Longitudinal trends and cross-sectional analysis of English national hospital antibacterial use over 5 years (2008-13); working towards hospital prescribing quality measures.

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Short running title: Antibacterial usage in English acute hospitals

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Summary

Background: There is global concern that antimicrobial resistance is a major threat to healthcare. Antimicrobial use is a primary driver of resistance but little information exists about the variation in antimicrobial use in individual hospitals in England over time or comparative use between hospitals.

Objectives: To collate, analyse and report issue data from pharmacy records of 158 National Health Service acute hospitals.

Methods: Cohort study of in-patient antibacterial use in acute hospitals in England analysed over a 5 years through a data warehouse from IMS, a leading provider of information, services and technology for the healthcare industry. Around 99% of National Health Service (NHS) hospitals were included in a country of 50 million resident population.

Results: There was a dramatic change in the usage of different groups of antibacterials between 2008 and 2013 with a marked reduction in use of first-generation cephalosporins by 25.7%, second-generation cephalosporins by 41%, but little change in use of third-generation cephalosporins (+5.7%) and fluoroquinolones (+1.6%). In contrast, co-amoxiclav, carbapenems and piperacillin/tazobactam increased by 60.1%, 61.4% and 94.8% respectively. There was a wide variation in the total and relative amounts of antibacterials used between individual hospitals.

Discussion: Longitudinal analysis of antibacterial use demonstrated remarkable changes in NHS hospitals, probably reflecting governmental and professional guidance to mitigate the risk of *Clostridium difficile* infection (CDI). The wide variation in usage between individual hospitals suggests potential for quality

improvement and benchmarking. Quality measures of optimal hospital antimicrobial prescribing need urgent development and validation to support antimicrobial stewardship initiatives.

Background.

Antimicrobial resistance is a global economic and clinical concern.[1] There are fears that antimicrobial chemotherapy –"may no longer be readily available in the near future"[2] though, in reality, it is more likely that we will see a gradual erosion of effectiveness. Several approaches have been advocated to stem this rise in resistance, notably (i) innovative collaborations with the pharmaceutical industry to create new antimicrobials;[3] (ii) manipulating environmental influences that select resistance[4] and (iii) attempting to conserve existing agents by promoting optimal use of antimicrobials and the increased use of more rapid diagnostics to guide decision making.[5]

Antimicrobial stewardship programmes aim to improve the quality of prescribing.[6,7] However, to be successful they require a better understanding of current antimicrobial usage in both hospital and out-patient (ambulatory) care. "If you can't measure it, you can't manage it' was the theme for a conference on antimicrobial stewardship in London UK in 2008.[8]

Since then there has been some progress in measuring national hospital-level antimicrobial use but little in the ability to compare individual hospital use[9]. Ecological studies on the use of antimicrobials have mainly been limited to national overviews, or data from individual centres.[10]

The European Surveillance of Antimicrobial Consumption Network (ESAC-net) at ECDC has developed a method to estimate the variation in antimicrobial prescribing in hospitals by serial point prevalence surveys (PPSs) with the aim of producing

reliable and standardized patient-linked data every 5 years at European, national, and local hospital levels.[11]

These PPSs can illustrate how antimicrobials are being prescribed but they are subject to several limitations. First, they only provide information over a very short time frame (often only one day) whereas some infections (eg community-acquired pneumonia) are seasonal; secondly, they are labour-intensive and data recording is made by a variety of individuals with the possibility of heterogeneity of interpretation and errors; thirdly, in large national or EU surveys data feedback is often long delayed.

Ecological studies based on routine surveillance of antimicrobial use may offer an additional and/or alternative method to study the relationship between antibacterial use and resistance and to support interventions designed to improve prescribing.[10] In order to start to study such relationships a validated source of antibacterial usage data must first be established. We therefore sought to source and review data on the total usage of antibacterials in acute hospital trusts in England over a five-year period.

