in either trial arm.

COVID substudy

During the closure of the main RCT during the first wave of the COVID-19 pandemic, a substudy was performed at five participating sites (UCLH, Royal Free Hospital, Watford, Aintree and Chelsea and Westminster) allowing the Pneumonia Panel to be used prospectively on ICU patients suspected of a secondary bacterial infection. Results were collected to help understand the microbiology of secondary respiratory infection in COVID-19 patients, as well as antimicrobial prescribing in COVID-19 patients and utility of the Pneumonia Panel.

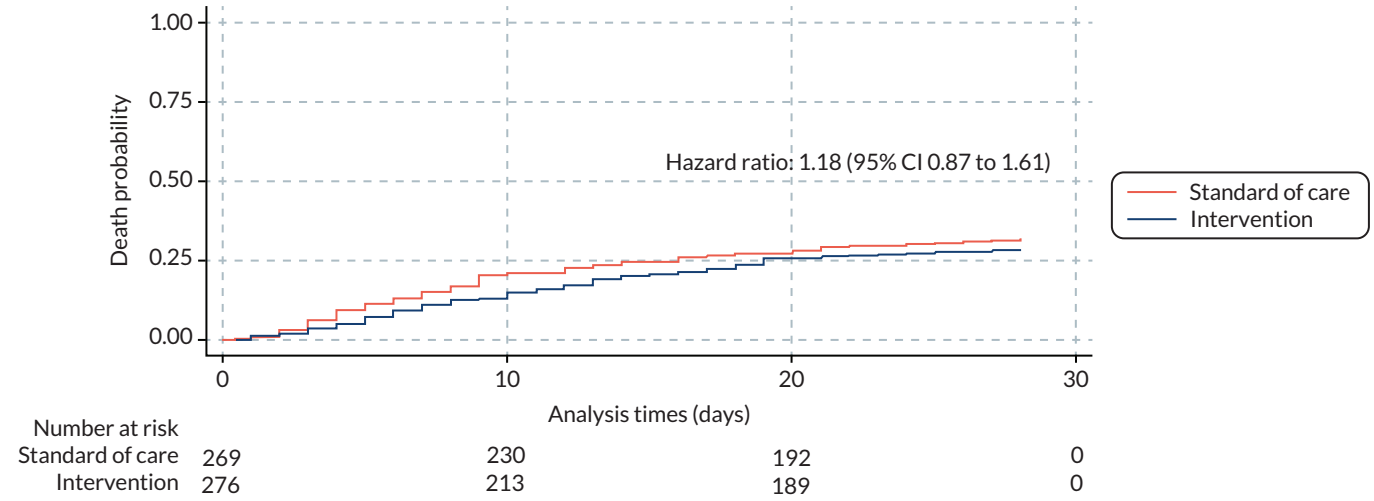


FIGURE 10 Kaplan–Meier plot for mortality.

A total of 157 tests were performed for 126 patients (31 patients were tested twice, 5 or more days apart) between March and May 2020. Also, 55.0% of tests had a bacterial pathogen identified, *Klebsiella pneumoniae* the most common organism. Pathogens found were those typically associated with HAP and VAP; community-associated bacteria and viruses were rare. Comparison with FilmArray results from an equivalent pre-COVID population in WP1 revealed *Klebsiella* spp. were more prevalent ($p \leq 0.008$) while *S. aureus*, *P. aeruginosa* and *Escherichia coli* ($p \leq 0.001$) were less common. Antibiotic data were available for 121 patients. Sixty-four per cent of patients were on antibiotics 24 hours before FilmArray testing; this figure rising to 74% 24 hours after testing (*Table 11*). Twenty-two out of 44 patients with positive results continued on the same antibiotic 24 hours after the test, 19 patients were changed following a positive result including 5 changes from inactive to active therapy. Among the remaining 23 patients who were off antibiotics prior to the test, 16 were commenced on antibiotics within 24 hours following a positive result. Antibiotics were stopped in 10/34 patients within 24 hours of a negative test result.

Discussion

INHALE WP3 was a pragmatic trial, including any critically ill adult or child with HAP or VAP for whom the treating clinician had decided to start or change antibiotics. Placing the diagnostic in the ICU and providing a prescribing algorithm, tailoring treatment to the pathogen(s) and AMR gene(s) detected, allowed for evidence-based therapy to be prescribed some 36 times faster than in the standard-of-care arm. The Pneumonia Panel led to a highly significant, 21% absolute improvement in antibiotic stewardship (relative change 37%), defined as the proportion of HAP and VAP patients on active and proportionate therapy 24 hours post randomisation. This advantage persisted at 72 hours. In

TABLE 11 Antimicrobial therapy in COVID-19 patients before and after FilmArray was performed

Spectrum of antimicrobial therapy	24 hours before positive FIlmArray	24 hours after positive FilmArray	24 hours before negative FilmArray	24 hours after negative FilmArray
No antibiotics	23	10	20	24
Inactive antibiotics or antibiotics for negative result	12	7	34	32
Appropriate spectrum	7	16	N/A	N/A
Broader spectrum than necessary	25	34	N/A	N/A

N/A, not applicable.

addition, patients in the intervention arm were three times less likely to be on inactive antibiotic therapy 24 hours post randomisation. Despite these significant improvements, INHALE WP3 failed to confirm non-inferiority of clinical cure at 14 days.

Secondary clinical outcome measures – mortality and evolution of the SOFA score – also favoured the control arm but differences were not significant. Given the borderline results, there is uncertainty whether we have observed a small but meaningful effect in favour of the control arm or perhaps confounding 'noise', recognised to commonly affect ICU trials.

Many previous evaluators assert, based upon laboratory results, that deployment of rapid diagnostics *might* improve antibiotic prescribing, although findings are variable and not definitive. This RCT's results considerably contribute to this current state of knowledge, in that they demonstrate very clear and significant advantages in time to diagnosis, antibiotic stewardship and reduction in the proportion of patients on initial inactive therapy.

Nonetheless, non-inferiority of clinical cure was not met and exploratory analyses suggested that the patients driving this result were predominantly those from whom a pathogen had been isolated and who had received antibiotics deemed 'active and proportionate' (data not shown). We offer several possible explanations.

First, this result remains within the bounds of chance variation.

Second, we have more closely examined our definition of 'clinical cure' in pneumonia, which was to the European Medicine Agency standard.[19] The 'cure' assessment was made at 14 days by the Intensivist who had been responsible for the patient, who by then was unblinded to the trial arm. Assessment of pneumonia 'Cure' is acknowledged as subjective.[20] Lack of blinding in the assessment of cure was a limitation of the design. We note that this judgement represents a composite outcome influenced by many factors, besides continuing infection. Third, we considered whether our algorithm's recommendations prompted inferior treatment. This seems unlikely: cure was more frequent in those who received treatment consistent with the algorithm compared to those who did not (data not shown), suggesting that it was not driving failures. Fourth, we noted poorer clinical outcomes in the intervention arm concentrated at particular sites, whose in-depth analysis was not possible for want of statistical power.

Fifth, COVID-19: cure rates were worse for COVID-19 patients, and differences in cure rates between arms were more pronounced. Anecdotally, clinicians reported that COVID-19 complicated the judgement of clinical cure in this cohort.

Last, there is the disturbing possibility that HAP and VAP are not, ab initio, infections caused by the few species sought by culture or multiplex PCR. Rather, the early stages may entail aspiration events, with mixed oral anaerobes, or dysbiosis of a putative lung flora not routinely looked for by either standard or molecular techniques. In short, our results may reflect organisms and/or inflammatory processes, undetected by classical and molecular microbiology are additional important drivers of pneumonia. Metagenomics techniques may provide more insight into this possibility. If this is the case, then brief early broad antimicrobial therapy may be advantageous, just as it is universally accepted against the mixed flora typical of intra-abdominal sepsis. Results here indicated a greater usage of broad-spectrum antibiotics like carbapenems and piperacillin-tazobactam in the control arm.

Use of the Pneumonia Panel in COVID-19 patients revealed a subtly different epidemiology of HAP and VAP compared to non-COVID-19 patients. The Pneumonia Panel influenced antimicrobial prescribing in patients with both positive and negative results and increased the proportion of patients receiving appropriate therapy. The relatively low proportion of appropriate therapy overall reflects the uncertainties and challenges clinicians faced in the first wave of the COVID-19 pandemic.

Work package 4: behavioural study

Understanding antibiotic decision-making processes in ICU settings, where uncertainty is the norm, is key to optimising AMS programmes and the introduction of new rapid molecular microbiology diagnostic tests into clinical practice. Little is understood about clinicians' perceptions of using these tests. Clinicians' endorsement and uptake of rapid molecular

diagnostics are crucial to maximise engagement with any future integration into routine care. Yet, adoption may be impeded if users harbour unaddressed concerns or if device usage is incompatible with local practice. Therefore, to support optimal implementation, it is vital we understand these better.

Aims

The overarching aim of WP4 was to assess clinicians' willingness to adopt molecular diagnostics and treat patients based on their results, by exploring ICU clinicians' attitudes towards molecular diagnostics and antibiotic prescribing both before and after deployment of the 'Pneumonia Panel'. We conducted four separate but related studies which addressed the following objectives.

Objectives

1. To explore clinicians' perceptions of antibiotic decision-making and the social and environmental aspects surrounding these perceptions ('contextual factors') (Study 1).
2. To explore clinicians' general perceptions about the use of rapid molecular microbiology diagnostic tests as a prescribing aid (Study 2).
3. To explore clinicians' perspectives of the use of the 'Pneumonia Panel' test in ICU after implementation in the INHALE RCT (WP3) (Study 3).
4. To explore clinicians' perceptions about antibiotics and the 'Pneumonia Panel' at the time of prescribing, and how these and other contextual factors may influence their antibiotic decision-making for patients with suspected HAP/VAP (Study 4).

Study 1: exploring clinicians' perceptions of antibiotic prescribing for patients with hospital-acquired pneumonia/ventilator-associated pneumonia in intensive care unit

Some text in this section has been reproduced with permission from Pandolfo *et al.*[21] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

Objective: Study 1 explored how clinicians' beliefs, perceptions and other contextual factors influenced ICU clinicians' antibiotic prescribing for HAP/VAP patients.

Method: Focus groups and interviews were conducted with clinicians in four English ICUs. Focus groups explored contextual factors perceived to influence antibiotic decisions. Interviews investigated antibiotic decision-making processes using two clinical vignettes depicting fictitious pneumonia patients (see *Appendix 5*). Data were analysed using thematic analysis, applying the Necessity Concerns Framework (NCF). The NCF has been used extensively to understand patients' medication adherence, positing that decisions to start and continue with treatments are influenced by how individuals judge the necessity for treatment relative to their concerns about the actual or potential adverse consequences of doing so. This is the first study to apply the NCF to prescribing behaviour. All focus groups and interviews were audio-recorded, anonymised and transcribed.

Results: We conducted 4 focus groups and 34 semistructured interviews with 35 clinicians (*Table 12*).

Analysis of the transcripts identified two key themes: (1) clinicians' perceptions of antibiotic necessity outweighing concerns, and (2) contextual factors (*Figure 11*).

Clinicians' perceptions of antibiotic necessity outweighing concerns

Clinicians' antibiotic decisions were influenced by their judgement of the necessity for prescribing/not prescribing, relative to their concerns about potential adverse consequences. Clinicians' perceptions about the necessity for antibiotics were heavily influenced by their beliefs that antibiotic prescriptions would successfully protect both their patients from deterioration and themselves from the potential consequences of undertreatment (e.g. guilt, litigation). Clinicians also described concerns about prescribing antibiotics. These generally concentrated on AMR; however, the

TABLE 12 Characteristics of study participants[21]

	Focus groups	Vignette-based interviews
Number of participants	**Total**: 26	**Total**: 34[a]
	Hospital 1: 11	*Hospital 1*: 11
	Hospital 2: 5	*Hospital 2*: 10
	Hospital 3: 5	*Hospital 3*: 7
	Hospital 4: 5	*Hospital 4*: 6
Participants' roles	*Hospital 1*: 5 ICU consultants, 2 ICU middle-grade trainees, 1 ICU early-career trainee, 1 clinical microbiologist, 1 ICU pharmacist, 1 health psychologist	*Hospital 1*: 4 ICU consultants, 4 ICU middle-grade trainees, 3 ICU early-career trainees
	Hospital 2: 1 ICU consultant, 3 ICU pharmacists, 1 infectious diseases consultant	*Hospital 2*: 3 ICU consultants, 7 ICU middle-grade trainees
	Hospital 3: 2 ICU middle-grade trainees, 2 ICU pharmacists, 1 nurse	*Hospital 3*: 2 ICU consultants, 5 ICU middle-grade trainees
	Hospital 4: 2 ICU consultants, 1 ICU middle-grade trainee, 1 clinical microbiologist, 1 ICU pharmacist	*Hospital 4*: 2 ICU consultants, 4 ICU early-career trainees

a Interviews occurred individually, except in one case where one early-career trainee and one middle-grade trainee were interviewed together.

desire to protect the individual patient was often prioritised over these societal concerns. Few clinicians described antibiotic toxicity to be a key influencer. Clinical uncertainty frequently complicated the balancing of antibiotic necessity against concerns. Clinicians' decisions to initiate or continue antibiotics often signified 'erring on the side of caution'.[21] This approach was reinforced by previous experiences of negative consequences ('being burnt') which motivated prescribing 'just in case' of infection.

Contextual factors

Data highlighted that prescribing decisions were also context dependent such as prescribing antibiotics out-of-hours, input from external team members, and local prescribing norms.

Discussion: Findings highlight the complex nature of antibiotic prescribing in ICU. Clinicians must juggle two sometimes contradictory imperatives: (1) protect the patient (and prescriber) now, versus (2) safeguard societal future (e.g. against AMR). Clinicians viewed antibiotics' necessity (i.e. protection for their patients and themselves) as outweighing concerns about antibiotic toxicity and AMR. Findings suggest that stewardship initiatives may be more effective if they address clinicians' desire to protect with a prescription.

Study 2: exploring clinicians' general perceptions of rapid multiplex molecular diagnostic technology and its potential role in improving prescribing decisions

Objective: Study 2 was conducted to explore ICU clinicians' general beliefs about rapid molecular diagnostics.

Methods: These data come from the Study 1 interviews but were analysed separately to explore clinicians' beliefs about rapid molecular diagnostics. The data met Fine and Kurdek's criteria for publishing multiple reports from one data set.[22] Interview data were analysed using thematic analysis, applying the NCF.

Study 2 has been published by Pandolfo *et al* 2021.[23]

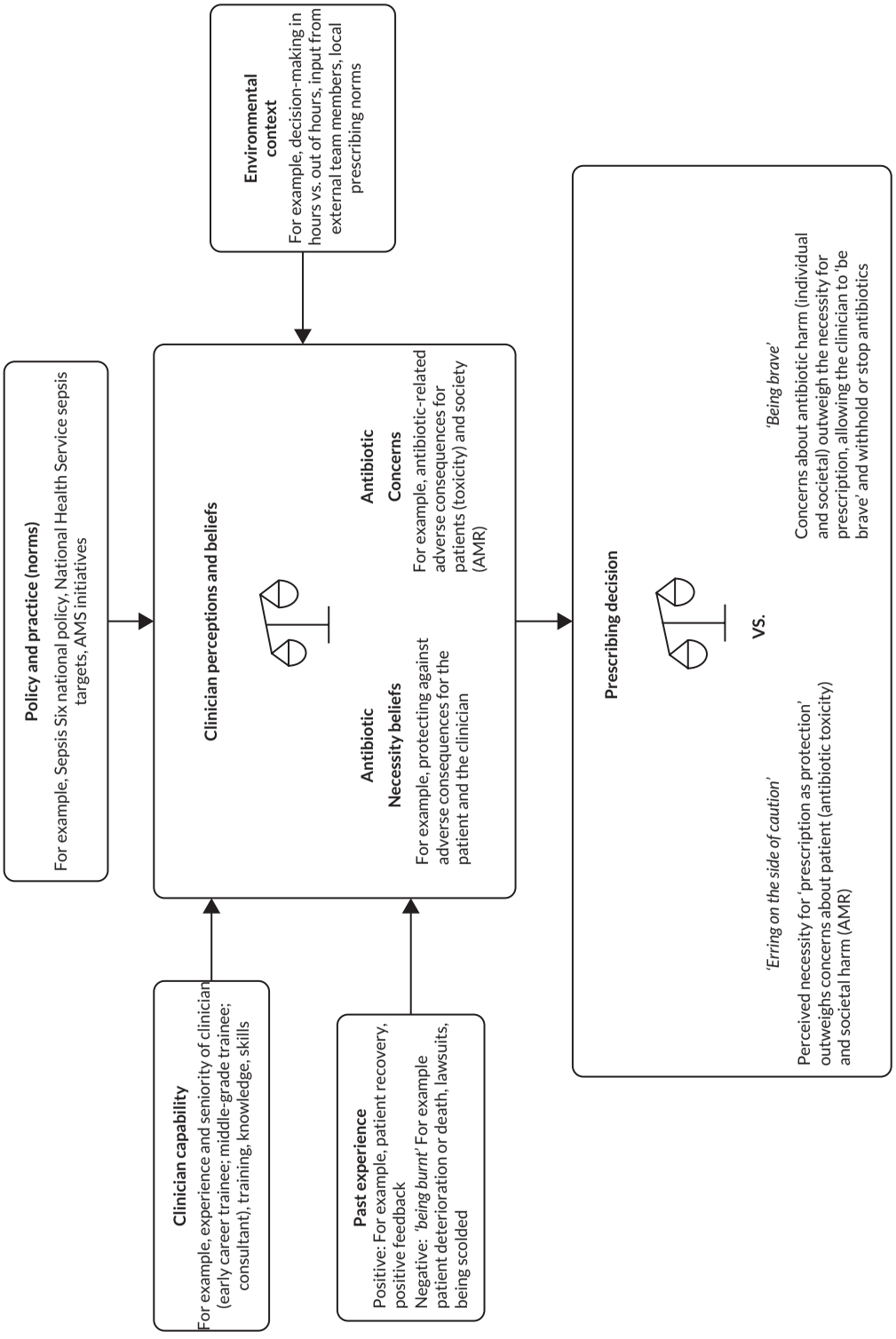


FIGURE 11 Factors influencing ICU clinicians antibiotic prescribing in clinical uncertainty.

Results: Analysis was conducted on 34 semistructured interviews with 35 critical care doctors working in four ICUs in the UK (see *Table 12*). We identified two key themes reflecting clinicians' general perceptions of rapid molecular microbiology diagnostic technology and its potential role in improving prescribing decisions: (1) clinicians' perceived potential of molecular diagnostics to improve antibiotic prescribing (rapid molecular diagnostic necessity) and (2) clinicians' concerns about how test results could be implemented into practice (rapid molecular diagnostic concerns).

Rapid molecular diagnostic necessity

Clinicians' perceptions that rapid molecular diagnostic tests are necessary stemmed from beliefs that positive results would facilitate targeted antimicrobial therapy; that negative results would signal the absence of a pathogen, and consequently that having the molecular diagnostic results would bolster prescribing confidence.

Rapid molecular diagnostic concerns

Concerns about the use of rapid molecular diagnostic tests included unfamiliarity with the device's capabilities, worry that it would detect non-pathogenic bacteria, uncertainty whether it would fail to detect pathogens, and discomfort with withholding antibiotics until receiving test results.

Discussion: Our findings highlight the importance of prescribers' beliefs as determinants of molecular diagnostic uptake. Although clinicians were broadly open to using molecular diagnostics, they harboured concerns about their capabilities and integration into practice. This research highlights that there are still unanswered questions and uncertainties among clinicians regarding the place of rapid molecular diagnostic technologies in ICU.

Study 3: exploring clinicians' perceptions of the 'Pneumonia Panel' in intensive care unit, within the context of their actual antibiotic prescribing within the INHALE randomised controlled trial (work package 3)

Objective: This study examines actual antibiotic prescribing in ICU settings within the context of the INHALE RCT (WP3). It explores how molecular diagnostics were applied in practice with particular emphasis on the specific beliefs that reinforced clinicians' perceptions of the necessity to apply molecular diagnostics and those that enhanced concerns about doing so.

Method: Semistructured interviews were conducted with clinicians with experience of using the 'Pneumonia Panel' test for at least one INHALE intervention arm patient. Data were analysed using thematic analysis, applying the NCF, to examine factors reinforcing the necessity for, and increasing concerns about, use of the 'Pneumonia Panel'.

Study 3 has been published by Stewart *et al.*[24]

Results: Twenty semistructured interviews with ICU clinicians (16 ICU consultants, 4 consultant clinical microbiologists) were transcribed and analysed. We identified two key themes relevant to clinicians' perceptions about using the 'Pneumonia Panel' within context of their actual prescribing: (1) factors reinforcing the necessity for the 'Pneumonia Panel', and (2) factors increasing concerns about using the 'Pneumonia Panel'.

Factors reinforcing the necessity for the 'Pneumonia Panel' test

Many clinicians described that the rapidity of the results of the 'Pneumonia Panel' enabled earlier refinement of antimicrobial therapy. Clinicians also described how often the results were used in combination with other evidence (e.g. inflammatory markers in blood tests). Clinicians felt that both positive and negative 'Pneumonia Panel' results increased their confidence in prescribing under conditions of clinical uncertainty, particularly when results corroborated the patient's clinical picture and other results. Many perceived that positive 'Pneumonia Panel' results improved antibiotic choice and stewardship. Clinicians also valued negative results; some described de-escalating or stopping antibiotics as a result because bacterial respiratory infection was unlikely or interpreted negative results to signal a non-respiratory infection.

Factors increasing concerns about using the 'Pneumonia Panel' test

Clinicians had variable knowledge of the test's inherent limitations; for example, some were unsure of the panel's targets and were subsequently concerned about the improper treatment of drug-resistant organisms and atypical infections. Some highlighted doubts about the consistency and quality of the respiratory samples and their impact

on 'Pneumonia Panel' result reliability. Many clinicians also had worries that false-positive/negative results may encourage antibiotic over- and undertreatment, respectively. There was uncertainty about how results would integrate with existing stewardship initiatives and communications and wanted clarification on the test's evidence base for clinical usage.

Discussion: Clinicians perceived 'Pneumonia Panel' results to have improved their antibiotic decision-making and local AMS. However, much like our findings from Study 2, clinicians also harboured a number of concerns about the application of molecular diagnostics. The prevalence of these concerns suggests that there may be considerable barriers towards the implementation of these tests, and that experience of using molecular diagnostic technology does not necessarily simplify the decision to prescribe broad-spectrum antibiotics. It is essential that these barriers are addressed, possibly through the integration of behavioural support into implementation strategies.

Study 4: investigating clinicians' 'in the moment' views about antibiotics and rapid molecular diagnostic tests, and how these and other contextual factors may relate to clinicians' prescribing for patients with suspected hospital-acquired/ventilator-associated pneumonia

Objective: Study 4 investigated the specific factors influencing clinicians' antibiotic prescribing decisions, and whether these varied for patient cases in the INHALE RCT (WP3) intervention arm compared with control arm. This study also explored clinicians' perceptions of their prescribing adherence to local Trust guidelines and the INHALE trial prescribing algorithm recommendations.

Methods: EMAs were designed to capture ICU clinicians' decision-making processes for specific antibiotic decisions for INHALE patients. Clinicians making antibiotic decisions in both study arms in the RCT were asked to complete a short 1-minute questionnaire within 24 hours of their prescribing decision (see *Appendix 6*). One questionnaire was completed per prescribing decision. Questionnaires explored factors influencing their prescribing, and clinicians' self-reported adherence to (1) local Trust guidelines, (2) 'Pneumonia Panel' results and (3) INHALE trial prescribing algorithm (*Figure 12*). Descriptive statistics were run to present an overview of factors influencing prescribing decisions. We also explored whether these factors significantly differed between test arms using chi-square analyses.

Study 4 has been published by Stewart *et al.*[25]

Results: We received 282 eligible questionnaires (159 intervention arm questionnaires; 123 control arm questionnaires) (*Table 13*).

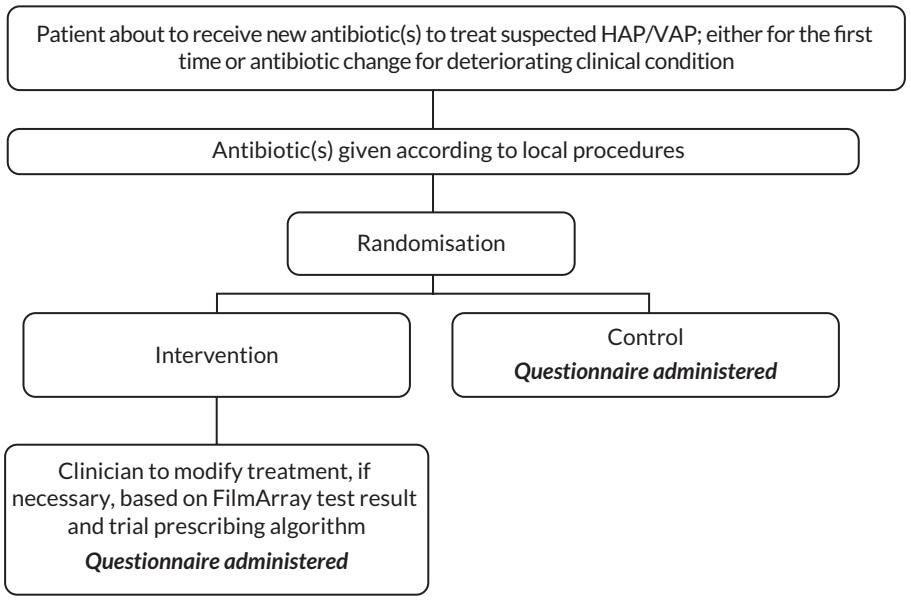


FIGURE 12 Ecological momentary assessment questionnaire administration flow diagram.

TABLE 13 An overview of clinician specialty/grade completing questionnaires for each prescribing instance

	Total, 282 cases	Control, 123 cases (43.62%)	Intervention, 159 cases (56.38%)
ICU consultant	192 (68.09%)	85 (69.11%)	107 (67.30%)
ICU middle-grade trainee	51 (17.6%)	21 (17.07%)	27 (16.98%)
ICU early-grade trainee	1 (0.35%)	0	1 (0.63%)
Consultant microbiologist	37 (13.12%)	15 (12.20%)	22 (13.84%)
Nurse practitioner	2 (0.71%)	1 (0.81%)	1 (0.63%)
Unknown	2 (0.71%)	1 (0.81%)	1 (0.63%)

Factors influencing antibiotic prescribing decisions

Most factors were only influential for a small proportion of decisions (*Figure 13*). 'Trust guidelines/Unit SOPs' was the most frequently reported factor to influence antibiotic decisions across the total sample (56.7%; *N* = 160). They influenced significantly more control arm antibiotic decisions (74.0%; *N* = 91), compared with intervention arm decisions (43.4%; *N* = 69), $\chi^2(1) = 26.43$, $p < 0.001$. No other variables differed significantly between arms (all $p > 0.05$).

Influence of staff

Clinicians often indicated other staff members to influence their prescribing decisions, mostly ICU consultants (63.48%, *N* = 179). Staff influence did not significantly differ between arms (*Figure 14*).

Influence of other contextual factors

The relevance of other contextual factors for prescribing decisions varied (*Figure 15*). Clinicians frequently identified the clinical deterioration of a patient and laboratory or radiological evidence of deterioration to be relevant factors for their antibiotic decisions. Significantly fewer clinicians agreed that the initial antibiotic prescription for respiratory tract infection or other infection was appropriate and did not need to be changed for control arm decisions (22.0%; *N* = 28), compared with intervention arm decisions (47.5%; *N* = 76), $X^2(1) = 18.67$, $p < 0.001$.

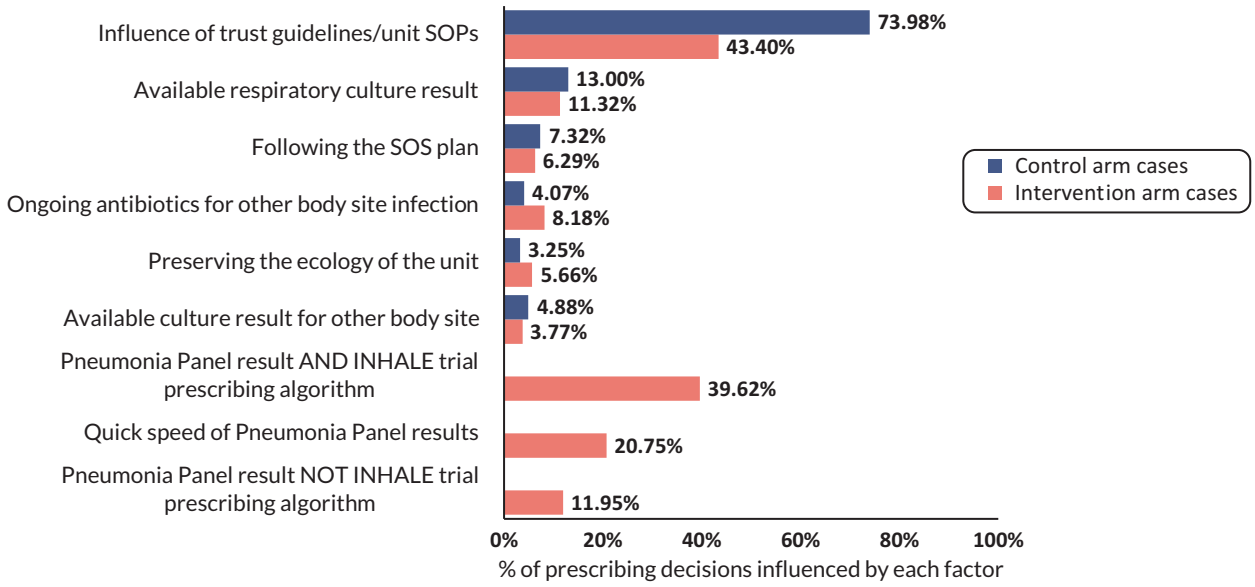


FIGURE 13 The percentage of prescribing decisions influenced by each factor.

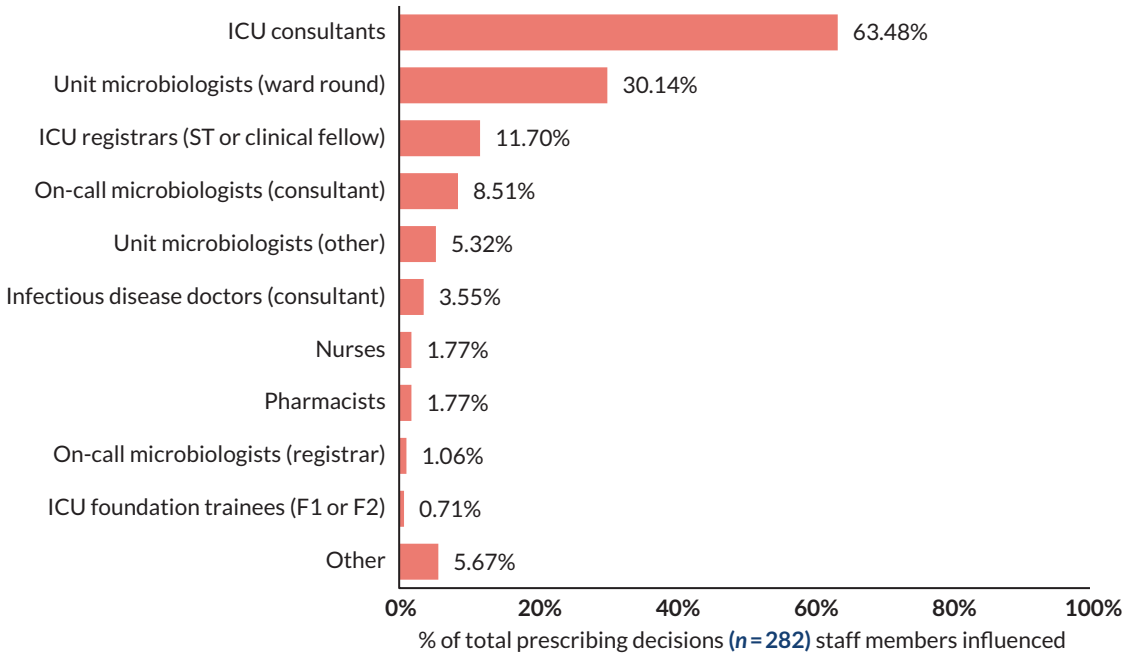


FIGURE 14 The percentage of total prescribing decisions (*N* = 289) influenced by other staff members.

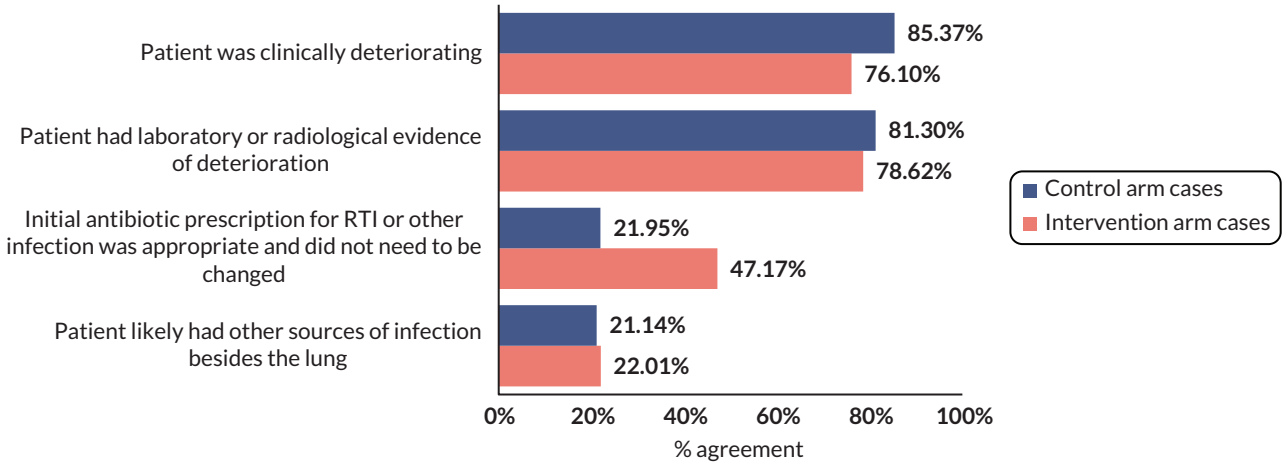


FIGURE 15 The percentage of clinicians agreeing with each statement relating to their prescribing decision. RTI, respiratory tract infection.

Clinicians' confidence in, and perceived prescribing adherence to, Trust guidelines

Confidence in local trust prescribing guidelines was low, with clinicians reporting a lack of confidence in guidelines in 25.9% (*N* = 69) of cases from the whole sample. Only 66.4% (*N* = 75) of clinicians had confidence in guidelines in control arm cases, compared with 79.74% (*N* = 122) of intervention arm cases, $\chi^2(1) = 6.05$, $p = 0.014$. Clinicians reported a surprisingly high level of prescribing non-adherence to Trust guidelines. Across the total sample, 24.6% (*N* = 69) of prescribing decisions were reported to not be consistent with Trust guidelines.

Clinicians' confidence in, and perceived prescribing adherence to, INHALE algorithm recommendations

Across intervention arm cases, clinicians' confidence in, and prescribing adherence to, 'Pneumonia Panel' results and INHALE trial algorithm recommendations was relatively low. In 88.3% (*N* = 98) of cases, clinicians considered the INHALE trial prescribing algorithm to be easy to interpret and understand, and in 82.7% (*N* = 82) of cases, clinicians had confidence in what the algorithm was recommending (see *Table 6*). However, only 59.6% (*N* = 62) of clinicians perceived their decisions as adherent to the prescribing algorithm.

Discussion

Hospital guidelines support the choice of empirical antibiotics with an unknown organism; the INHALE trial prescribing algorithm guided choices against an identified organism. Findings reveal frequent distrust of local guidelines and algorithm recommendations, with consequent non-adherence. Distrust was rooted in prescribers' beliefs about antibiotic prescribing, and the use of 'Pneumonia Panel' results for individual patients.

Overarching work package 4 conclusion

Taking together all findings, our data show that the availability of rapid molecular microbiology diagnostic tests does not necessarily lead to implementation in practice as a prescribing decision aid. Many clinicians are reluctant to eschew initial broad-spectrum antibiotics and stop them early, considering their use to be necessary to protect the patient and themselves, 'erring on the side of caution'. The proximal need to protect was often perceived as more imperative than the more distal threat of antibiotic resistance. The introduction of new technology alone therefore does not deliver. To realise the potential for prescribing technologies such as the Pneumonia Panel to improve AMS, we need to look beyond the technology itself. There is a need for a 'technology plus' approach that acknowledges the challenges that clinicians face when applying technological solutions to the care of individual patients. Clinical decisions are strongly influenced by prescribers' beliefs and 'clinical instincts' which are sometimes at odds with the scientific data. In such situations, the data and related guidelines may be less persuasive. There are implications for the design of support tools for clinicians to get the best from technological advances. Further, our work also highlights a need for 'behaviourally intelligent' guidelines, which reflect an understanding of human factors such as perceptions and beliefs.

Work package 5: health economics

Introduction

Hospital-acquired pneumonia and VAP have large implications for both health and healthcare resource use.[26] For this reason, the INHALE programme included a health-economic component to evaluate the resource implications of molecular diagnostics and to inform healthcare decision-making. Although a separate WP, WP5 involved close collaboration with WPs 1, 2 and 3. Components of WP5 included: estimation of molecular diagnostics cost-per-test; trialling of health-economic data collection alongside WP1 and WP2; and conducting a cost-effective analysis alongside WP3. A further component included health-economic modelling of HAP and VAP. The aim of the health-economic work was to estimate the cost-effectiveness of the molecular diagnostic near patient test to determine whether the test represents an efficient use of healthcare resources.

Methods

Work carried out alongside work packages 1 and 2

Within WP2, the health economists inputted into the design of data collection proformas and databases to include variables relevant to health economics. Collected data included: length of stay in ICU; intensity of ICU stays (number of organs supported); usage of antimicrobials; total length of hospital stays; and tests such as X-rays and imaging. Additionally, links were established with hospitals involved in WP2 to establish acceptable methods for obtaining data on charges for the ICU and hospital stays. The feasibility of obtaining data on health-related quality of life (HRQoL) using the EQ-5D-5L at 21 days was investigated. Preliminary costing work was performed to establish an estimated cost-per-test of the diagnostic tests used in WP. This involved testing staff completing questionnaires to establish details of staff time and other resources required to provide tests. Details of costs for equipment and consumables were derived from the study team and the manufacturers of the tests.

Model development work

To inform a health-economic model of the cost-effectiveness of HAP/VAP, we conducted a review of models utilised in economic evaluation of HAP/VAP interventions. To inform the likely structure of any model, we also attempted to define a clinical pathway for the treatment of HAP/VAP within an ICU (see *Appendix 7*, *Figure 17*). This was informed by means of interviews with intensive care physicians. This clinical pathway, alongside lessons learnt from the review of models, was used to inform a simple model structure which was modelled in Microsoft Excel® (Microsoft Corporation,

Redmond, WA, USA) and was informed with data obtained from the review of modelling structures as well as directly from WP3 (see *Appendix 8*, *Figure 18* and *Table 23*).