Methods

Design

This was an ecological study in which data on antibacterial agents (British National Formulary [BNF] Class 5.1, anatomic, therapeutic, chemical [ATC] Class J01) dispensed to in-patients were collected from 98% (n=158) of National Health Service (NHS) Hospital Trusts (i.e. groups of hospitals under the same management) in England between April 2008 and March 2013. Inpatient dispensing was identified from hospital pharmacy systems. Longitudinal analysis of these data over a five-year

period between 2009 and 2013 and cross-sectional analysis of the 2012-13 period was undertaken.

Data collection

Hospital pharmacies in the UK provide aggregate monthly data on all medicines issued to in-patients, wards and clinics to IMS http://www.imshealth.com/portal/site/imshealth, a leading provider of information, services and technology for the healthcare industry. In return IMS reimburses the hospital trusts for these data and provides databases and analytical support that is used for benchmarking by more than 10 regional groups in the UK. IMS receives data from 99% of acute hospitals in England. Three Trusts were excluded from this study for either contractual reasons or data quality issues identified in the study period.

Data were collected at hospital (not nursing homes) level from issues to wards, clinics and patients and these were then grouped for each acute hospital trust. All data, regardless of the time period to which it related, were grouped according to the trust definitions that applied in 2012-13 (i.e. they are comparative over time at a hospital level even if trusts or hospitals have merged and demerged over a time period). All data were converted to the WHO standard Defined Daily Dose and ATC classifications.[12] The hospital trusts were anonymised prior to analysis as per contracts put in place by those trusts with IMS Health, so further examination of the characteristics of each were not available for analysis. Dispensing for out-patients and out-patient clinics were excluded.

Where cross sectional analysis was undertaken, the standard ECDC denominator data, 1000 BD, for each hospital were obtained to ensure

standardization for hospital size and activity [13]. Admission data for all hospital trusts in England for each year were also obtained[14].

During the observation period the Department of Health, and professional societies issued number of reports and guidance documents which may have influenced antimicrobial prescribing in English hospitals.

These are reported in Table 1.

Data cleaning

Descriptions of products, wards and specialties varied from trust to trust. Where dosage was patient dependent, quantities were provided as free text. As data fields were not used consistently in all trusts, the data received from hospital pharmacies were standardized on receipt, following investigation of the pharmacy system and structure by IMS.

After standardization, data were examined for size and trend breaks at hospital and product level. A dedicated field team that also provides analytical support to NHS regions investigated unknown product or ward descriptions. The resulting dataset was also used for reports for the National Health Service (NHS), the UK Department of Health and interested pharmaceutical companies.[15]

Despite this cleaning, a number of caveats should be noted with regard to the data supplied by hospital pharmacies to IMS:

Reconstitution services A small number of hospitals purchased some or all reconstituted medicines (mainly for parenteral administration) from specialist private reconstitution services. Records of such purchases were not always held within the hospital pharmacy system. However, only one hospital in the study was unable to provide IMS with information relating to usage of antibiotics sourced via such a reconstitution service. In addition, the data extracted from pharmacy systems did

not always record the quantity of reconstituted product dispensed within the pharmacy system. The volumes of drug so affected is unknown but an analysis of data relating to antibiotics containing clavulanic acid, amoxicillin or teicoplanin showed a total of only 4 lines of data had been dropped between 2010-2013.

Private patients and ward level data

Private patient and ward-level data. These data included antibiotics dispensed to private patients in NHS hospitals but private hospital usage was not included in the analysis.

Parallel imports and special formulations. Some hospital pharmacies imported medicines from overseas, referred to as parallel imports. Parallel imports were not included directly in the IMS Hospital Pharmacy Audit data, but, where drugs were available in the same strength and form as a UK pack, the volume of the parallel import was expressed in terms of equivalent UK packs. Where, however, the parallel import was not available in a UK strength and form, then these products were ignored. In the study period, the UK tended to be a net exporter of products rather than an importer, and hospitals were required to stop all parallel export in 2010[16]. It is therefore unlikely that the use of parallel imports affects this study to any extent. Some hospitals also bought in special formulations of non-licensed products. These were not included in the IMS data.

One-stop" dispensing. Many hospitals have adopted a scheme whereby medicines used during inpatient stay are continued for several days when the patient leaves the hospital. Antimicrobials issued in this fashion would thus constitute discharge medication, with the patient required to finish the prescribed course. Such dispensing was fully included in the present data where the trust allocated such dispensing to in-patients within its pharmacy system.

Day surgery usage. All Trusts included in this study created a specific cost centre for day case theatres, to which they were able to allocate drug use. All day case use was allocated to out-patient by IMS except in the case of three Trusts where returns were shown as in-patient use. In the five years to March 2014, the returns allocated to in-patient use totalled less than 50 packs. Day surgery use was thus excluded from this study.

Results

Longitudinal analysis

Data were obtained from 158 NHS hospital trusts in England that covered a resident population of around 50 million over a five-year period from 2008 to 2013 (NHS financial year runs from April 1st of the preceding year to March 31st of the stated year). As shown in Figure1 and Table 2, the total 12-monthly usage of all antibacterial agents increased by 12.6% between 2008-09 and 2012-13.

Figure 2 describes the changes in total antibacterial usage using two different population denominators. During the 5-year period reported there was a reduction in total patient days in English hospitals of 8.4%, whilst there was an *increase* in the number of patient admissions of 7.0% and a reduction in average length of stay (from 5.7 days to 5.2 days) of 8.8%.[14] Taking these changes into account, there was an approximate 23% increase in antibiotic usage (DDDs) per 1000 patient bed days but a much smaller increase of 5.2% DDDs/1000 patient admissions (Figure 2).

Changes in the use of individual groups of agents over time are shown in Table 2. (Data are for DDDs issued each year in 98% of English NHS acute hospital trusts). Among the β-lactams, there was a marked increase in the use of piperacillin/tazobactam (94.8%), carbapenems (61.4%) and co-amoxiclav (60.1%), a slight increase in use of unprotected amoxicillin/ampicillin (9.1%), but a 17.2%

reduction in the use of flucloxacillin. There was also a reduction in the overall use of cephalosporins with a 24.7% fall in first-generation cephalosporins (cefadoxil, cefalexin and cefradine), a 41.0% fall in second-generation cephalosporins (cefaclor and cefuroxime) but a 5.7% increase in use of third-generation cephalosporins (cefixime, cefotaxime, cefpodoxime, ceftazidime and ceftriaxone). Interestingly, use of third-generation cephalosporins decreased between 2008-09 and 2010-11 but increased thereafter (Table 2).

Increases in use were seen in the other main classes of antibiotics including glycopeptides (30%), aminoglycosides (23.3%), macrolides (19.7%), tetracyclines (14.1%) and trimethoprim (11.4%).

Cross-sectional analysis

Data on usage of antibacterials were compared across 157 NHS hospital trusts in England for the year 2012-13. Data from one hospital was omitted from this stage of the analysis, because its DDD/1000 BD profile was substantially different from the rest of the cohort.

As shown in Figure 3, there was marked variation in the total use of antibacterials between trusts, ranging from 81 to 2869 DDDs per 1000 BDs, The median value for these data was 1234 DDD/1000 BDs (IQR=264) and the mean 1297 DDD/1000 BDs (SD 460). A similar degree of inter-hospital variation was seen for individual classes of antibiotics. Figures 4 and 5 show the distribution of usage of fluoroquinolones and cephalosporins respectively, across all hospital trusts in England. These groups of agents had been the subject of governmental advice to reduce their usage as they had been associated with *Clostridium difficile* infection (CDI). Figure 6 shows the distribution of carbapenem use within English hospitals which ranged from 0 to 167 DDDs per 1000 bed days. Figure 7 shows the distribution for piperacillin/tazobactam

which ranged from 0 to 140 DDDs per 1000 bed days across all these hospitals.