A review of previous health-economic models in HAP/VAP was published by Wagner *et al.*[27]

Economic evaluation alongside work package 3

The methods used in the economic analysis conducted alongside the clinical trial conducted in WP3 are described in detail in the health-economic analysis plan. The health-economic analysis was conducted from the perspective of NHS secondary care and compared the Pneumonia Panel supported by an algorithm translating its outputs into treatment advice to 'standard-of-care', two separate economic analyses were conducted using the clinical trial's coprimary outcomes. First, we calculated the additional cost per additional person on active and proportionate antimicrobial therapy within 24 hours of clinical diagnosis ('stewardship'). A second analysis looked at additional cost per additional clinical cure of pneumonia at 14 days ('cure'). In both cases, if one treatment strategy led to lower overall costs and was more effective than the other, we defined this as dominating the other treatment strategy (and, so by definition, cost-effective). Details of resource use included: days in ICU; total hospital stay; use of standard microbiology culture and susceptibility testing; use of Pneumonia Panel; prescribed antimicrobials; use of chest X-rays; and use of computed tomography (CT) scans. Costs for ICU and total hospital stays were obtained from hospital finance departments and represented hospital income. We also estimated ICU costs using NHS reference costs. For the cost of the Pneumonia Panel, we updated costing methodology developed in WP1 and WP2. Details of the methodology used to derive the Pneumonia Panel cost-per-test are given in *Appendix 9*. For other costs, we obtained relevant costs from NHS reference costs or directly from hospital trusts. Our base-case analysis included costs based on ICU costs and the costs for the Pneumonia Panel (intervention group only). Costs related to the use of other tests and antimicrobials were not included in the base case as they would be included in the ICU costs and hence would represent double counting. Additionally, we present a cost analysis that extends the base case to include all ICU admissions and income from the general hospital admission. This is referred to as total hospital cost. All costs identified were in 2020–1 Great British pounds, apart from early work to estimate cost of test used in WP1 and WP2 which were in 2018–9 Great British pounds.

The economic analysis alongside WP3 has been published by Wagner *et al.*[28]

Healthcare-related quality of life

We included an estimation of HRQoL using the EQ-5D-5L instrument taken at 21 days,[29] either in hospital or via the 21-day telephone interview. For those in hospital this was limited to those considered well enough to complete the questionnaire. The EQ-5D-5L was valued using a published scoring method.[30] We did not intend for this to be used in the economic evaluation as large numbers of individuals in each arm would not be expected to be able to complete this. Instead, we intended this to inform economic modelling.

Results

Work alongside work packages 1 and 2

Initial cost-per-test results constituted one element of the evidence considered in the selection of the diagnostic to be taken forward into WP3. Costs covered either purchase or leasing the machine, costs associated with consumables, quality assurance tests and staff time. Costs were compiled for the year 2018. Cost-per-test was £189 for the BioFire FilmArray Pneumonia Panel and £288 for the Curetis Unyvero. Cost-per-test was based on an annual throughput of 360 tests per year. By far the largest component of costs related to costs of equipment and consumables. Operator time was a negligible part of overall costs, at £2 per test.

Work package 2 showed that it was possible to collect health-economic resource use data as part of the clinical trial and that it was possible to collect data on hospital income for both the ICU stay and the wider inpatient stay. Results showed that ICU costs were high with mean adult costs of £42,136 (2017–8 Great British pounds) per person. Costs were considerably higher for those with VAP compared to HAP (£59k vs. £22k). Antibiotic costs constituted only a small component of total ICU costs, with mean total antibiotic costs for 21 days of £333 per adult. An EQ-5D-5L score was obtained in 43 of 107 adults at 21 days (40%).

Work alongside work package 3: within-trial analysis

Resource use

Estimates of the cost-per-test of the Pneumonia Panel were updated based on information available during WP3 (see *Appendix 9*, *Table 25*). The mean usage of diagnostic tests is shown in *Table 14*. Usage of tests other than the Pneumonia Panel was similar between arms, with no significant differences. A breakdown of all costs examined is given in *Table 15*. As expected, resources related to the use of tests and antibiotics are a small component of overall costs and costs are driven by stays in the ICU and other hospital departments. The costs of other resource use (barring Pneumonia Panel use) are similar and differences between groups are not statistically significant. For total costs in the base case (from randomisation to ICU discharge), the difference for the intervention groups was −£7802 (95% CI −15,696 to 92). When other inpatient costs are added to ICU costs, the estimated difference between the intervention and control arms increased to −£11,539 (95% CI −25,295 to 2217).

Economic evaluation of stewardship

The results of the economic analysis looking at stewardship are given in *Table 16*. Costs and proportional difference presented are for the difference between the intervention group and the control. ORs are compared to the control group. Base-case results are presented in the first row of the table, which show inpatient costs limited to ICU costs. Subsequent rows show a variety of sensitivity and subgroup analyses. In the base case, total costs are lower in the

TABLE 14 Comparison of use of diagnostics between arms (using all available data)

	Control (*n* = 269)		Intervention (*n* = 276)			
Test use	Mean	SD	Mean	SD	Diff in means	*p*
Pneumonia Panel	0.0	0.0	1.0	0.1	1.0	< 0.0001
Respiratory RM culture and PCR	2.3	2.3	2.2	2.0	−0.1	0.4092
X-ray	4.1	3.5	4.1	3.7	0.0	0.8947
CT scan	0.3	0.6	0.3	0.6	0.0	0.8242

RM, routine microbiology.

Note
Utilises available data among 529 participants who had stewardship and/or clinical cure outcomes, and ICU costs available.

TABLE 15 Unadjusted differences in mean costs (intervention minus control) with 95% CIs

	Control (*n* = 269)		Intervention (*n* = 276)				
Cost	Mean (£)	SD (£)	Mean (£)	SD (£)	Diff in means (£)	95% CI	
Pneumonia Panel	0	0	198	17	198	196	200
ICU stay	40,951	53,658	32,951	36,989	−8000	−15,894	−106
Microbiological culture and viral PCR	87	46	83	41	−4	−11	4
Antibiotics	634	881	631	990	−3	−163	157
X-ray	185	158	187	167	2	−26	28
CT	42	81	43	81	2	−13	15
Base case: Pneumonia Panel + ICU (from randomisation)	40,951	53,658	33,148	36,989	−7802	−15,696	92
Total costs: Pneumonia + all ICU stay(s) + general admission income	75,998	82,935	64,459	59,709	−11,539	−25,295	2217

Note
Uses available data from 529 participants who had stewardship and/or clinical cure outcomes, and ICU costs available.

TABLE 16 Economic evaluation of stewardship, base case, sensitivity analysis and subgroup analysis

Economic analysis	Control *N*	Intervention *N*	Difference[a]	Mean	95% CI		Interpretation
Base case	256	263	Cost (£)	−7373	−14,905	307	Intervention dominates
			Steward. OR	2.51	1.76	3.79	
			Steward. prop.	0.2	0.12	0.28	
Base case censored to 14 days	256	263	Cost (£)	−1217	−3322	691	Intervention dominates
			Steward. OR	2.51	1.81	3.75	
			Steward. prop.	0.2	0.13	0.28	
Base case excluding ICU stays > 200K	250	260	Cost (£)	−4116	−9443	1350	Intervention dominates
			Steward. OR	2.44	1.73	3.73	
			Steward. prop.	0.19	0.11	0.27	
Base case adjusted[b]	243	242	Cost (£)	−7508	−15,167	−57	Intervention dominates
			Steward. OR	2.53	1.75	3.92	
			Steward. prop.	0.19	0.12	0.27	
Total costs: Pneumonia Panel + whole ICU stay + spell income	208	212	Cost (£)	−10,901	−23,743	1834	Intervention dominates
			Steward. OR	3.18	2.18	5.12	
			Steward. prop.	0.24	0.16	0.33	
Base-case complete case only	223	237	Cost (£)	−9202	−17,508	−1185	Intervention dominates
			Steward. OR	2.73	1.84	4.32	
			Steward. prop.	0.21	0.13	0.3	
Base-case reference costs	256	263	Cost (£)	−10,712	−22,994	969	Intervention dominates
			Steward. OR	2.51	1.74	3.74	
			Steward. prop.	0.2	0.12	0.27	
Subgroup: adult	219	222	Cost (£)	−6874	−14,651	607	Intervention dominates
			Steward. OR	2.7	1.81	4.31	
			Steward. prop.	0.21	0.13	0.3	
Subgroup: child	37	41	Cost (£)	−11,114	−39,190	15,684	Intervention dominates
			Steward. OR	1.66	0.583	4.92	
			Steward. prop.	0.11	−0.10	0.31	
Subgroup: has COVID at rand	87	91	Cost (£)	−6589	−20,489	5691	Intervention dominates
			Steward. OR	4.17	2.27	8.55	
			Steward. prop.	0.32	0.19	0.46	
Subgroup: no COVID at rand	146	148	Cost (£)	−6883	−17,524	2759	Intervention dominates
			Steward. OR	1.77	1.15	2.89	
			Steward. prop.	0.12	0.03	0.21	

continued

TABLE 16 Economic evaluation of stewardship, base case, sensitivity analysis and subgroup analysis (*continued*)

Economic analysis	Control *N*	Intervention *N*	Difference[a]	Mean	95% CI		Interpretation
Subgroup: HAP	83	78	Cost (£)	1198	−7258	10,692	Intervention more costly, more effective (ICER = 131[b])
			Steward. OR	1.52	0.774	2.91	
			Steward. prop.	0.09	−0.06	0.23	
Subgroup: VAP	173	184	Cost (£)	−12,151	−21,260	−2266	Intervention dominates
			Steward. OR	3.15	2.03	5.31	
			Steward. prop.	0.24	0.15	0.34	

ICER, incremental cost-effectiveness ratio.
a For differences OR = OR and prop. is change in proportion with appropriate and proportionate antibiotics.
b ICER value is additional cost per person with improved stewardship.

Note
All adjusted for site.

intervention arm (−£7373); however, this difference is not significant (95% CI −14,905 to 307). For the base-case analysis, we find that the intervention arm dominates: total costs are lower, and stewardship is improved. The finding of dominance is robust under the different sensitivity analyses conducted. The one exception to this is for the subgroup looking at participants with HAP only. In this case, the intervention group is both more costly and more effective. Cost reduction was highest among children compared to adults, and among those with VAP compared to those with HAP. The uncertainty in three of these analyses is plotted on the cost-effectiveness planes in *Figure 16* (left column).

Economic evaluation of clinical cure

The results of the economic analysis of clinical cure are given in *Table 17*. Base-case results are presented in the first row, again with inpatient costs limited to those of the ICU. We find that the intervention has lower total costs but is less effective across all presented analyses. The uncertainty in three of these analyses is plotted on the cost-effectiveness planes in *Figure 16* (right column).

TABLE 17 Economic evaluation of clinical cure, base case, sensitivity analysis and subgroup analysis

Economic analysis	Control *N*	Int *N*	Difference	Mean	95% CI		Interpretation
Base case	259	263	Cost (£)	−7147	−15,198	27	Intervention less costly, but less effective
			Cure OR	0.689	0.461	0.985	
			Cure prop.	−0.08	−0.17	−0.00	
Base case censored to 14 days	259	263	Cost (£)	−1107	−3128	775	Intervention less costly, but less effective
			Cure OR	0.689	0.468	0.959	
			Cure prop.	−0.08	−0.16	−0.01	
Base case excluding ICU stays > 200K	253	260	Cost (£)	−3992	−9921	1623	Intervention less costly, but less effective
			Cure OR	0.671	0.462	0.952	
			Cure prop.	−0.09	−0.17	−0.01	
Base case adjusted	247	241	Cost (£)	−6933	−14,773	679	Intervention less costly, but less effective
			Cure OR	0.597	0.375	0.874	
			Cure prop.	−0.10	−0.17	−0.02	

TABLE 17 Economic evaluation of clinical cure, base case, sensitivity analysis and subgroup analysis (*continued*)

Economic analysis	Control *N*	Int *N*	Difference	Mean	95% CI		Interpretation
Total costs: Pneumonia Panel + whole ICU stay + spell income	210	212	Cost (£)	−10,995	−23,843	1234	Intervention less costly, but less effective
			Cure OR	0.714	0.466	1.04	
			Cure prop.	−0.08	−0.16	0.01	
Base-case complete case only	224	237	Cost (£)	−9249	−17,646	−435	Intervention less costly, but less effective
			Cure OR	0.667	0.442	0.989	
			Cure prop.	−0.09	−0.17	−0.00	
Base-case reference costs	259	263	Cost (£)	−10,390	−22,380	439	Intervention less costly, but less effective
			Cure OR	0.689	0.479	0.981	
			Cure prop.	−0.08	−0.16	−0.00	
Subgroup: adult	222	223	Cost (£)	−6870	−14,353	−225	Intervention less costly, but less effective
			Cure OR	0.68	0.448	1.01	
			Cure prop.	−0.09	−0.18	0	
Subgroup: child	37	40	Cost (£)	−9670	−35,691	18,083	Intervention less costly, but less effective
			Cure OR	0.748	0.208	2.58	
			Cure prop.	−0.04	−0.15	0.12	
Subgroup: has COVID at rand	89	91	Cost (£)	−5638	−20,254	6280	Intervention less costly, but less effective
			Cure OR	0.57	0.296	1.02	
			Cure prop.	−0.12	−0.26	0	
Subgroup: no COVID at rand	147	147	Cost (£)	−6893	−16,342	2989	Intervention less costly, but less effective
			Cure OR	0.695	0.405	1.13	
			Cure prop.	−0.07	−0.16	0.02	
Subgroup: HAP	83	79	Cost (£)	1034	−7648	10,304	Control dominates
			Cure OR	0.758	0.391	1.58	
			Cure prop.	−0.05	−0.17	0.08	
Subgroup: VAP	176	184	Cost (£)	−11,477	−21,134	−2432	Intervention less costly, but less effective
			Cure OR	0.668	0.422	1.02	
			Cure prop.	−0.09	−0.19	0	

Note
All adjusted for site.

Investigating differences in intensive care unit costs

One uncertainty with the data was the degree to which results were being driven by differences in mortality between the study groups. To investigate this, *Table 18* shows ICU cost analyses split by mortality at day 28 and cure status at 14 days. If results were driven purely by differences in mortality, we would expect to see differences disappear when we split by this this parameter. However, although *Table 18* shows that cost differences are lower in individuals who died by day 28, they persist for both those alive and those who died at this time point (though no differences are statistically significant). Thus, differences in mortality may only partially explain any differences in costs. Similarly, observed differences in costs may have resulted from differences in cure rates at 14 days between groups; *Table 18* also shows results divided by those who had and did not have clinical cure at 14 days. If results were driven by differences

TABLE 18 Unadjusted differences in mean ICU costs from randomisation to ICU exit (death or discharge) with 95% CIs: (1) overall; (2) split by mortality by 28 days; and (3) by clinical cure at 14 days

	Control			Intervention			
ICU costs	*N*	Mean (£)	SD (£)	*N*	Mean (£)	SD (£)	Mean difference in £ (95% CI)
All	224	44,763	56,878	237	34,746	38,839	−10,017 (−18,985 to −1049)
Alive at, or discharged by, 28 days	161	54,161	63,820	163	43,016	43,337	−11,145 (−23,090 to 799)
Died by 28 days	63	20,747	17,593	74	16,531	14,831	−4216 (−9775 to 1343)
Not cured	82	53,513	68,633	107	37,332	42,273	−16,182 (−33,221 to 858)
Cured	142	39,711	48,376	130	32,619	35,795	−7092 (−17,198 to 3013)

Note
Restricted to participants with finance-department provided cost data and clinical cure outcome.

in clinical cure, we would expect differences to narrow when divided by clinical cure category. In the case of costs, differences persist when subdivided into cure and not cured; further, it appears that the biggest difference in costs is for those individuals who were not cured at 14 days where costs are substantially higher in the control group (though not statistically significant – the 95% CI includes zero).

Economic modelling

The results of a simple economic model using data from the health-economic within-trial analysis are given in *Appendix 8* (*Figures 18*, *19* and *Table 24*). Data are used from the literature to estimate the cost per QALY using estimates from WP3. Broadly, conclusions are compatible with the 'within trial' results showing that the intervention group is associated with lower costs, but as estimates of clinical cure at 28 days are lower the estimated QALYs are also lower. The analysis also illustrates the considerable uncertainty in these results.

EuroQol-5 Dimensions, five-level version scores

EuroQol-5 Dimensions, five-level version scores were obtained for 78 individuals. These are presented in *Appendix 10* (*Table 26* and *Figure 20*).

Discussion

Summary of main findings

We found it was feasible to collect resource use and hospital finance data in INHALE. As expected, that the single most important item of resource use was the cost of ICU stays, and differences in this item far exceeded the unit cost of the Pneumonia Panel. For the RCT, we found a reduction in estimated ICU costs in the intervention arm; this difference persisted across a variety of assumptions and subgroup analyses, though differences were generally not statistically significant. For the cost-effectiveness analyses, results differed by type of analysis. For the stewardship outcome, we found that the intervention dominated control, as it offered both lower costs and better stewardship. For the clinical cure outcome, we did not find advantages for the intervention arm in terms of clinical cure and hence could not conclude an economic advantage for the Pneumonia Panel test on this basis.

Strengths of the study

The economic component was conducted alongside well-conducted clinical studies, including a large randomised controlled definitive trial. Hence, we were able to collect good-quality data. Data completeness was also good as each participating Trust had good engagement with the study. Through links with each Trust, we were able to obtain finance data on most participants, meaning that participants could be matched with a reliable estimate of trust income from that participant.

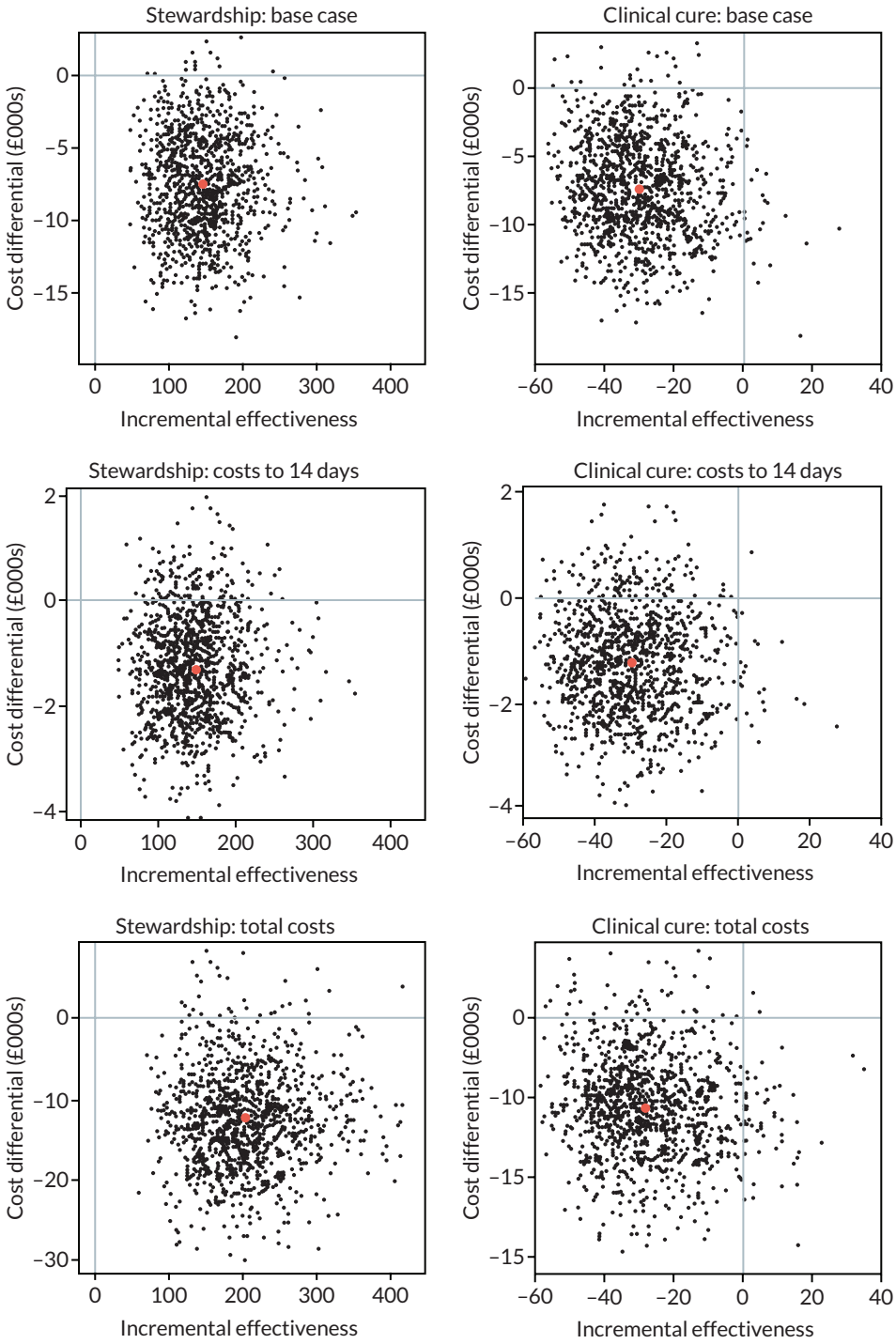


FIGURE 16 Cost-effectiveness plane resulting from the bootstrap resampling for stewardship and clinical cure, for base case, to 14 days, and total costs.