Discussion

The data in this study appear to reflect the success of national policies intended to reduce the use of cephalosporins which, with fluoroquinolones, have been identified as risk factors associated with the development of CDI.[17] Previous substantial reductions in the usage of fluoroquinolones and cephalosporins have been associated with a corresponding substantial increase in the use of co-amoxiclav, piperacillin/tazobactam, teicoplanin and meropenem[9]. Since 2007 there has been a substantial fall in CDI rates in England from 2007/8 until 2011/12 with the reported absolute numbers of CDIs decreasing from 33,442 to 7,670.[18] This was associated with a four-fold reduction in fluoroquinolone and a three-fold reduction in cephalosporin use over this period[9]. It is interesting to note that over this period of time there was declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream Enterobacteriaceae from the UK [19].

However the present study has shown a consequent rise in the use of carbapenems and anti-pseudomonal penicillins which is a cause of considerable concern due to the global spread of carbapenamases-producing Enterobacteriaceae.[20]

This cross-sectional analysis of antibacterial usage across 158 hospital trusts in England offers interesting scope for understanding differences in use as the study observed a five-fold difference between hospital trusts in the total use of antibacterials in 2012-13. Similar magnitude of drug usage ranges is seen with fluoroquinolones, cephalosporins and carbapenems. Possible reasons for this variation include: (1) Differences in case-mix in terms of clinical specialties (eg oncology); (2) Variation in historical use of certain agents; (3) Variation in rates of

antimicrobial resistance; (4) Variation in the development of antimicrobial stewardship [21]. A benchmarking exercise in France demonstrated how consideration of just four variables (proportion of patient-days in intensive care, surgery or medicine and presence of an infectious diseases physician) explained 84% of the inter-hospital variability in antibacterial consumption [22].

Hospitals that have predominantly paediatric in-patients would be expected to lie at the far left hand side of all these graphs as they would appear to use, in unadjusted DDD, fewer antibacterials, as the doses are substantially lower. Similarly, those hospitals that have a high proportion of respiratory patients e.g. cystic fibrosis specialist centres may be expected to have a proportionally higher usage of third-generation cephalosporins and carbapenems. Clearly further work is needed to refine such indicators with links to patient case mix, microbiological sensitivities, level of antimicrobial stewardship and patient outcomes. However, such type of data analysis is a further step towards developing risk adjusted benchmarking between hospitals.

The World Health Organization recently published a list of Critically Important Antimicrobials (CIA) for Human Medicine and many countries have adopted these and developed policy around them.[23] This has been recognised by the Council of the European Union.[24] The WHO lists seeks the prioritization of the antimicrobials characterized as critically important for most urgent development of risk management strategies in order to preserve their effectiveness in human medicine and notes that increased volume of usage directly relates to development of resistance. Thus the importance of measuring dispensing volumes and the ability to compare trends and total antimicrobial usage between countries and between hospitals within countries should contribute to greater sophistication in determining

the cause and trends in antimicrobial resistance.[25] In England, following the Department of Health's Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infections recommendation, the Department of Health in collaboration with the National Health Service Commissioning Board has set up the English Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR), which provides detailed information on total-risk adjusted hospital antibiotic prescribing and rates of use of the key CIA's.

Comparison with other data

Antibiotic use in French hospitals has been noted as among the highest in Europe with median antibiotic use ranging from 60 DDD/1000 patient days (PD) in long-term care and psychiatric hospitals to 633 DDD/1000 PD in teaching hospitals and up to 1466 DDD/1000 PD in intensive care units (ICUs)[22]. In Swiss hospitals between 2004 and 2008, the total consumption of systemic antibiotics rose from 461 to 540 DDD per 1000 occupied bed-days, and from 1016 to 1143 DDD per 1000 occupied bed-days in the intensive care units[26]. Our study reported a higher average of antibacterial use than those in the French hospitals. However, this might be partly explained by differences in the number or classification of hospital beds. For example in France in 2011 there were 637.2 beds per 100,000 inhabitants whereas in the UK there were 289.6 beds per 100,000 inhabitants.[27] The inference from this is either there are more patients requiring hospitalisation in France or else beds are occupied with patients who are less severely ill. Considerable care must be taken when comparing prescribing rates between countries with different healthcare systems and different definitions of hospital and ambulatory care beds. Furthermore with falling duration of stay by patients in NHS hospitals and stable or reducing bed numbers, using patient days may not offer a useful population denominator; patient