Limitations of study

Given the setting within critical care, it proved infeasible to collect HRQoL beyond a subset of patients; consequently, we could not use this as an outcome measure. Additionally, it was not feasible to follow up participants beyond the 21-day telephone interview, so longer-term outcomes relating to the study were not possible within the trial-based analysis. Long-term modelling would potentially be able to address these issues, and this was explored in *Appendix 8*. However, in the study, we did not have good data on the long-term outcomes of individuals who had HAP/VAP. As has been used in the literature, we substituted estimated QALYs from a study of sepsis. Therefore, we feel these results are interesting but inherently speculative. Consequently, the headline results we present in our conclusions were those provided by the 'within-trial' analysis.

A further limitation of the current study was that for the cost-effectiveness study looking at antibiotic stewardship, it was not possible within the bounds of the current study to quantify the benefits of improved stewardship. If better stewardship was able to reduce future antibiotic resistance, it would confer future benefits. Estimating a monetary value for reduced resistance would enable this to be incorporated into estimates of cost-effectiveness and would likely lead to better decisions regarding the implementation of interventions capable of improving stewardship.

Conclusion

The additional cost of the Pneumonia Panel (£198) represents a very small component of total ICU costs and are typically below 2% of total costs per ICU patient. We found a reduction in total costs with patients in the intervention arm averaging £33,148, and patients in the control arm averaging £40,951. However, it remains unclear how this arises. There was evidence of Pneumonia Panel being cost-effective in terms of stewardship, but not for clinical cure; consequently, we cannot conclude an economic advantage for the Pneumonia Panel. However, this does not take account of the potential benefit of improved stewardship in terms of reduced AMR.

Patient and public involvement

Patient and public involvement (PPI) in INHALE has been an integral part of the programme. The INHALE PPI panel have been actively engaged in all stages, from inception, at a workshop held during the design of the stage one application right up until the final stages, reviewing the outputs and taking part in the Heath Research Authority 'Make it Public' workshop, highlighting best practice of PPI in research.

Established in 2016, the PPI panel comprised of six members (seven initially, one resigned during 2021) meeting quarterly and contacted remotely to receive feedback on Programme updates and outputs from the Research team and contribute their ideas and suggestions for change. Three PPI representatives attended the biannual INHALE Research Programme Meetings. Two PPI panel members were part of the Trial Management Group (TMG) for the INHALE WP3 RCT and participated in TMG meetings. One independent PPI member also sat on the Programme Steering Committee (PSC), providing oversight. Meetings were initially face to face, but during the pandemic inclusivity of all panel members was maintained remotely by use of teleconferencing, captioning software, telephone and by mailing hard copy documents.

Being able to work so closely with the same PPI group, receive honest feedback, be held accountable for decisions in the research and have a group playing the critical friend were invaluable in the Programme and it led to a number of changes.

The PPI panel supported the substantial changes made by the Research team, such as the addition of more sites to WP1 and substitution of NovoDiag with ONT MinION. They also advocated for a diverse mix of hospitals to be carried forward into the trial, which the study team has reflected in the 12 sites initially opened for the trial.

A number of significant PPI proposals were implemented, including:

- requesting the addition of postal consent following their review of WP2 ethics approval and recommending a time limit for consent to be implemented, as well as wording changes
- suggesting a study website with a prominent PPI section
- recommending that participants be unblinded to the treatment arm in WP3
- raising concerns with the PSC and core team on the weighting of some scores after reviewing the INHALE diagnostic machine selection criteria.

They also reviewed and commented on all patient-facing information for the Programme including suggesting a participant thank you and newsletter that was disseminated to trial participants. These suggestions had a huge impact, and we were approached to present our PPI work at Health Research Authority Workshop for best practice in public involvement.

The PPI group have been supporting dissemination of results by advising on a trial infographic (see *Appendix 11*), attending workshops and public science festivals to publicise output from the programme. In addition, an evaluation has been produced by two members of the panel, identifying lessons learnt, based upon a questionnaire circulated to the panel and Research team and using the INVOLVE standards. This will be written up as a blog post.

Overall discussion

The INHALE programme has proven to be a successful piece of research that met the original objectives. At the start, several rapid molecular diagnostics for HAP and VAP were evaluated; both in terms of laboratory performance and within the broader context of treating this highly complex group of patients. The Pneumonia Panel emerged as the most suitable, and was chosen for the RCT, where the test placed at the point of care in ICU was used to guide treatment. Clinician perceptions of molecular diagnostics and antibiotic stewardship were monitored throughout and revealed useful insights into clinician prescribing behaviour. Costs and savings associated with use of the test were calculated.

The INHALE programme revealed important lessons about the implementation of rapid molecular diagnostics, not only for HAP and VAP in the context of critical care but for infectious disease diagnostics in general. One of the big successes of the RCT was placement of the Pneumonia Panel at the point of care within the participating ICUs rather than in the microbiology laboratory. This meant that the time advantage the test offers was maximised as time was not lost due to transport or from batching of samples. Furthermore, clinicians appeared to have better buy-in to the test as they felt more ownership of it. The enthusiasm among clinicians and the speed at which results were obtained no doubt contributed to successful recruitment during the WP3 trial. Following an initial extension due to COVID-19, the trial completed recruitment 2 months ahead of schedule. We believe that to have successfully embedded an infection diagnostic in the ICU setting was truly a 'World First' innovation. However, further work is needed for such a change to become commonplace, safe and tractable. Issues of oversight and relationships between test result and clinical action need to be considered before considering widespread implementation.

Use of the Pneumonia Panel clearly influenced antimicrobial prescribing and had a sizeable positive effect on AMS. This was despite clinicians expressing reservations regarding de-escalation of antibiotics for seriously ill patients. This finding corroborates other studies which also successfully used molecular diagnostics to improve antimicrobial prescribing.[31,32] INHALE also showed that, despite its cost, the use of the Pneumonia Panel was responsible for a saving in overall ICU costs. This observation, though not yet fully explained, will undoubtedly help promote uptake of the test in healthcare systems.

Equality, diversity and inclusion

The research took place at a number of different hospital types, located in different parts of the country; hence providing broad participation. In WP3, there was a slight over-representation of Asian and Black ethnic groups, compared to the generational population of the UK. The trial also had a pragmatic design, accepting all patients with HAP or VAP, meaning its findings are applicable to a broad population.

Limitations

Despite achieving an improvement in AMS, the trial did not demonstrate equivalence of clinical cure. This result was surprising and notably key secondary outcomes such as SOFA and mortality also skewed to favour standard care. However, findings were not statistically significant, and it remains to be determined whether improved stewardship brought about a small but real negative effector whether we simply observed noise caused by participant's various comorbidities, in ICU trials. Another significant limitation was the fact that the relatively low prevalence of acquired AMR in the UK meant that the test's ability to quickly detect AMR genes could not be fully tested. The third limitation was caused by the COVID-19 pandemic, substantially changing the types of patients that were recruited. Indeed, some of the effects surrounding clinical cure were most pronounced in this population but the reasons why are not clear. Finally, in terms of cost findings, a limitation is the comparatively short follow-up meaning that cost differences that may have occurred over a longer follow-up may not be valued. Furthermore, improved stewardship may have long-term cost benefits in terms of reduced antibiotic resistance and associated costs. However, quantification of this is likely to be highly complex and unpredictable and was considered beyond the scope of the current work. One may imagine a

scenario where improved AMS is associated with higher short-term costs but result in savings that are separated from the intervention, either temporally, geographically or both.

Conclusions

Overall, INHALE clearly demonstrates that molecular diagnostics for severe pneumonia are considerably faster and more sensitive than traditional culture-based methods. Use of such tests can influence antimicrobial prescribing in the ICU. However, the effect on clinical outcomes of de-escalating antimicrobial therapy as guided by the test is not clear. Doctors are generally positively disposed to such tests, but our behavioural work highlights that the availability of such tests does not necessarily lead to implementation in practice as a prescribing decision aid, with many clinicians hesitant to de-escalate antibiotics early based on test results. The optimal integration of such technology into practice will require a 'technology plus' approach that acknowledges the challenges that clinicians face when applying technological solutions to the care of individual patients. Use of molecular diagnostics can lead to cost savings, but the drivers behind these are not yet understood. Crucially, further work is needed to translate the results of molecular diagnostics to optimal therapy and improved clinical outcomes.

Future work

The central premise of any future must be to establish certainty on whether molecular test-driven improvement in antibiotic stewardship leads to altered clinical outcomes. If this is conclusively shown to be the case, then downstream work must explore the reasons why and develop prevention strategies. We have already secured funding through the NIHR's Programme Development Grant scheme to perform further analysis of existing WP3 participants to understand whether worsening clinical cure was real and what the drivers were. We will collect more information about the participants and recalculate clinical cure using a newly developed more objective definition. We will explore relationships between the exact antibiotics prescribed and clinical outcomes. Current analysis looked at suitability of antibiotics at specific time points, but we will expand this to the whole duration of treatment. Should these post hoc analyses fail to yield conclusive results, then the next stage would be to carry out a second clinical trial, specifically designed and powered to look at differences in clinical outcomes between study arms, with a more rigorous objectively define primary outcome.

If additional work demonstrates that improved stewardship leads to worse outcomes, then one would assume the likely explanation for this would be the presence of additional organisms, not detected by culture or PCR, that nevertheless have a role in driving progression of pneumonia. Dysbiosis of the lung microbiome may also play a role. Therefore, diagnostic techniques such as metagenomics[4,33] that provide a complete overview of the microbial composition of the lung may be helpful. Exploring the utility of these in management of pneumonia would be beneficial.

Our behavioural work highlights that the proximal need to protect the patient is often perceived as more imperative than the more distal threat of antibiotic resistance. Consequently, it would be useful for future work to focus on design and development of behavioural interventions/support materials to help clinicians make complex antibiotic prescribing decisions and implement such technology into practice. This could involve increasing concerns about the toxicity of broad-spectrum antibiotics.

In terms of health economics, useful future work would involve recalculating estimates of cost-effectiveness using the newly developed definition of cure which will form part of future work described above. Work to better characterise factors driving apparent reduction in costs in the intervention arm would also be beneficial. We also intend to develop the simple model presented here to include stewardship. Long-term work should focus on calculating how interventions such as this may impact the cost of AMR.

Implications

Until additional work exploring the impact the intervention on cure has been completed, the implications of this research are not fully clear. At present, we note that molecular diagnostics are faster and more sensitive than routine culture and can be successfully deployed at the point of care. Should our future work prove that there is no detriment to clinical outcomes resulting from diagnostic-guided prescribing, then we would wholeheartedly recommend the widespread introduction of these tests to the NHS. However, if that is not the case and detrimental effects observed from improved stewardship are demonstrated to be real, then this finding could have very wide-reaching implications for antimicrobial therapy and microbiological diagnosis of pneumonia, indicating a significant overhaul of current therapeutic practices may be required.

Additional information

CRediT contribution statement

Virve I Enne (https://orcid.org/0000-0002-0250-6377): Conceptualisation, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualisation, Writing – original draft, Writing – reviewing and editing.

Sarah-Jane F Stewart (https://orcid.org/0000-0003-2396-9028): Data curation, Formal analysis, Methodology, Visualisation, Writing – original draft, Writing – review and editing.

Adam P Wagner (https://orcid.org/0000-0002-9101-3477): Data curation, Formal analysis, Investigation, Methodology, Validation, Visualisation, Writing – original draft, Writing – reviewing and editing.

David Turner (https://orcid.org/0000-0002-1689-4147): Conceptualisation, Funding acquisition, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – reviewing and editing.

Charlotte Russell (https://orcid.org/0000-0002-9335-5681): Data curation, Investigation, Project Administration, Writing – original draft.

Juliet High (https://orcid.org/0000-0003-2555-2349): Data curation, Methodology, Project administration, Supervision, Visualisation, Writing – original draft, Writing- reviewing and editing.

Susan Stirling (https://orcid.org/0000-0001-6663-7846): Data curation, Formal analysis, Methodology, Visualisation, Writing – reviewing and editing.

Julie A Barber (https://orcid.org/0000-0001-5762-762X): Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Writing – reviewing and editing.

Robert Horne (https://orcid.org/0000-0002-3068-8438): Conceptualisation, Funding acquisition, Methodology, Supervision, Visualisation, Writing – reviewing and editing.

David M Livermore (https://orcid.org/0000-0002-9856-3703): Conceptualisation, Funding acquisition, Methodology, Supervision, Validation, Visualisation, Writing – original draft, Writing – reviewing and editing.

Vanya A Gant (https://orcid.org/0000-0001-6985-4969): Conceptualisation, Funding acquisition, Methodology, Validation, Visualisation, Writing – original draft, Writing – reviewing and editing.

Acknowledgements

The INHALE investigators and authors of this report would like to thank the following individuals for their contributions to the research.

INHALE study staff and team members

Hollian Richardson, Brenda Nominakur and Dewi Owen for their contributions to WP1.

Alp Aydin, Federico Ricciardi and Rossella Baldan for their contributions to WP1 and WP2.

Antony Colles for data management throughout the programme.

Kerry Dresser, Zaneeta Dhesi, Kerry Roulston and Naseem Ahmed for their contributions to WP3.

Alyssa Pandolfo, Natalie Bidad, Zoe Moon, Yogini Jani, Thomas Reader and Stephen Brett for their contributions to WP4.

Ann Marie Swart, David Brealey and Justin O'Grady for general contributions to all work packages.

INHALE clinical site PIs and staff

Institution	Study group members	Work package
Aintree University Hospital	Robert Parker Ian Turner-Bone Laura Wilding Ben Morton	WP1, WP3
Birmingham Children's Hospital	Jane Cassidy Helen Winmill Carly Tooke Philip Milner	WP3
BUPA Cromwell Hospital	Eleanor Tudtud Jeronimo Cuesta Zoran Aman	WP1, WP2, WP3
Chelsea and Westminster Hospital NHS Foundation Trust	Suveer Singh Rhian Bull Jaime Carungcong Patricia Correia da Costa Luke Moore Nabeela Mughal	WP1, WP3
City Hospitals Sunderland	Alistair Roy	WP1
Dudley Group NHS Foundation Trust	Julian Sonksen Karen Reid	WP1, WP3
GOSH	Mark Peters Olugbenga Akinugbe Lauran O'Neill Nigel Klein Helen Vander Ana Luisa Tomas	WP1, WP2, WP3
Guy's and St. Thomas' NHS Foundation Trust	Meera Chand Jonathan Edgeworth	WP1
James Paget University Hospitals NHS Foundation Trust	Michael Karlikowski Julie North	WP1, WP3,
NNUHs	Tim Leary Helen Williams Parveez Moondi Catherine Tremlett	WP1, WP2
North Middlesex University Hospital	Jeronimo Cuesta	WP1
Queen Elisabet Hospital Kings Lynn	Mark Blunt	WP1
Royal Brompton and Harefield Hospitals	Angela Arambujo Kamal Liyanage Pooja Patel	WP3
Royal Free Hospital	Daniel Martin Mark de Neef Helder Filipe Sara Garcia Mingo Damian Mack	WP1, WP3

Institution	Study group members	Work package
Royal Liverpool University Hospital	Ingeborg Welters Christopher Parry David Shaw Karen Williams Victoria Waugh	WP1, WP3
UCLH	David Brealey Georgia Bercades Ingrid Hass Deborah Smyth	WP1, WP2, WP3, WP4
University Hospitals of North Midlands NHS Trust	Nehal Patel Minnie Gellamucho	WP1, WP3
West Hertfordshire Hospitals NHS Trust	Valerie Page Hala Kandil Xiaobei Zhao	WP3

INHALE Programme Steering Committee
Prof. Paul Dark, Dr Andre Charlett, Ms Susan Bennett, Prof. Paul Aveyard, Prof. Robert Masterton.

INHALE patient and public involvement panel
Elizabeth Cooper, Jennie Griffiths, Margaret McWilliams, Patrick Thompson, Penny Vicary, Amander Wellings, Rebecca Harmston.

INHALE Data Monitoring Committee
Prof. Martin Llewelyn, Dr Katie Saunders, Prof. John Simpson, Dr Rosy Reynolds, Dr Giovanni Satta.

INHALE Antibiotic Stewardship Outcome Adjudication Committee
Dr Benny Cherian, Dr Matthew Dryden, Dr Peter Riley, Dr Ruan Simpson.

We would additionally like to thank bioMérieux and ONT for providing instruments and consumables; bioMérieux also provided logistics support. We would also like to thank the NIHR Clinical Research Network for support, The UCL Joint Research office for sponsorship and NCTU for support.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. *#datasaveslives* You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

The data dictionary and deidentified patient data analysed and presented in this study are available from NCTU following publication, on reasonable request and subject to appropriate data sharing agreements. The statistical analysis plan for WP3 is publicly available at https://norwichctu.uea.ac.uk/inhale/.

Ethics statement

For WP1, inclusion of the study within the UCL DNA Infection Bank ethical framework (REC 17/LO/1530) was sought, allowing collection of anonymised surplus clinical specimens and associated data. Approval was given on 18 July 2016.

For WP2, ethical permission was sought and received from Camden and Kings Cross research ethics committee, reference REC 16/LO/1618 on 28 September 2016. This included WP5 data collection and was later amended and approved on 8 February 2018 to include WP4 work.

For WP3, the trial was approved by the London-Brighton and Sussex Research Ethics Committee (19/LO/0400) and HRA approval was obtained on 9 April 2019. This application included WP4 and WP5 work and was later amended and approved on 6 April 2020 to include the COVID-19 observational substudy.

Information governance statement

University College London (UCL) is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

Under the Data Protection legislation University of East Anglia (UEA) and UCL are the Data Processors; UCL is the Data Controller and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for UCL's Data Protection Officer here www.ucl.ac.uk/legal-services/privacy/participants-health-and-care-research-privacy-notice

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJVG0801.

Primary conflicts of interest: Infrastructure support for this was provided by the NIHR University College London and Imperial College London Biomedical Research Centres. biomérieux provided FilmArray Torch instruments, Pneumonia Panel tests and QC materials free of charge. ONT provided reagents free of charge. The manufacturers had no input into the conception, design, data analysis or interpretation of the study and no input into writing of the manuscript.

Virve I Enne reports consultancy and speaker fees from bioMérieux, personal fees from Alchemab Therapeutics, and in-kind contributions from Inflammatix Inc. Adam Wagner reports multiple grant funding from the NIHR (NIHR133013; NIHR133455; NIHR131889; NIHR131573; NIHR128550; NIHR200171; NIHR200020). Vanya A Gant reports speaker fees from bioMérieux and consultancy fees from Gilead, MSD, Pfizer and Shionogi. Juliet High reports consultancy fees from bioMérieux. David Livermore reports personal fees from Adjutec, AstraZeneca, bioMérieux, Centauri, GenPax, GSK, Hikma, Merck/MSD, Nordic, Paion, Pfizer, Shionogi, Sumitovant, Summit, Thermofisher, Wockhardt and Zambon, He also reports shareholdings from Dechra, GenPax, GSK, Merck, Oxford Nanopore and PerkinElmer/Revvity, comprising < 10% of portfolio value. He also has nominated holdings in Arecor, Celadon Pharmaceuticals, Destiny Pharma, Eluceda Ltd, Genedrive, Poolbeg, Probiotix Health, SkinBiotherapeutics, Trellus and Verici Dx (all of which have research/products pertinent to medical and diagnostic innovation) through Enterprise Investment Schemes but has no authority to trade these shares directly. All are outside the submitted work. David M Livermore served as an assessor on the HTA Healthcare Associate infection Board (2008–9).

All other authors declare no competing interests.

Copyright and credit statement

Publications

Journal articles

Charalampous T, Kay GL, Richardson H, Aydin A, Baldan R, Jeanes C, *et al.* Nanopore metagenomics enables rapid clinical diagnosis of bacterial lower respiratory infection. *Nat Biotechnol* 2019;**37**:783–92. URL: https://ueaeprints.uea.ac.uk/id/eprint/71681

Dhesi Z, Enne VI, O'Grady J, Gant V, Livermore DM. Rapid and point-of-care testing in respiratory tract infections: an antibiotic guardian? *ACS Pharmacol Transl Sci* 2020;**3**:401–17. https://doi.org/10.1021/acsptsci.0c00027

Wagner AP, Enne VI, Livermore DM, Craig JV, Turner DA; INHALE Study Group. A review of health economic models and ventilator associated pneumonia (VAP). *J Hosp Infect* 2020;**106:**745–56. https://doi.org/10.1016/j.jhin.2020.09.012

High J, Enne VI, Barber JA, Brealey D, Turner DA, Horne R, *et al.* INHALE: the impact of using FilmArray Pneumonia Panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia on antimicrobial stewardship and patient outcomes in UK Critical Care-study protocol for a multicentre randomised controlled trial. *Trials* 2021;**22**:680. https://doi.org/10.1186/s13063-021-05618-6

Pandolfo A, Horne R, Jani Y, Reader TW, Bidad N, Brealey D, *et al*. Intensivists' beliefs about rapid multiplex molecular diagnostic testing and its potential role in improving prescribing decisions and antimicrobial stewardship: a qualitative study. *Antimicrob Resist Infect Control* 2021;**10**:95. https://doi.org/10.1186/s13756-021-00961-4

Enne VI, Aydin A, Baldan R, Owen DR, Richardson H, Ricciardi F, *et al.* Multicentre evaluation of two multiplex PCR platforms for the rapid microbiological investigation of nosocomial pneumonia in UK ICUs: the INHALE WP1 study. *Thorax* 2022;**77**:1220–8. https://doi.org/10.1136/thoraxjnl-2021-216990

Pandolfo A, Horne R, Jani Y, Reader TW, Bidad N, Brealey D, *et al.* Understanding decisions about antibiotic prescribing in ICU: an application of the Necessity Concerns Framework. *BMJ Qual Saf* 2022;**31**:199–210. https://doi.org/10.1136/bmjqs-2020-012479

Stewart SJF, Pandolfo A, Moon Z, Jani Y, Brett SJ, Brealey D, *et al*. UK clinicians' attitudes towards the application of molecular diagnostics to guide antibiotic use in ICU patients with pneumonias: a quantitative study. *J Antimicrob Chemother* 2024;**79**:123–7. https://doi.org/10.1093/jac/dkad355

Enne VI, Stirling S, Barber JA, High J, Russell C, Brealey D, *et al.* INHALE WP3, a multicentre, open-label, pragmatic randomised controlled trial assessing the impact of rapid, ICU-based, syndromic PCR, versus standard-of-care on antibiotic stewardship and clinical outcomes in hospital-acquired and ventilator-associated pneumonia. *Intensive Care Med* 2025;**51**:272–86. https://doi.org/10.1007/s00134-024-07772-2

Stewart SJF, Pandolfo AM, Jani Y, Moon Z, Brealey D, Enne VI, *et al.* Guidelines vs mindlines: a qualitative investigation of how clinicians' beliefs influence the application of rapid molecular diagnostics in intensive care. *Antimicrob Agents Chemother* 2025;**69**:e0115624. https://doi.org/10.1128/aac.01156-24

Wagner AP, Enne VI, Gant V, Stirling S, Barber Ja, Livermore DM *et al.* Cost-effectiveness of rapid, ICU-based, syndromic PCR in hospital-acquired pneumonia: analysis of the INHALE WP3 multi-centre RCT. *Critical Care* 2025;**29**(1):352. https://doi.org/10.1186/s13054-025-05428-1

Stewart SJF, Enne VI, Pandolfo AM, Jani YH, Brealey D, Brett SJ, *et al.* Machine says yes, doctor says no: an ecological momentary assessment analysis examining clinicians' perceptions of, and their antibiotic prescribing behaviour when using rapid molecular diagnostic tests in intensive care. *Antimicrob Resist Infect Control* 2026;**15**:42. https://doi.org/10.1186/s13756-025-01690-8

Conference presentations

Jeanes C, Richardson H, Ozongwu C, Personne Y, Enne VI, O'Grady J. Presented as oral presentation at 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Vienna, April 2017.

Aydin S, Owen DR, Richardson H, Baldan R, Charalampous T, Gant V, *et al. Rapid Metagenomic Sequencing to Predict the Antimicrobial Resistance of Bacteria Directly from Endotracheal Aspirates in VAP Patients.* Presented as late-breaker poster presentation at 28th ECCMID, Madrid, April 2018.

Owen DR, Richardson H, Aydin S, Baldan R, Nomamiukor B, Gant V, *et al. A Comparison of Routine Microbiology Culture, Comprehensive Culture and 16S Metagenomic Sequencing in Identifying Bacterial Pathogens in Hospital-Acquired Pneumonia.* Presented as poster presentation at 28th ECCMID, Madrid, April 2018.

Richardson H, Charalampous T, Baldan R, Aydin S, Owen D, Kay G, *et al. Rapid Metagenomic Sequencing-Based Investigation of Hospital-Acquired and Ventilator-Associated Pneumonia.* Presented as oral presentation at 28th ECCMID, Madrid, April 2018.

Enne VI, Aydin A, Richardson H, Owen D, Baldan R, Russell C, *et al. INHALE WP1: An Observational Study Comparing the Performance of Two Multiplex PCR Platforms against Routine Microbiology for the Detection of Potential Pathogens in Patients with Suspected Hospital-Acquired/Ventilator-Associated Pneumonia (HAP/VAP) across 15 UK Intensive Care Units (ICUs).* Presented as poster presentation at 29th ECCMID, Amsterdam, April 2019.

Enne VI, Baldan R, Russell C, Aydin A, Richardson H, Owen D, *et al. INHALE WP2: Appropriateness of Antimicrobial Prescribing for Hospital-Acquired and Ventilator-Associated Pneumonia (HAP/VAP) in UK ICUs Assessed against PCR-Based Molecular Diagnostic Tests.* Presented as a poster presentation at 29th ECCMID, Amsterdam, April 2019.

Owen DR, Alfassam H, Arumainayagam C, Aydin A, Richardson H, Baldan R, *et al. Prediction of the Antimicrobial Resistance Profiles of E. coli and K. pneumoniae Directly from Respiratory Samples Using Oxford Nanopore Technologies (ONT) MinION Nanopore Metagenomic Sequencing.* Presented as a mini-oral presentation at 29th ECCMID, Amsterdam, April 2019.

Wagner AP, Turner D, Enne VI, Baldan R, Russell C, Livermore DM. *Health Economics of Nosocomial Pneumonia in UK Intensive Care Units (ICU): An Exploratory Study.* Presented as ePoster at 40th International symposium of Intensive Care and Emergency Medicine (ISICEM), held online in September 2020.

Enne VI, Aydin A, Baldan R, Owen D, Richardson H, Ricciardi F, *et al. Rapid Identification of Antibiotic Resistance in Respiratory Samples Using the Automated Biofire FilmArray and Curetis Unyvero Rapid PCR-Based Pneumonia Panels.* Presented as ePoster presentation at 31st ECCMID conference, which took place online in July 2021.

Pandolfo AM, Jani Y, Brett SJ, Brealey D, Singh S, Enne VI, *et al. Understanding ICU Clinicians' Beliefs about Broad-spectrum Antibiotic Usage and Molecular Diagnostic Utility During the COVID-19 Pandemic.* Presented as oral presentation at 31st ECCMID conference, which took place online in July 2021.

Pandolfo AM, Horne R, Jani Y, Reader TW, Bidad N, Brealey D, *et al. Understanding Prescribers' Beliefs about Molecular Diagnostic Tests as Barriers and Facilitators to Test Uptake in ICUs: A Qualitative Study*. Presented as oral presentation at 31st ECCMID conference, which took place online in July 2021.

Dhesi Z, Brealey D, High J, Gant V, De Neef M, Page V, *et al. Utility of a 29-mRNA Host-Response Assay, together with PCR-Based Rapid Pathogen Diagnostics to Identify Pneumonias in Intensive Care Unit (ICU) Patients.* Presented as poster presentation at 32nd ECCMID Congress, Lisbon, April 2022.

Enne VI, Stirling S, Barber JA, High J, Russell C, Dresser K, *et al. INHALE WP3: Clinical Outcomes and Antimicrobial Stewardship Analyses from of a Multi-Centre RCT (INHALE) Testing the Utility of Rapid Multiplex PCR for Hospital-Acquired and Ventilator-Associated Pneumonia in Critical Care.* Presented as oral presentation at IDWeek 2022, Washington, DC. *Open Forum Infectious Diseases*, Vol 9, Suppl_2, 2022.

Pandolfo AM, Horne R, Jani Y, Moon Z, Brealey D, Enne VI, *et al. Understanding Intensive Care Clinicians' Beliefs of Rapid Multiplex Molecular Diagnostic Tests in Clinical Practice: A Qualitative Application of the Necessity Concerns Framework.* Presented as oral presentation at 32nd ECCMID Congress, Lisbon, April 2022.

Roulston K, Dhesi Z, Livermore DM, Gant V, Enne VI. *Impact of Filmarray (bioMerieux) for the Diagnosis of Bacterial Pneumonia in COVID-19 Patients on Antibiotic Prescribing Decisions at Five UK ICUs.* Presented as oral presentation at 32nd ECCMID Congress, Lisbon, April 2022.

Stewart SJF, Moon Z, Pandolfo AM, Jani Y, Brett S, Brealey D, *et al. ICU Clinicians' Beliefs about Prescribing Broad Spectrum Antibiotics and Attitudes towards Rapid Molecular Diagnostics within the Context of COVID-19*. Presented as poster presentation at 32nd ECCMID Congress, Lisbon, April 2022.

Dhesi Z, Enne VI, Barber J, Russell C, High J, Gant V, *et al. Microbiology of Hospital-Acquired and Ventilator Associated Pneumonia as Detected by Multiplex PCR in Intensive Care Unit Patients from the UK: An INHALE Sub-study*. Presented as flash talk presentation at 33rd ECCMID Congress, Copenhagen, April 2023.

Enne VI, Stirling S, Barber JA, High J, Russell C, Dresser K, *et al. INHALE WP3: Clinical Outcomes and Antimicrobial Stewardship Analyses from of a Multi-Centre RCT (INHALE) Testing the Utility of Rapid Multiplex PCR for Hospital-Acquired and Ventilator-Associated Pneumonia in Critical Care.* Presented as oral presentation at 33rd ECCMID Congress, Copenhagen, April 2023.

Stewart SJF, Pandolfo A, Enne VI, Russell C, Moon Z, Jani Y, *et al. ICU Clinicians' Perceptions of Rapid Multiplex PCR for Diagnosis of Pneumonia and Barriers to Application in Practice: An INHALE Trial Sub-Study.* Presented as poster presentation at 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Copenhagen, April 2023.

Wagner AP, Turner D, Stirling S,Barber J, Enne VI, Gant V, *et al. Economic Evaluation of the INHALE Trial: Are Rapid Molecular Diagnostics Cost-Effective for the Management of Nosocomial Pneumonia in UK Intensive Care Units (ICU)?* Presented as poster presentation at 33rd ECCMID Congress, Copenhagen, April 2023.

Enne VI, Aydin A, Richardson H, Owen D, Baldan R, Russelll C, *et al. INHALE WP1: Variability of Routine Microbiology for the Investigation of Hospital-Acquired and Ventilator-Associated Pneumonia (HAP/VAP) across 11 Laboratories Serving 15 UK ICUs.* Presented as an e-poster oral presentation at 29th ECCMID, Amsterdam, April 2021.

Other

Pre-print

Dhesi Z, Enne VI, Brealey D, Livermore DM, High J, Russell C, *et al.* 2020. Organisms causing secondary pneumonias in COVID-19 patients at 5 UK ICUs as detected with the FilmArray test. *MedRvix*. https://doi.org/10.1101/2020.06.22.20131573

Work package 3 statistical analysis plan

https://norwichcrtu.uea.ac.uk/ctudocs_public/inhale/Analysis%20plan%20v1.0%20-%20INHALE%2022-02-2022.pdf

Health-economic analysis plan

https://norwichcrtu.uea.ac.uk/ctudocs_public/inhale/heap_1_4.pdf

Thesis

Dhesi Z. *Rapid Diagnosis and Treatment of Hospital-Acquired and Ventilator-Associated Pneumonia in Intensive Care Unit Patients*. Doctoral thesis [MD (Res)], UCL (University College London). 2021.

Lay dissemination

The INHALE WP3 results have been depicted in an infographic for more accessible dissemination – see *Appendix 11*. The team also sent a study update and a thank you letter to participants of WP3, an initiative suggested by the PPI panel. The infographic will be sent out once the corresponding paper is published.

The PPI panel also produced a poem about the research – a video recording of it can be viewed here: www.youtube.com/watch?v=7_2bqWlJzFE

One of the PPI panel members also wrote a blog about participation in research for those with problems accessing the internet, see: https://arc-eoe.nihr.ac.uk/news-blogs/blogs/blog-why-people-should-be-involved-who-do-not-have-internet

In addition to production of the above outputs, the team have also participated in various public engagement events for dissemination of the research to lay audiences. These were the Royal Free Trust open day, UCLH open day, the Rise of Resistance Festival, the HRA Make it Public conference, the Science Museum Build a Body event and the Norwich Science Festival.

For the latter two events, the INHALE team developed an educational game to teach visiting children about antimicrobial resistance and the role of diagnostics.

References

1. Enne VI, Aydin A, Baldan R, Owen DR, Richardson H, Ricciardi F, *et al*. Multicentre evaluation of two multiplex PCR platforms for the rapid microbiological investigation of nosocomial pneumonia in UK ICUs: the INHALE WP1 study. *Thorax* 2022;**77**:1220–8. URL: https://discovery.ucl.ac.uk/id/eprint/10145520/ (accessed 5 December 2025).
2. Bello G, Pennisi MA, Di Muzio F, De Pascale G, Montini L, Maviglia R, *et al*. Clinical impact of pulmonary sampling site in the diagnosis of ventilator-associated pneumonia: a prospective study using bronchoscopic bronchoalveolar lavage. *J Crit Care* 2016;**33**:151–7.
3. Russell CD, Koch O, Laurenson IF, O'Shea DT, Sutherland R, Mackintosh CL. Diagnosis and features of hospital-acquired pneumonia: a retrospective cohort study. *J Hosp Infect* 2016;**92**:273–9.
4. Charalampous T, Kay GL, Richardson H, Aydin A, Baldan R, Jeanes C, *et al*. Nanopore metagenomics enables rapid clinical diagnosis of bacterial lower respiratory infection. *Nat Biotechnol* 2019;**37**:783–92.
5. Pan-ngum W, Blacksell SD, Lubell Y, Pukrittayakamee S, Bailey MS, de Silva HJ, *et al*. Estimating the true accuracy of diagnostic tests for dengue infection using Bayesian latent class models. *PLOS ONE* 2013;**8**:e50765.
6. Lim C, Paris DH, Blacksell SD, Laongnualpanich A, Kantipong P, Chierakul W, *et al*. How to determine the accuracy of an alternative diagnostic test when it is actually better than the reference tests: a re-evaluation of diagnostic tests for scrub typhus using Bayesian LCMs. *PLOS ONE* 2015;**10**:e0114930.
7. Murphy CN, Fowler R, Balada-Llasat JM, Carroll A, Stone H, Akerele O, *et al*. Multicenter evaluation of the BioFire FilmArray pneumonia/pneumonia plus panel for detection and quantification of agents of lower respiratory tract infection. *J Clin Microbiol* 2020;**58**:e00128.
8. Gadsby NJ, McHugh MP, Forbes C, MacKenzie L, Hamilton SKD, Griffith DM, Templeton KE. Comparison of Unyvero P55 Pneumonia Cartridge, in-house PCR and culture for the identification of respiratory pathogens and antibiotic resistance in bronchoalveolar lavage fluids in the critical care setting. *Eur J Clin Microbiol Infect Dis* 2019;**38**:1171–8.
9. Pickens C, Wunderink RG, Qi C, Mopuru H, Donnelly H, Powell K, Sims MD. A multiplex polymerase chain reaction assay for antibiotic stewardship in suspected pneumonia. *Diagn Microbiol Infect Dis* 2020;**98**:115179.
10. Webber DM, Wallace MA, Burnham CAD, Anderson NW. Evaluation of the BioFire FilmArray Pneumonia Panel for detection of viral and bacterial pathogens in lower respiratory tract specimens in the setting of a tertiary care Academic Medical Center. *J Clin Microbiol* 2020;**58**:e00343.
11. Papazian L, Klompas M, Luyt CE. Ventilator-associated pneumonia in adults: a narrative review. *Intensive Care Med* 2020;**46**:888–906.
12. Melsen WG, Rovers MM, Groenwold RHH, Bergmans DCJJ, Camus C, Bauer TT, *et al*. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis* 2013;**13**:665–71.
13. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, *et al*. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med* 2013;**173**:2039–46.
14. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, *et al*. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996;**22**:707–10.
15. Leteurtre S, Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc F; Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP). PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *Crit Care Med* 2013;**41**:1761–73.
16. Enne VI, Stirling S, Barber JA, High J, Russell C, Brealey D, *et al*. INHALE WP3, a multicentre, open-label, pragmatic randomised controlled trial assessing the impact of rapid, ICU-based, syndromic PCR, versus

standard-of-care on antibiotic stewardship and clinical outcomes in hospital-acquired and ventilator-associated pneumonia. *Intensive Care Med* 2025;**51**:272–86. https://doi.org/10.1007/s00134-024-07772-2

17. High J, Enne VI, Barber JA, Brealey D, Turner DA, Horne R, *et al*.; INHALE Study Group. INHALE: the impact of using FilmArray Pneumonia Panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia on antimicrobial stewardship and patient outcomes in UK Critical Care – study protocol for a multicentre randomised controlled trial. *Trials* 2021;**22**:680.
18. Agresti A, Caffo B. Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. *Am Stat* 2000;**54**:280–8.
19. European Medicines Agency. *Guideline on the Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections*. London: European Medicines Agency; 2011.
20. Mathioudakis AG, Fally M, Hansel J, Robey RC, Haseeb F, Williams T, *et al*.; Pneumonia Outcomes Group. Clinical trials of pneumonia management assess heterogeneous outcomes and measurement instruments. *J Clin Epidemiol* 2023;**164**:88–95.
21. Pandolfo A, Horne R, Jani Y, *et al*. Understanding decisions about antibiotic prescribing in ICU: an application of the Necessity Concerns Framework. *BMJ Quality and Safety* 2022;**31**:199–210.
22. Fine MA, Kurdek LA. Publishing multiple journal articles from a single data set: issues and recommendations. *J Fam Psychol* 1994;**8**:371–9.
23. Pandolfo A, Horne R, Jani Y, Reader TW, Bidad N, Brealey D, *et al*. Intensivists' beliefs about rapid multiplex molecular diagnostic testing and its potential role in improving prescribing decisions and antimicrobial stewardship: a qualitative study. *Antimicrob Resist Infect Contr* 2021;**10**:95.
24. Stewart SF, Pandolfo AM, Jani Y, Moon Z, Brealey D, Enne VI, *et al*. 2025 Guidelines vs mindlines: a qualitative investigation of how clinicians' beliefs influence the application of rapid molecular diagnostics in intensive care. *Antimicrob Agents Chemother* 2025;**69**:e0115624.
25. Stewart SJF, Enne VI, Pandolfo AM, Jani YH, Brealey D, Brett SJ, *et al*. Machine says yes, doctor says no: an ecological momentary assessment analysis examining clinicians' perceptions of, and their antibiotic prescribing behaviour when using rapid molecular diagnostic tests in intensive care. *Antimicrob Resist Infect Control* 2026;**15**:42. https://doi.org/10.1186/s13756-025-01690-8
26. Edwards SJ, Wordsworth S, Clarke MJ. Treating pneumonia in critical care in the United Kingdom following failure of initial antibiotic: a cost–utility analysis comparing meropenem with piperacillin/tazobactam. *Eur J Health Econ* 2012;**13**:181–92.
27. Wagner AP, Enne VI, Livermore DM, Craig JV, Turner DA. A review of health economic models and Ventilator Associated pneumonia (VAP). *J Hosp Infect* 2020;**106**:745–56. URL: https://discovery.ucl.ac.uk/id/eprint/10123475 (accessed 5 December 2025).
28. Wagner AP, Enne VI, Gant V, Stirling S, Barber JA, Livermore DM, *et al*. Cost-effectiveness of rapid, ICU-based, syndromic PCR in hospital-acquired pneumonia: analysis of the INHALE WP3 multi-centre RCT. *Critical Care* 2025;**29**:352.
29. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;**20**:1727–36.
30. Hernández Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from a UK population study. *PharmacoEconomics* 2023;**41**:199–207.
31. Darie AM, Khanna N, Jahn K, Osthoff M, Bassetti S, Osthoff M, *et al*. Fast multiplex bacterial PCR of bronchoalveolar lavage for antibiotic stewardship in hospitalised patients with pneumonia at risk of Gram-negative bacterial infection (Flagship II): a multicentre, randomised controlled trial. *Lancet Respir Med* 2022;**10**:877–87.
32. Poole S, Tanner AR, Naidu VV, Borca F, Phan H, Saeed K, *et al*. Molecular point-of-care testing for lower respiratory tract pathogens improves safe antibiotic de-escalation in patients with pneumonia in the ICU: results of a randomised controlled trial. *J Infect* 2022;**85**:625–33.

33. Langelier C, Kalantar KL, Moazed F, Wilson MR, Crawford ED, Deiss T, *et al*. Integrating host response and unbiased microbe detection for lower respiratory tract infection diagnosis in critically ill adults. *Proc Natl Acad Sci USA* 2018;**115**:E12353–62.

34. Collins CD, Schwemm AK. Linezolid versus vancomycin in the empiric treatment of nosocomial pneumonia: a cost–utility analysis incorporating results from the ZEPHyR trial. *Value Health* 2015;**18**:614–21.

35. Drummond M, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programme*. 3rd edn. Oxford: University Press; 2005.

36. Jones KB. *A Unit Costs of Health and Social Care 2021*. Canterbury: Personal Social Services Research Unit, University of Kent; 2021.

Appendix 1 Features and target panels of the Curetis Unyvero Pneumonia Panel and the BioFire FilmArray Pneumonia Panel multiplex PCR tests

TABLE 19 Target panels and features of PCR tests

Characteristic	Curetis Unyvero HPN Hospitalised Pneumonia Panel	BioFire FilmArray Pneumonia Panel *plus*
Technology	Automated sample preparation, multiplex PCR and microarray detection of targets	Automated sample preparation and nested PCR
Regulatory status	CE-IVD[1]	CE-IVD and FDA Cleared[2]
Hands-on preparation time	2 minutes, using a standard pipette to transfer sample to the sample tube. Bacteria are then lysed for 30 minutes in the 'Lysator' before transfer to the cartridge.	2 minutes, using a proprietary flock swab to transfer the sample to a sample tube, which is loaded into the test pouch with the aid of a loading station.
Run-time	5 hours	1 hour 15 minute
Bacteria sought	*A. baumannii* complex *Citrobacter freundii* *Enterobacter cloacae* complex *E. coli* *H. influenzae* *K. aerogenes* *Klebsiella oxytoca* *K. pneumoniae* *Klebsiella variicola* *M. catarrhalis* *Morganella morganii* *Proteus* spp. *P. aeruginosa* *Serratia marcescens* *Stenotrophomonas maltophilia* *S. pneumoniae*	*Acinetobacter calcoaceticus-baumannii* complex *Enterobacter cloacae* complex *E. coli* *H. influenzae* *K. aerogenes* *Klebsiella oxytoca* *K. pneumoniae* *M. catarrhalis* *Proteus* spp. *P. aeruginosa* *Serratia marcescens* *Streptococcus agalactiae* *S. pneumoniae* *Streptococcus pyogenes*
Atypical organisms and Fungi sought	*Chlamydophila pneumoniae* *Legionella pneumophila* *Mycoplasma pneumoniae* *Pneumocystis jirovecii*	*Chlamydophila pneumoniae* *Legionella pneumophila* *Mycoplasma pneumoniae*
Viruses sought	None	Adenovirus Coronaviruses OD43, NL63, HKU1 and 229E Human metapneumovirus Human rhinovirus/enterovirus Influenza A Influenza B Parainfluenza virus Respiratory syncytial virus MERS coronavirus

continued

TABLE 19 Target panels and features of PCR tests (*continued*)

Characteristic	Curetis Unyvero HPN Hospitalised Pneumonia Panel	BioFire FilmArray Pneumonia Panel *plus*
AMR genes sought	*ermB* *mecA* *mecC* bla_{TEM} bla_{SHV} bla_{IMP} bla_{KPC} bla_{NDM} bla_{OXA-23} $bla_{OXA-24/40}$ bla_{OXA-48} bla_{OXA-58} bla_{VIM} *sul1* *gyrA83* *gyrA87* *mecA/C* and MREJ	bla_{KPC} bla_{NDM} $bla_{OXA-48\ like}$ bla_{VIM} bla_{IMP} bla_{CTX-M}

Note

Appendix 2 INHALE criteria for hospital-acquired/ventilator-associated pneumonia diagnostic test progression to the randomised controlled trial phase of the study (work package 3)

The following criteria are proposed to choose the diagnostic test for progression to INHALE WP3, where it will be used to guide the treatment of patients.[1]

Evidently, the test must be safe and simple to use, practical to implement, economic and as accurate as possible. For more detailed descriptions of the data analyses and definitions of the gold standard and concordance categories, please refer to the INHALE WP1 Revised Primary Outcome document.

Essential criteria

Two criteria are critical for any machine to be considered for progression to WP3. Any machine not meeting these 'Essential Criteria' cannot be used in the RCT and will not be evaluated using the desirable criteria.

1. **Implementability.** The machine must be sufficiently developed to allow routine use in the NHS. The hands-on time required to process samples must be < 45 minutes and the machine must be usable by an operator with skill levels expected of a Biomedical Scientist Band 5 or lower. The test must have/or be close to obtaining CE-IVD marking.
2. **Concordance.** Major discordance, that is failures by the test to find pathogen(s) detected by routine microbiology must account for < 5% of all tests performed.

Desirable criteria

Machines meeting the above 'Essential criteria' (1 and 2) will be scored against following desirable criteria. The maximum total score is 150.

- Overall concordance. A measure of the overall accuracy of the test compared to the gold standard. **1 point** is awarded for every % point over 55% overall concordance. (Maximum **45 points**)
- Sensitivity for detection of common pathogens (i.e. *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, *Klebsiella oxytoca*, *E. coli*, *Enterobacter cloacae*, *E. aerogenes*, *A. baumannii*, *H. influenzae* and *S. pneumoniae*). (**2 points** for every 'win', i.e. the best sensitivity against a particular pathogen, maximum **20 points**)
- Breadth of panel. Each PCR test seeks some targets that the other cannot, principally resistance genes for Curetis and viruses for BioFire (for details, see Unique PCR targets appendix). The number of detections of unique targets will be compared. (Maximum **15 points**)
- Time to result. 1 point allocated for each 30 minutes < 8 hours, the common dosage interval for antibiotics. (Maximum **15 points**)
- Cost of tests and equipment, measured as cost-per-test, a composite measure of both costs. Cheapest test is awarded the maximum points. One point is deducted from others for every 10% increase in price compared to the cheapest. (Maximum **15 points**)
- Failure rate of the test/machine. The maximum score is available for no failures. One point is deducted for each 0.5% of failures. (Maximum **15 points**)
- Footprint and space occupied. Special considerations for installation. Smallest machine is awarded maximum points. One point is deducted for each square foot in size compared to the smallest. (Maximum **5 points**)

- The quality and speed of customer service in the event of breakdown, ordering, installation and so on. Average score based on assessment from individual users who have dealt with manufacturers during the study. (Maximum **5 points)**
- Consumable logistics, that is space required for storage, storage temperature, shelf life, delivery speed, delivery cost. One point for best-performing machine for each criterion. (Maximum **5 points**)
- Ease of use. Average scored based on assessments from individual users who have operated machines during the study. (Maximum **10 points**)

This scoring system is designed to be as unambiguous as possible, but some criteria inevitably involve a degree of subjectivity (e.g. ease of use). Once data analysis has been performed, the data will be used to determine scores for criteria 3, 4, 5 and 8. Manufacturer data will be used to determine scores for criteria 6, 7, 9 and 11. Members of the study team (8 individuals) who have been using machines will score the tests on criteria 10 and 12. Scoring will take place prior to the INHALE programme meeting on 10 July 2018. At the meeting, all the evidence available for scoring will be presented along with tentative scores.

TABLE 20 Non-essential **c**riteria for HAP/VAP diagnostic test progression to RCT phase of the inhale study (WP3)[1]

Criterion	Description	Point scoring	Maximum available points
Overall concordance	A measure of the overall accuracy of the test compared to the gold standard.	1 point is awarded for every % point over 55% overall concordance	45 points
Sensitivity	Sensitivity for detection of common pathogens (i.e. *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, *K. oxytoca*, *E. coli*, *E. cloacae*, *E. aerogenes*, *A. baumannii*, *H. influenzae* and *S. pneumoniae*)	2 points for every 'win', i.e. the best sensitivity against a particular pathogen	20 points
Breadth of panel	Each PCR test seeks some targets that the other cannot, principally resistance genes for Curetis and viruses for BioFire.	Maximum points for most detections of unique targets, other tests awarded points as a proportion of unique detection	15 points
Time to result	Time to result	1 point allocated for each 30 minutes < 8 hours, the common dosage interval for antibiotics	15 points
Cost of tests and equipment	Cost-per-test, a composite measure of both test and equipment cost.	Cheapest test is awarded the maximum points. 1 point is deducted from others for every 10% increase in price compared to the cheapest.	15 points
Failure rate	Failure rate of test and/or machine, full or partial.	1 point deducted for each 0.5% of failures	15 points
Footprint and space occupied	Amount of space required to host machine	Smallest machine awarded maximum points.	5 points
Customer service	The quality and speed of customer service in the event of breakdown, ordering, installation and so on.	Average score based on assessment from individual users who have dealt with manufacturers during the study.	5 points
Consumable logistics	Space required for storage of consumables, storage temperature, shelf life, delivery speed, delivery cost.	1 point for best-performing machine for each criterion	5 points
Ease of use	User perception and experience	Average scored based on assessments from individual users who have operated machines during the study.	10 points
Total			**150 points**

Source
Reproduced with permission from Enne *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The table includes minor additions and formatting changes to the original text.

Appendix 3 INHALE work package 3: antibiotic prescribing guidance for use with FilmArray result

Considerations

1. Adjust dosages for renal function as per manufacturer's SPC.
2. For patients already on antimicrobial treatment for infections necessitating specific regimens, for example infective endocarditis/meningitis – please discuss with Microbiology how best to adapt their treatment for organism(s) found by FilmArray.
3. Pregnant and paediatric patients: Please note general recommendations regarding use of fluoroquinolones, tetracyclines, colistin, temocillin and ceftazidime-avibactam. See www.medicines.org.uk/emc/ for specifics.
4. Please be aware that BioFire FilmArray does not detect *Stenotrophomonas maltophilia.* If *S. maltophilia* infection is suspected, please adjust therapy accordingly in at risk populations.

TABLE 21 To be used when ONE organism is detected by FilmArray

First	***Second***		***Third***			
What organism was found and if the patient allergic to β-actams	***If NO resistance genes found, this is the advised Rx***		***If resistance genes found, this is your advised Rx***			
			Resistance marker			
	None		CTX-M	KPC or OXA-48	IMP, NDM or VIM	*mecA* or *mecC*
No organisms found	Antibiotics should be stopped unless there is clear evidence for probable or proven bacterial infection severe enough to warrant them					
Any virus	Coamoxiclav + antiviral if appropriate					
	Cefuroxime + antiviral if appropriate					
	Levofloxacin + antiviral if appropriate					
		None	CTX-M	KPC or OXA-48	IMP, NDM or VIM	*mecA* or *mecC*
	Any virus + 1 or more bacteria	Treat as indicated for bacterial infection and add antiviral treatment where appropriate				
Organism	*A. baumannii*	Meropenem[a]				
		Meropenem[a]				
		Colistin alone or in combination[b] if clinically appropriate				
	E. aerogenes, *E. cloacae*, *E. coli*, *K. pneumoniae or K. oxytoca*	Temocillin (2 g TDS)	Temocillin (2 g TDS)	Ceftazidime-avibactam[c]	Colistin alone or in combination[b] if clinically appropriate	
	E. aerogenes, *E. cloacae*, *E. coli*, *K. pneumoniae or K. oxytoca*	Ceftriaxone (*Klebsiella* spp. and *E. coli*) or Meropenem for *Enterobacter* spp.	Meropenem	Ceftazidime-avibactam[c]	Colistin alone or in combination[b] if clinically appropriate	

First	Second		Third		
What organism was found and if the patient allergic to β-actams	If NO resistance genes found, this is the advised Rx		If resistance genes found, this is your advised Rx		
		Levofloxacin or ciprofloxacin	Colistin alone or in combination[b] if clinically appropriate	Colistin alone or in combination[b] if clinically appropriate	Colistin alone or in combination[b] if clinically appropriate
	Proteus spp. or *Serratia marcescens*	Piperacillin-tazobactam for Serratia sp. or temocillin 2 g TDS for Proteus sp.	Temocillin 2 g TDS for Proteus sp. OR meropenem for Serratia sp.	Ceftazidime-avibactam[c]	Fosfomycin[d]
		Ceftriaxone	Meropenem	Ceftazidime-avibactam[c]	Fosfomycin[d]
		Fosfomycin[d]	Fosfomycin[d]	Fosfomycin[d]	Fosfomycin[d]
	H. influenzae	Coamoxiclav			
		Cefuroxime			
		Doxycycline or levofloxacin or ciprofloxacin			
	M. catarrhalis	Coamoxiclav			
		Cefuroxime			
		Doxycycline or levofloxacin or ciprofloxacin			
	P. aeruginosa	Ceftazidime (2 g TDS)	Meropenem	Ceftazidime-avibactam[c]	Colistin alone or in combination[b] if clinically appropriate
		Ceftazidime (2 g TDS)	Meropenem	Ceftazidime-avibactam[c]	Colistin alone or in combination[b] if clinically appropriate
		Colistin alone or in combination[b] if clinically appropriate	Colistin alone or in combination[b] if clinically appropriate	Colistin alone or in combination[b] if clinically appropriate	Colistin alone or in combination[b] if clinically appropriate

continued

TABLE 21 To be used when ONE organism is detected by FilmArray (*continued*)

First	Second		Third	
What organism was found and if the patient allergic to β-actams	*If NO resistance genes found, this is the advised Rx*		*If resistance genes found, this is your advised Rx*	
	S. aureus	Flucloxacillin[e]		Glycopeptide[f] or linezolid
		Cefuroxime		Glycopeptide[f] or linezolid
		Glycopeptide[f] or linezolid		Glycopeptide[f] or linezolid
	Streptococcus agalactiae, *S. pneumoniae* or *Streptococcus pyogenes*	Amoxicillin		
		Cefuroxime		
		Glycopeptide[f] or linezolid		
	C. pneumoniae, *L. pneumophila*, *M. pneumoniae*	Macrolide[g] or levofloxacin or ciprofloxacin		
		Macrolide[g] or levofloxacin or ciprofloxacin		
		Macrolide[g] or levofloxacin or ciprofloxacin		

a In units with high rates of carbapenem resistance, or if experiencing outbreak of carbapenem-resistant *A. baumannii*, follow same recommendations as for treatment in case of allergy.
b Colistin can be combined with an appropriate second antimicrobial such as rifampicin or tigecycline. The choice is left open according to local preference.
c Please discuss with microbiologist before prescribing.
d Consider adding colistin as metallo β-lactamase likely to be present in undetected host organism.
e If clinical picture suggests PVL-positive *S. aureus*, consider ordering PVL test and switching to linezolid.
f Vancomycin or teicoplanin.
g Clarithromycin or azithromycin.

Key

No known allergy to antibiotics.
Mild allergy to β-lactams, that is rash.
Severe allergy to β-lactams, that is anaphylaxis.
Not applicable.

TABLE 22 Recommended treatment for combination of TWO or more organisms are detected by FilmArray

First, What combination of bacteria have been found?						**Second:** Therapy if no resistance genes	***Third:* if resistance genes found**			
A. baumannii	*Enterobacteriales: E. aerogenes, E. cloacae, E. coli, K. pneumoniae, K. oxytoca, Proteus* sp., *Serratia marcescens*	*P. aeruginosa*	*H. influenzae/ M. catarrhalis*	*S. aureus*	*Streptococcus agalactiae, S. pneumoniae* or *Streptococcus pyogenes*		*mecA/C* found	CTX-M found	*C. pneumoniae, L. pneumophila* OR *M. pneumoniae*	Carbapenemase found
Does the mixture include *Acinetobacter*? If YES, stay with this block; if NO, go to next block										
+	Any one or more second organism found					Meropenem[a]	Add Glycopeptide[b] or linezolid	-	Add Macrolide[c] or levofloxacin or ciprofloxacin	Discuss with microbiology
+	± Any one or more second organism found					Meropenem[a]	Add Glycopeptide[b] or linezolid	-	Add Macrolide[c] or levofloxacin or ciprofloxacin	Discuss with microbiology
+	Add levofloxacin or ciprofloxacin[d]	Add levofloxacin or ciprofloxacin[d]	Add levofloxacin or ciprofloxacin[d]	Add glycopeptide[b] or linezolid	Add glycopeptide[b] or linezolid	Colistin combination	Add glycopeptide[b] or linezolid	Discuss with microbiology	Add macrolide[c] or levofloxacin or ciprofloxacin	Discuss with microbiology
First, What combination of bacteria have been found?						**Second:** Therapy if no resistance genes	***Third:* if resistance genes found**			
A. baumannii	*E. aerogenes, E. cloceae, E. coli, K. pneumoniae, K. oxytoca, Proteus* sp., *Serratia marcescens*	*P. aeruginosa*	*H. influenzae/ M. catarrhalis*	*S. aureus*	*Streptococcus agalactiae, S. pneumoniae* or *Streptococcus pyogenes*		*mecA/C* found	CTX-M found	*C. pneumoniae, L. pneumophila* or *M. pneumoniae*	Carbapenemase found
If NO *Acinetobacter*: but ≥1 *Pseudomonas*/Enterobacteriales found start here										
-	+ (at least one)		±	±	±	Piperacillin/tazobactam	Add Glycopeptide[b] OR Linezolid	Escalate to Meropenem	Add Macrolide[c] or levofloxacin or ciprofloxacin	Discuss with microbiology
-	+ (at least one)		±	±	±	Meropenem	Add glycopeptide[b] or linezolid	-	Add macrolide[c] or levofloxacin or viprofloxacin	Discuss with microbiology
-	Add levofloxacin or ciprofloxacin[d]	Add levofloxacin or ciprofloxacin[d]	Add levofloxacin or ciprofloxacin[d]	Add glycopeptide[b] or linezolid	Add glycopeptide[b] or linezolid	Colistin combination as indicated	Add glycopeptide[b] or linezolid	Discuss with microbiology	Add macrolide[c] or levofloxacin or ciprofloxacin	Discuss with microbiology
If NO *Acinetobacter* NO *Pseudomonas* and NO Enterobacteriaceae, start here										
None of these			Any 2 or more of these			Coamoxiclav	Add glycopeptide[b] or linezolid		Add macrolide[c] or levofloxacin or ciprofloxacin	

continued

TABLE 22 Recommended treatment for combination of TWO or more organisms are detected by FilmArray (*continued*)

First, What combination of bacteria have been found?						**Second:** Therapy if no resistance genes	**Third:** *if resistance genes found*			
A. baumannii	*Enterobacteriales: E. aerogenes, E. cloacae, E. coli, K. pneumoniae, K. oxytoca, Proteus* sp., *Serratia marcescens*	*P. aeruginosa*	*H. influenzae/ M. catarrhalis*	*S. aureus*	*Streptococcus agalactiae, S. pneumoniae* or *Streptococcus pyogenes*		*mecA/C* found	CTX-M found	*C. pneumoniae, L. pneumophila* OR *M. pneumoniae*	Carbapenemase found
None of these			Any 2 or more of these			Levofloxacin	Add glycopeptide[b] or linezolid		Add macrolide[c] or levofloxacin or ciprofloxacin	
None of these			Any 2 or more of these			Levofloxacin	Add glycopeptide[b] or linezolid		Add macrolide[c] or levofloxacin or ciprofloxacin	

+ organism present, – organism absent, ± either present or absent

a Add colistin in areas of high carbapenem resistance among *A. baumanii.*

b Vancomycin or teicoplanin.

c Clarithromycin or azithromycin.

d Consider adding tigecycline of fosfomycin if fluoroquinolone resistance is locally prevalent.

PLEASE READ THIS TABLE FROM LEFT TO RIGHT; Coloured boxes refer to allergy status as in Table 21.

Key

No known allergy to antibiotics.

Mild allergy to β-lactams i.e. rash.

Severe allergy to β-lactams, i.e. anaphylaxis.

Not applicable.

Appendix 4 INHALE Microbiology Committee terms of reference

1. The Committee will comprise four voting members: one from the INHALE team (Prof. David Livermore) and three independents (Drs Matthew Dryden, Benny Cherian and Peter Riley). It will be chaired by Dr Vicky Enne (non-voting). Additional non-voting attendees are Dr Vanya Gant who presents clinical cases and Ms. Charlotte Russell taking notes.
2. The Committee meets *c.* monthly via teleconference. Each meeting lasts 2 hours and handles on average 15–20 patients per meeting. Longer face-to-face meetings will be held towards the end of the study to clear backlog. Each meeting will handle a balance of patients from both study arms.
3. The Committee will be blinded to the study arm of each patient when making categorisation decisions. In practice, this will be achieved through production of uniform data reports for both arms by Norwich Clinical Trials Unit (NCTU). Actual study numbers will be obscured to avoid identification of the study arm.
4. Dr Gant will present each case based on the report produced by NCTU. His outline will detail:
    A. FilmArray and routine microbiology results. ALL results by both methods will be considered for each patient, irrespective of their trial arm. FilmArray results for control arm patients will be generated centrally by the study team and treating clinicians would not have been aware of them.
    B. The patient's clinical condition and comorbidities at diagnosis of HAP/VAP.
    C. Details of antimicrobial prescribed for the pneumonia.
    D. Details of confounders including other concurrent infections and antibiotics prescribed for these.
    E. Details of eventual patient outcomes will not be included to avoid influencing decisions.

5. The Committee will decide collectively whether antimicrobial prescribing for the HAP or VAP was (a) microbiologically active and (b) proportionate at 24 and 72 hours post randomisation. that is four primary decisions will be made per patient.
6. In the case of disagreement among Committee members, the decision will be referred for external adjudication by Dr Ruan Simpson, who does not participate in meetings. Dr Simpson will also independently adjudicate 10% of decisions as a QC measure, to ensure the robustness of decision making by the Committee.
7. In addition, the Committee will categorise all relevant antimicrobials (or their combinations) as 'broad-spectrum' or 'narrow-spectrum'. A small number of older broad-spectrum antibiotics that are now heavily compromised by resistance (e.g. cotrimoxazole, tetracycline and chloramphenicol) are assigned a separate category as 'old'. The resulting list will be used to answer the secondary question of whether the patient was on narrow-spectrum antimicrobials at 24 and 72 hours. Patients not on antibiotics at these time points are noted.
8. In addition to the primary and secondary outcomes listed in points 5 and 7 above, the Committee also makes a note of a number of additional factors that influence their decisions. These are:
    A. Patients with no positive microbiology or FilmArray results (completely negative result).
    B. For patients with no positive microbiology, the Committee considers whether the clinical condition is severe enough to warrant continuation of antimicrobial therapy.
    C. Patients in whom the only pathogen found is a virus.
    D. Patients in whom no antimicrobial therapy is justified because they are no longer thought to be infected at 24 and/or 72 hours.
    E. Patients for whom no decision can be reached because data are unlikely to be obtainable, owing, for example to death or withdrawal. The reason is noted.

F. Patients in whom either the FilmArray or routine microbiology result led to a concerning antimicrobial therapy being administered are noted and reported to the Data Monitoring Committee. These particularly include any case where the algorithm has or may have prompted use of an agent to which the pathogen ultimately found proves to be resistant.
G. Patients whose case reports suggests they did not meet eligibility criteria of the study.

9. In achieving their decisions regarding activity and proportionality, the Committee will be guided the following general principles:
   A. Antibiotics will be considered inactive when they are found inactive in vitro against the pathogen isolated, where the pathogen (if found by FilmArray only) has a gene that ordinarily causes resistance or where an inherently resistant pathogen is found.
   B. Antibiotics will be considered active where they are found active in vitro against the pathogen isolated. If a pathogen is detected by FilmArray only, and no susceptibility results are available, the Committee will make assumptions regarding likely activity based on local and national surveillance data.
   C. Proportionality will be judged on the basis whether the antibiotic has an unnecessarily broad spectrum for the pathogen(s) detected (e.g. meropenem vs. *H. influenzae*).
   D. Any antimicrobial that is judged to be inactive against the pathogens found will automatically also be disproportionate.
   E. The antimicrobial advocated on the master prescribing algorithm or its accepted local variants will be counted as active and proportionate against the pathogen specified on the algorithm unless the particular isolate proves to be resistant when grown [NB: this means that the Committee must accept the algorithm as reasonable].
   F. In cases where multiple organisms are found at different concentrations by FilmArray testing, the Committee may take the view that organism(s) present at low concentrations may be colonists that do not warrant treatment. For the time being, such decisions will be made on a case-by-case basis.
   G. For patients with completely negative microbiology results, the decision on whether prescribing is clinically appropriate and proportionate will be made in the context of the patient's clinical parameters. Such patients will be identified separately in the database, allowing them to be distinguished during analyses. For example, it would be considered appropriate and proportionate for a severely ill patient to receive broad-spectrum treatment, but it would be inappropriate and disproportionate in a patient with mild infection.
   H. Infections at other body sites, and antibiotics given to treat these, will be considered on a case-by-case basis.

10. The Committee's collective decisions for each recruited patient will be recorded manually during the meeting by a non-expert member of NCTU or the broader study team. They will be matched with study numbers and entered on the RedCAP database at a later date.

Appendix 5 Work package 4 vignettes

Adult vignettes

Scenario 1: a starting vignette

Frieda is 55 yo and was admitted to your ICU 10 days ago with acute, severe pancreatitis. She has suffered in the past from gall stones but, apart from intermittent pain they caused her no other problems. However, 12 days ago she presented to the ED with very severe abdominal pain and a diagnosis of (necrotising) pancreatitis was confirmed by a CT scan and a markedly raised amylase. Following admission she deteriorated on the ward with increasing abdominal distension, progressive cardiovascular and respiratory deterioration. She required intubation and ventilation and, for 48 hours required noradrenaline. She was started on a course of meropenem and TPN (intravenous food) via a central line at the time of intubation. Otherwise management was conservative.

10 days later and things are improving, she is no longer on vaso-actives, her abdomen is less distended and NG aspirates are decreasing, though the surgeons still feel TPN is warranted. She remains intubated but is slowly weaning from the ventilator (FiO_2 0.45, PSV 15/7) she is slowly waking up as the sedation is reduced. The meropenem was stopped 3 days ago.

You are covering the ICU tonight and the nurse at the bedside reports she has a new temperature of 38.1 °C. The chart shows no other temperatures over the last 4 days. There was nothing unusual about her morning bloods (CRP/WCC, raised but stable etc). She is also a bit more tachycardic, normally ~90 bpm, now ~100 bpm but blood pressure is maintained, urine output seems good and no change to her respiratory parameters or blood gas.

Her CVC looks clean, the abdomen is distended and appears tender on palpation (though no more than last night), and she has decreased air entry at both bases with occasional coarse crackles.

1. What is going through your mind here?
2. Would you start antibiotics?
3. How comfortable are you with your decision?
4. If you are not 100% sure you are doing the right thing, what information would you like (either existing tests or one from the future)?
5. If you had a device able to detect respiratory pathogens in 6 hours, would that change your approach (or levels of comfort)?
6. Does AMS factor into your prescribing decisions? In what ways?

Scenario 2: a stopping/de-escalating vignette

You have just taken over the care of John. He is 73 years old and was admitted with a fractured neck of femur. He has a history of moderate COPD but continues to smoke 15–20 cigarettes/day. His symptoms are managed by his GP using a combination of inhalers, allowing him to be independent; he has never been in hospital before. The fracture was successfully operated on the next day. John was slow to mobilise, and after three days he started to feel generally unwell, increasingly short of breath and developed a cough productive of yellow sputum. He was reviewed on the ward by the medical team, and started on appropriate antibiotics. However, he continued to worsen. When he was reviewed the next day, he was noted to be very tachypnoeic (35/min) and hypoxic (PaO_2 6.4 kPa on FiO_2 0.6). He had a heart rate of 110 and a temperature of 37.9 °C. There were some crackles heard at his right lung base and a widespread, fine, expiratory wheeze. His white cell count was 12 × 10^9/ml (neutrophilia) and his CRP was 64 mg/l (normal 0–5). A chest X-ray demonstrates clear consolidation/collapse of the right middle lobe. A diagnosis of hospital-acquired pneumonia was made. He was transferred to the ICU, where he was intubated and ventilated.

4 days later you take over his care on the ICU. He is slowly weaning from ventilation, he has had an occasional low-grade pyrexia (37.7 max), his CRP is falling (22) and WCC remains slightly elevated at 13 × 10^9/ml. An endotracheal aspirate was sent for culture soon after admission to the ICU but so far, no growth. Blood cultures, the atypical screen, flu A/B PCR and pneumococcal ag also remain negative. No other concerns have been raised.

1. **What would you like to do with the antibiotics? Please explain your rationale.**

(prompts if necessary)

1. **Stop both?**
2. **Stop one (which?)**
3. **Swap one or both to …?**
4. **Continue (1 or 2) until:**
   - **End of course: 5, 7, 10, 14 days (your call but please say)?**
   - **CRP and WCC normalised?**
   - **Patient is extubated?**
5. **Extend spectrum/narrow spectrum?**
2. **How comfortable are you with this decision?**
3. **What further evidence would you like?**
4. **Does AMS factor into your prescribing decisions? In what ways?**

Paediatric vignette

Scenario 1: a starting vignette

Amber is an 11-month-old admitted to your ICU with respiratory distress. She had been unwell for 48 hours with a mild temperature, cough and fast breathing. She was seen in A and E at her local hospital and referred to GOSH for concerns about breathing. Her respiratory distress worsened and her oxygen Sats started to decline following arrival on pediatric ICU. She had bilateral crackles and wheezes. A nasopharyngeal aspirate from the referring hospital revealed respiratory syncytial virus. The Intensivists felt she required intubation and ventilation.

A chest X-ray showed some patchy shadowing. She has a fever of 38.5 °C. Her CRP is 22.

1. What is going through your mind here?
2. Would you start antibiotics?
3. With no other information how comfortable are you with your decision?
4. If you are not 100% sure you are doing the right thing, what information would you like (either existing tests or one from the future)?
5. If you had a PCR device able to detect respiratory pathogens in 6 hours, would that change your approach (or levels of comfort)?
6. Does AMR factor into your prescribing decisions? In what ways?

Scenario 2: a stopping/de-escalating vignette

Peter, a 2-year-old born prematurely at 24 weeks with chronic lung disease, had been admitted to Pediatric ICU on four occasions with respiratory distress. Now he is 2 years old and was admitted a week ago (in December) with respiratory distress. The chest X-ray showed some increased shadowing but on a background of chronic lung disease. A nasopharyngeal aspirate had revealed respiratory syncytial virus and Influenza B when admitted. He was started on piperacillin/tazobactam and amikacin for suspected secondary bacterial chest infection. Tracheal aspirates grew commensals. He started to improve and is due to be weaned from the ventilator over the next 24 hours. His CRP is 29.

1. What would you like to do with the antibiotics?
   - _Stop both?
   - _Stop one (which?)
   - _Swap one or both to …?
   - _Continue (1 or 2) until:
   - _End of course: 5, 7, 10, 14 days (your call but please say)?
   - _Stop when he is extubated?
   - _Extend spectrum/narrow spectrum?

2. How comfortable are you with this decision?
3. What further evidence would you like?
4. Does AMR factor into your prescribing decisions? In what ways?

Appendix 6 Work package 4 ecological momentary assessment questionnaire

FUNDED BY NIHR National Institute for Health Research

About Your Prescribing Decision

By completing this questionnaire you agree to the use of the data contained herein for the INHALE WP4 trial. More information can be found in the INHALE WP4 Manual.

We are interested in your decision-making for your patient with a suspected LRTI who is part of the INHALE study. Please answer the questions below based on your **most recent antibiotic decision** for this patient.

1. Time and Date: _____

2. Have you received BioFire results and algorithm recommendations for this patient? ☐ Yes ☐ No ☐ Patient in control arm

3. Have you received this patient's post-randomisation respiratory culture results? ☐ Yes ☐ No ☐ Not applicable

4. Which of the following influenced your prescribing decision on this occasion? (**Tick all that apply**).

- ☐ Trust guidelines/Unit SOPs
- ☐ BioFire result AND prescribing algorithm
- ☐ BioFire result NOT prescribing algorithm
- ☐ Available respiratory culture result
- ☐ Available culture result for other body site
- ☐ Quick speed of BioFire results
- ☐ Following the SOS plan
- ☐ Preserving the ecology of the unit
- ☐ Ongoing antibiotics for other body site infection
- ☐ Other (please specify) _____

5. Which clinical staff influenced your prescribing decision on this occasion? (**Tick all that apply**).

- ☐ ICU consultants
- ☐ ICU registrars (ST or clinical fellow)
- ☐ ICU foundation trainees (year 1 or 2)
- ☐ Unit microbiologists (ward round)
- ☐ Unit microbiologists (other)
- ☐ On-call microbiologists (registrar)
- ☐ On-call microbiologists (consultant)
- ☐ Infectious disease doctors (registrar)
- ☐ Infectious disease doctors (consultant)
- ☐ Pharmacists
- ☐ Nurses
- ☐ Other (please specify) _____
- ☐ None of the above; no discussion with other staff

INHALE WP4 Questionnaire (v.1.0 22.08.2019) IRAS No. 250289

About This Patient

6. Please rate your **agreement** with the following statements relating to your prescribing decision for this patient.

	Disagree	Uncertain	Agree	Not Applicable
6.1 Patient was clinically deteriorating				
6.2 Patient had laboratory or radiological evidence of deterioration				
6.3 Patient likely had other sources of infection besides the lung				
6.4 Initial antibiotic prescription for RTI or other infection was appropriate and did not need to be changed				
6.5 I believed the BioFire results				
6.6 I found the **BioFire results** easy to interpret and understand				
6.7 I found the **algorithm** easy to interpret and understand				
6.8 I had confidence in what the **algorithm** was recommending				
6.9 I had confidence in what the **trust guideline** was recommending (see question 7)				

7. Was your decision consistent with trust guideline recommendations? Yes ☐ No ☐ Unsure ☐

8. Was your decision consistent with algorithm recommendations? (Test arm patients only)
Yes ☐ No ☐ Unsure ☐

9. Taking the above into account, could you give us some more information on why you decided to do what you did?

Please return the completed form to the survey administrator

To be completed by the survey administrator:

INHALE Patient ID: _____ Experimental condition: Control ☐ Intervention ☐

INHALE Clinician ID: _____ Clinician initials: _____

Clinician level and speciality: _____

INHALE WP4 Questionnaire (v.1.0 22.08.2019) IRAS No. 250289

Appendix 7 Simplified clinical pathway used to inform the health-economic model building

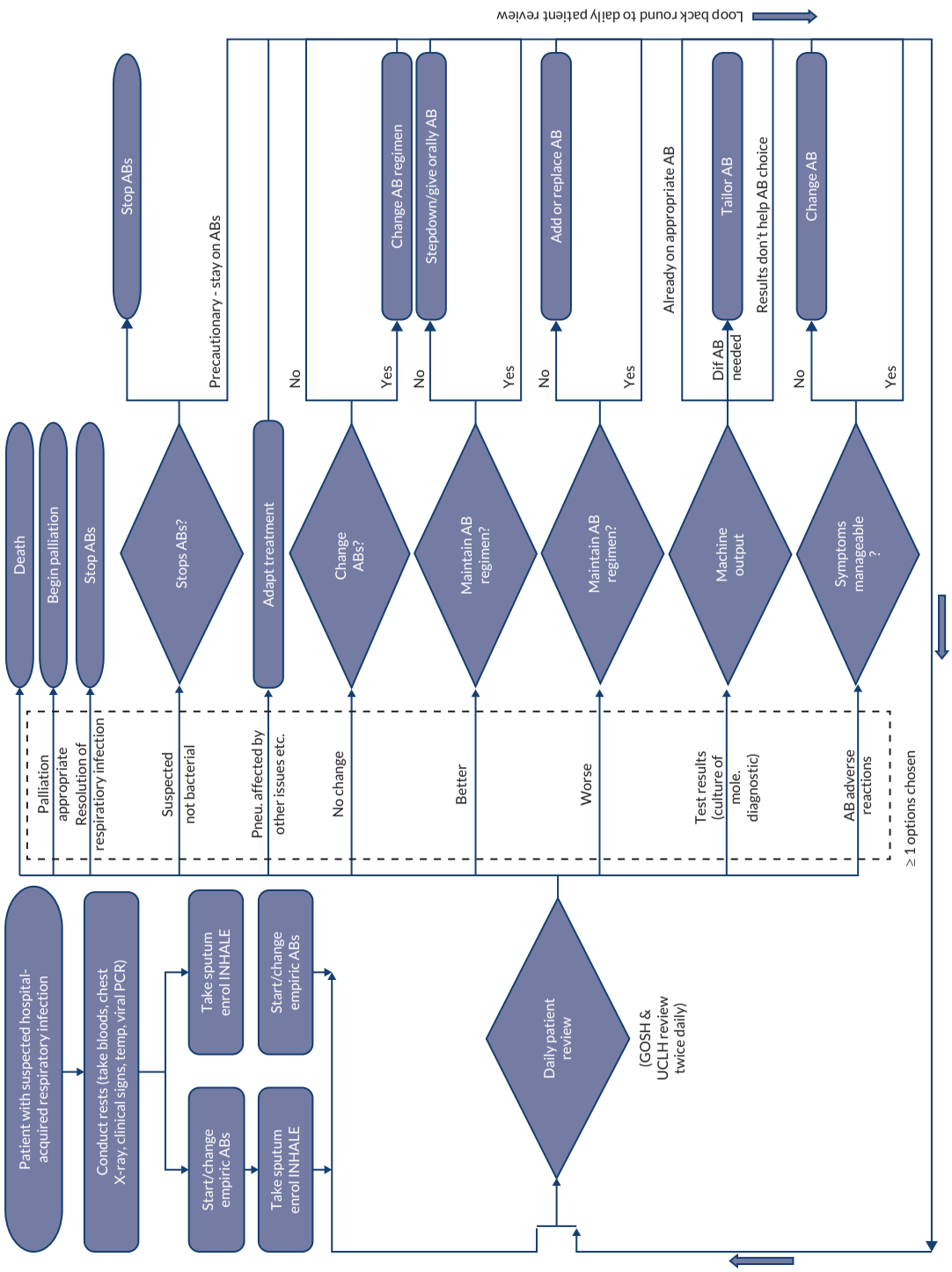


FIGURE 17 Simplified clinical pathway used to inform the health-economic model building resulting from discussions with clinical experts. AB, antibiotic.

Appendix 8 Health-economic model

A simple model structure was informed by the review of health-economic models in HAP/VAP and the clinical pathway. This is given in *Figure 18*. In this model, patients with HAP/VAP can receive either the intervention or the control. In either case, patients could have clinical cure at 14 days or not. For both, those with clinical cure and those without, patients could be alive at 28 days or not. To investigate the potential QALY effects of the intervention, we assumed that being alive at 28 days would carry a QALY benefit taken from the literature. In *Figure 18*, the square node represents a decision node, representing the choice of whether to implement the intervention on not. Given this decision, different events could occur – these are given by round 'chance' nodes. At each end node, costs and the probability of ending up at that node are calculated. Also calculated are expected benefits (in terms of QALYs). This allows for the expected costs and expected benefit of intervention to be calculated compared to the control.

Model parameters

The majority of model parameters are taken from the analysis of WP3 health-economic data and are given in *Table 23*. The probability of cure and 14 days for both the control and intervention groups were taken from the full health-economics data and were modelled using a beta distribution. A beta distribution is common in health-economic models for modelling probabilities as the beta distribution is constrained to be between 0 and 1. We also calculated probabilities of mortality at 28 days which were conditional on the 14-day cure status. Again, these were modelled using beta distributions. For the eight possible end nodes shown in *Figure 18*, we calculated a cost from trial data for that group of individuals. These values are shown in *Table 23* and were modelled using gamma distributions. Again, this distribution is often used to model cost data as it cannot take a value < 0 and can be skewed (as is typically seen in cost data). For those alive at 28 days, we assumed at QALY benefit taken from the literature.[34] These authors assumed survival was similar to the case for sepsis and assumed a mean survival of 15 years and a mean QALY value of 0.92.

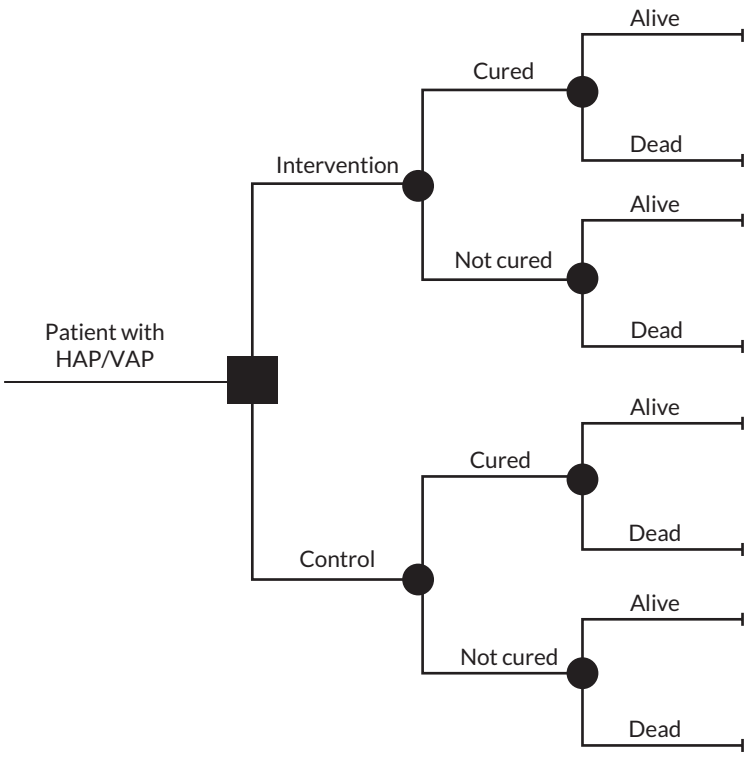


FIGURE 18 Health-economic model structure.

TABLE 23 Parameters used in the health-economic model

	Mean	Distribution	Source
Probabilities			
Probability of cure at 14 days – Control	0.65	Beta (alpha = 172, beta = 94)	WP3 health-economic analysis
Probability of cure at 14 days – Intervention	0.57	Beta (alpha = 152, beta = 116)	WP3 health-economic analysis
Probability dead at 28 days (control and cure)	0.13	Beta (alpha = 22, beta = 150)	WP3 health-economic analysis
Probability dead at 28 days (control and not cured)	0.50	Beta (alpha = 47, beta = 47)	WP3 health-economic analysis
Probability dead at 28 days (Intervention and cure)	0.08	Beta (alpha = 12, beta = 140)	WP3 health-economic analysis
Probability dead at 28 days (Intervention and not cured)	0.57	Beta (alpha = 66, beta = 50)	WP3 health-economic analysis
Cost			
Cost control – cured and alive	£39,214	Gamma (alpha = 0.7, beta = 57,080)	WP3 health-economic analysis
Cost control – cured and dead	£19,752	Gamma (alpha = 1.5, beta = 12,824)	WP3 health-economic analysis
Cost control – not cured and alive	£80,177	Gamma (alpha = 1, beta = 81,915)	WP3 health-economic analysis
Cost control – not cured and dead	£21,440	Gamma (alpha = 1.4, beta = 15,034)	WP3 health-economic analysis
Cost intervention – cured and alive	£32,565	Gamma (alpha = 0.9, beta = 37,295)	WP3 health-economic analysis
Cost intervention – cured and dead	£27,003	Gamma (alpha = 1.8, beta = 15,136)	WP3 health-economic analysis
Cost intervention – not cured and alive	£65,606	Gamma (alpha = 1.9, beta = 34,815)	WP3 health-economic analysis
Cost intervention – not cured and dead	£15,575	Gamma (alpha = 1.4, beta = 10,796)	WP3 health-economic analysis

Analysis

A decision tree model was constructed in MS Excel. This was a probabilistic model where parameters were modelled using random draws from appropriate distributions (see *Table 26* for details of distributions used). The model was run for a total of 5000 simulations. Uncertainty was modelled using incremental cost-effectiveness planes.

Results

Results of the simple model described above are presented in *Table 24*. Here, estimated total cost difference is −£6848 with the intervention group having a lower cost. Estimates of total QALY were higher in the control group, driven by the higher rates of 14-day cure in this group. *Figure 19* shows the incremental cost-effectiveness plane for this analysis. These show incremental analysis for each sample for the comparison of intervention compared to control. This shows the high degree of uncertainty in the model results. At a cost per QALY of £20,000, the intervention has a 43% chance of being the most cost-effective, with the control group having a 57% chance of being the most cost-effective option.

TABLE 24 Results from decision tree model

	Mean cost	95% percentile	Mean QALY	95% percentile
Control	£41,686	(7002 to 122,691)	10.24	(7.94 to 12.58)
Intervention	£34,838	(8758 to 87,353)	9.80	(7.65 to 12.09)
Incremental analysis	−£6848		−0.44	

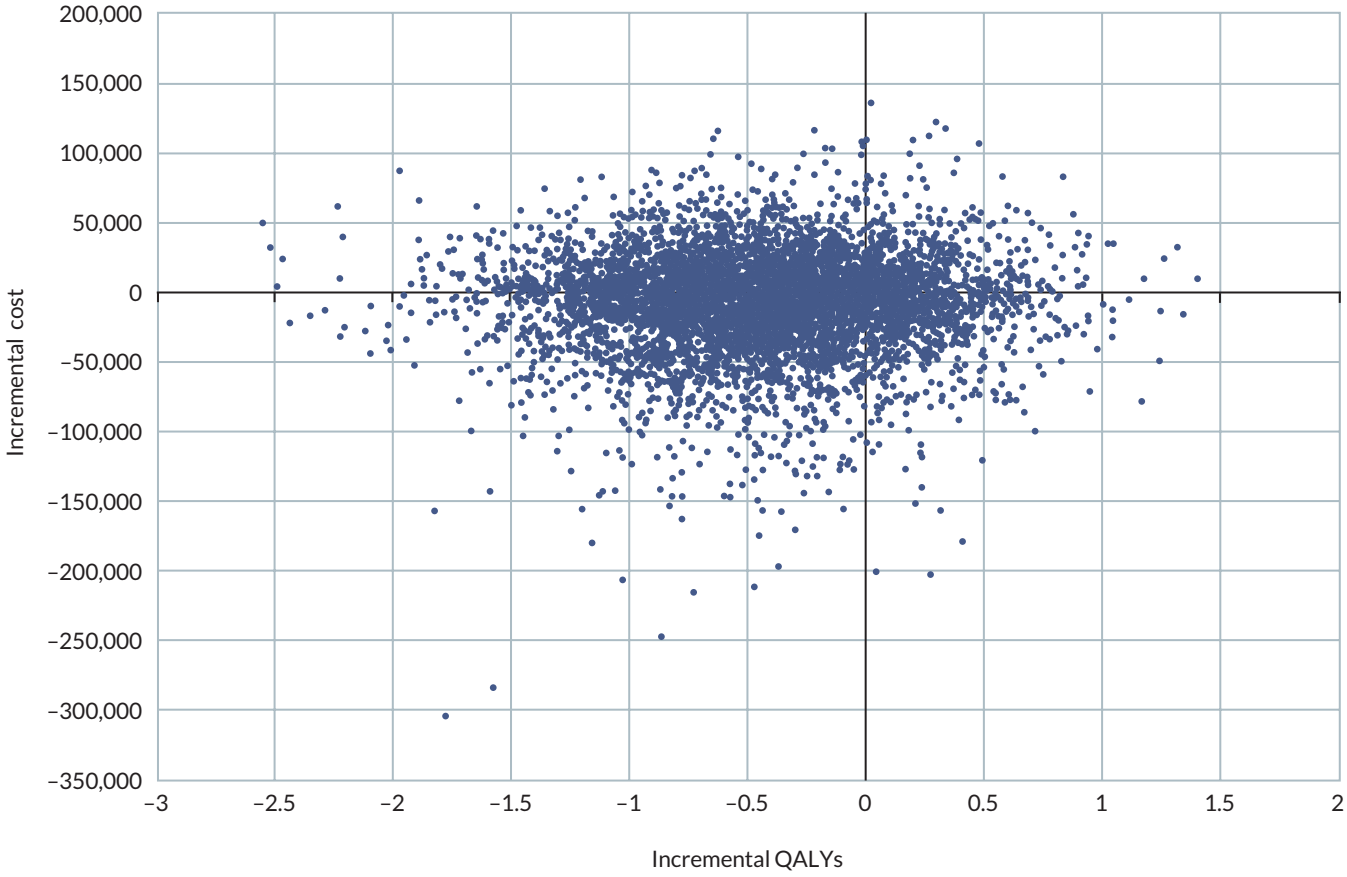


FIGURE 19 Incremental cost-effectiveness plane.

Discussion

Results of this simple model parallel those of the 'within-trial' economic analysis: when differential cure rates are considered, there is not a clear case for the intervention being cost-effective. However, there is large uncertainty inherent in this analysis, so we conclude no strong case for either alternative.

Appendix 9 Details of the costing methodology for the cost of the test used in the trial

An overview of the intervention costing is provided in *Table 25*. In the case of fixed costs, such as purchase costs, it is necessary to estimate the number of tests conducted per year to enable estimation of a cost-per-test. In the following cost estimates, we have assumed 30 tests will be conducted each month (360 annually), based on expert opinion.

There are broadly four cost components relating to the intervention: purchasing or leasing the BioFire FilmArray Pneumonia Panel; purchasing pneumonia panels; purchase of the QC reagents; and staff time to use the machine.

The FilmArray can either be purchased outright or leased from BioFire. As the machine would have a useful life in excess of 1 year, to calculate an appropriate annual cost it is necessary to annuitise the outright purchase cost – we use the formula from Drummond *et al.*,[35] in which we assumed: a resale value of zero; an operational lifetime of 5 years; and a discount rate of 3.5%. With a purchase price of £55,000, this gives an annual cost of £12,181. Figures provided by BioFire.

It costs £4697 to purchase 30 pneumonia panel tests (figures provided by BioFire). We estimate a cost of £10 for the delivery of this batch of tests (based on earlier WPs). This results in a cost-per-test for consumables of £157.

Figures provided by BioFire indicate a cost of $726 to order and have delivered six QC reagents (specifically, six pairs of positive and negative controls). Assuming an exchange rate of $1 = £0.74 (15 February 2022), this comes to a cost of £536. One QC reagent is used quarterly, but their shelf life does not last beyond a year: thus, we have assumed four reagents are used and two discarded annually.

Consulting with clinical members of the research team, it was assumed that it would take 5 minutes of clinician time to use the machine placed within the ICU. Similarly, they suggested it would be most likely that a band 6 nurse would process samples. Drawing a cost per hour of employment of £51 from Personal Social Services Research Unit, this results in a cost/test of £4.25.[36]

In total, across the cost components, this results in a cost-per-test of £196 when the BioFire FilmArray Pneumonia Panel is purchased outright, and £213 when leased.

TABLE 25 Costing of BioFire FilmArray Pneumonia Panel, based on a usage of 30 tests per month (360 annually)

		BioFire FilmArray Pneumonia Panel	
Intervention cost components		**Purchased**	**Leased**
BioFire Torch 2 FilmArray System purchase/lease	Purchase cost	£55,000	
	Resale value	£0	
	Operational lifetime (years)	5	
	Discount rate	3.5%	
	Annuitised cost	£12,181	£18,000
	Cost/test	**£34**	**£50**
Consumables i: Pneumonia panel	Panel purchase (30 tests)	£4697	
	Delivery/panel	£10	
	Cost/test	**£157**	

continued

TABLE 25 Costing of BioFire FilmArray Pneumonia Panel, based on a usage of 30 tests per month (360 annually) (*continued*)

Intervention cost components		BioFire FilmArray Pneumonia Panel	
		Purchased	**Leased**
Consumables ii: QC reagents (used once a quarter; two tests discarded due to shelf life)	Purchase and delivery of 6 tests	$726	
	Exchange rate	$1 = £0.74 (15 February 2022)	
	UK purchase cost	£536	
	Cost/test	**£1.49**	
Staff time to use machine	Staff time to use machine	5 minutes	
	Nurse band 6, cost per working hour	£51	
	Cost/test	**£4.25**	
Total cost/test		**£196**	**£213**

Appendix 10 EuroQol-5 Dimensions, five-level version

Where possible, an EQ-5D-5L value was obtained from participants at 21 days. For most participants this could not be obtained; however, we were able to obtain values from 78 individuals (76 providing completed responses and 2 incomplete responses were given). EQ-5D-5L responses were valued using the published Hernandez algorithm. There were 4 individuals aged below 18 (ages: 6, 7, 13, 17), for whom an age of 18 was assumed so their responses could be valued using the valuation algorithm.

Originally, this was intended to inform the health-economic modelling; however, owning to small numbers this was not used – instead, the economic model uses literature values taken from a study of sepsis. Values obtained are given in *Table 26*. These are divided into those who gave a value in hospital (n = 47) and those who have a value in the 21-day telephone interview (n = 29). As expected, overall health as stated by the EQ-5D-5L is low at 0.481. Again, as expected, those who were able to be discharged home reported better health than those still in hospital with a mean utilities of 0.665 and 0.377, respectively. Beyond the overall scores, it can be informative to view the distribution of the responses to the five individual questionnaire items. This is shown in *Figure 20*. These scores vary from 1 (least severe/no problem) to 5 (most severe). The domain with the most severe responses was usual activities, followed by mobility and self-care.

TABLE 26 EuroQol-5 Dimensions, five-level version values obtained at 21 days

Location at 21 days	*N*	Minimum	Q1	Median	Mean	Q3	Maximum
All	76	−0.31	0.224	0.593	0.500	0.754	0.987
Still in hospital	47	−0.31	0.086	0.445	0.381	0.669	0.987
At home	29	0.055	0.620	0.699	0.692	0.842	0.987

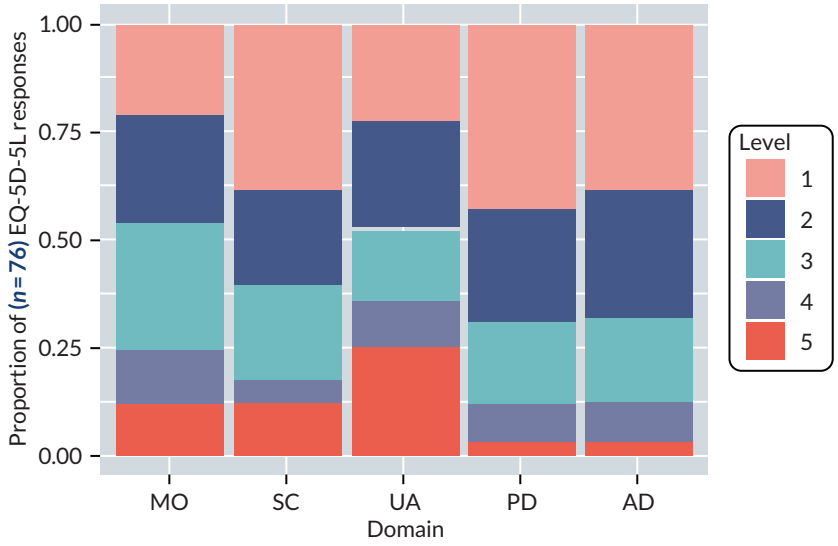
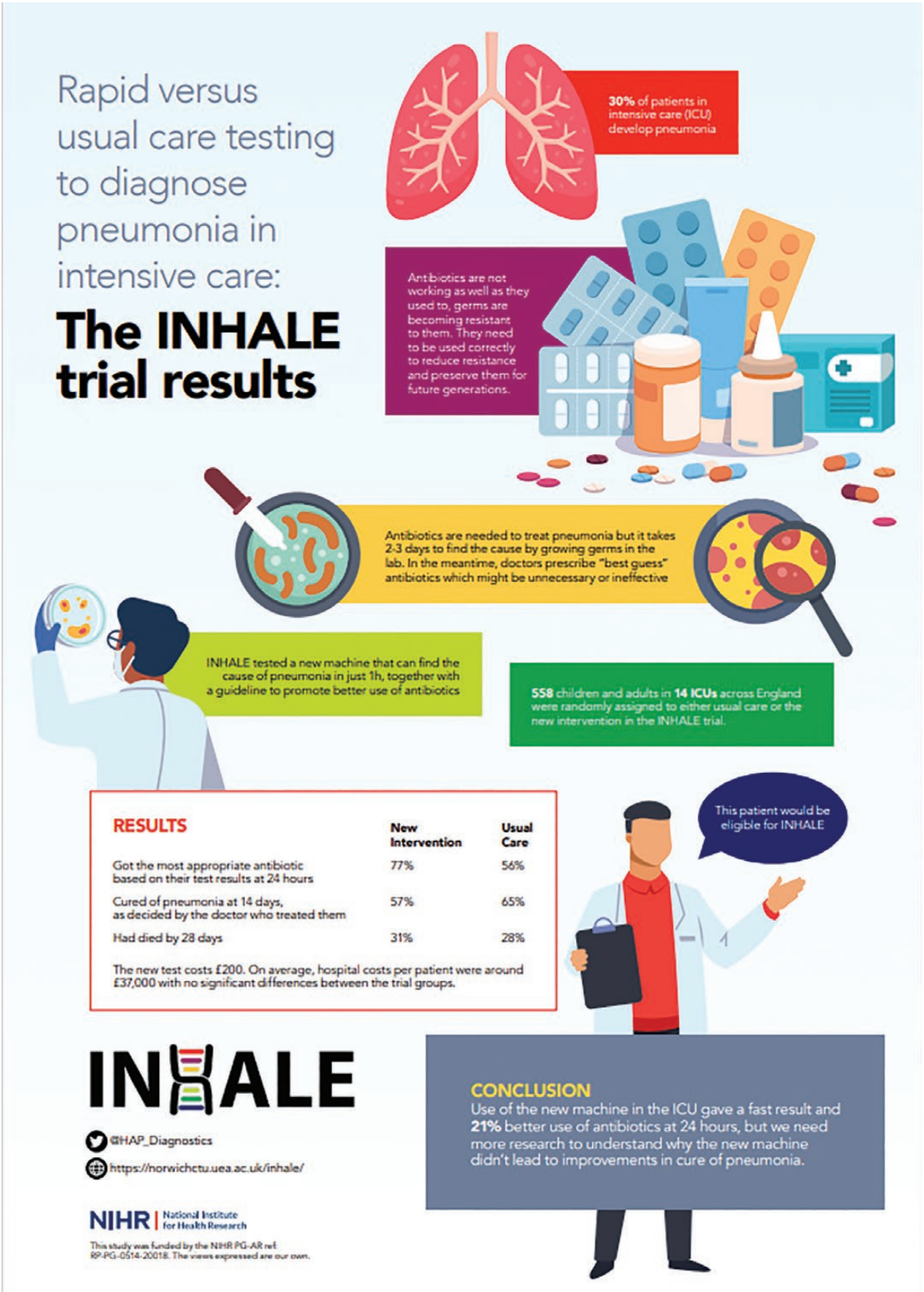


FIGURE 20 Individual EQ-5D-5L responses. How EQ-5D-5L respondents with complete data split in responses (from 1 – 'no problems' to 5 – 'extreme problems') across the measure's five dimensions [mobility (MO), self-care (SC), usual activities (UA), pain/discomfort (PD) and anxiety/depression (AD)].

Appendix 11 INHALE infographic



EME
HSDR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library