301 admissions might be a more appropriate indicator especially when making
302 international comparisons. Indeed, a phenomenon of intensification of antibiotic use
303 (expressed as DDDs/100 patient-days) has been described in Dutch hospitals
304 associated with decreasing length of stay, despite no change to the number of
305 individual patients exposed to antibiotics [28]. An alternative approach was taken by
306 the authors of a study in 70 US hospitals which employed days of therapy (DOT) and
307 length of therapy (LOT) to benchmark antibacterial usage.[29] There is, as yet, no
308 single agreed method of comparing hospital prescribing use, although the Trans
309 Atlantic Task Force on Antimicrobial Resistance (TATFAR) is working to develop
310 these standards.[30] Ecological studies allow comparisons to be made and whilst they
311 will never replace patient-linked data that link diagnosis, co-morbidity,
312 microbiological culture and susceptibility data and outcomes they are helpful in
313 understanding trends in usage of these critical antimicrobials. Patient-linked data
314 require sophisticated individual patient issue data and complex alignments and
315 standardization of healthcare databases. These patient-linked data will not replace
316 disease specific databases where tight process control and incentives can improve
317 clinical outcomes[31]. Electronic prescribing systems are still not widespread across
318 UK hospitals but when they are they will be expected to push the development of
319 quality indicators and comparative analyses.[9]
320 There are a number of limitations of this work and which require further research.
321 The database has no linkage to patient data such as diagnosis, investigations,
322 microbiological results and outcomes. Although the coverage of hospital trusts is
323 almost complete there were no data available on the type of hospitals from which the
324 data come, which might explain differences in antimicrobial usage.

Conclusions

There has been a remarkable change in the use of antibacterials in English hospitals over the last 5 years with a worrying increase in reliance on a very small number of critically important antibacterials.

Longitudinal analysis of antimicrobial consumption offers a useful instrument for observing trends in consumption over a number of years for individual hospitals, groups of hospitals or whole countries. The level of analysis now available allows the development of quality measures focused both on safely reducing total hospital antibiotic prescribing and reductions in key antibiotics such as carbapenems.

Cross-sectional data can provide useful benchmarking data for antimicrobial usage in individual hospitals and identify outliers, but the optimal denominator, numerator and risk adjustment remains to be determined. We believe this is the first time a database on antimicrobial usage has been created that is able to examine usage in the majority of individual hospitals within a single large country. The formation and work of the national programme will facilitate the continuous monitoring of antimicrobial usage and linkage with resistance on a national level and enable comparison with other countries. The impact on antimicrobial resistance of this dramatic reduction in use of specific classes of antibiotics in English hospitals remains to be seen.

Transparency declarations

JC Chaired the Antimicrobial Stewardship Sub-Group of the Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection. (Travel expenses only). Has Chaired and presented at meetings supported by Astellas. Honoraria received.

PS – Is employed by IMS Health. IMS Health provides information services to the pharmaceutical industry and governments, including the manufacturers of antibiotics and the Department of Health.

DAO – none declared

EC - none declared

MD - none declared

CF - none declared

KH – Occasional consultant to Astellas, MSD and AstraZeneca.

AH – none declared

PH – none declared

APJ is Editor-in-Chief of the Journal of Antimicrobial Chemotherapy but took no part in and did not influence the editorial process.

DML is partly self-employed and consults for numerous pharmaceutical and diagnostic companies, including Achaogen, Adenium, Allecra, Astellas, AstraZeneca, Bayer, Basilea, bioMerieux, Cubist, Curetis, GSK, Kalidex, Merck, Meiji Seika, Pfizer, Roche, Tetraphase and Wockhardt; he holds grants from Basilea, Cubist, Meiji Seika, Merck; has received lecture honoraria or travel reimbursement from AstraZeneca, Curetis, GSK, J&J, Merck, Novartis, Pfizer and Tetraphase and holds shares in Dechra, Eco Animal Health, GSK, Merck and Pfizer, collectively amounting to <10% of portfolio value.

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CMcN - none declared

SW - none declared

SH – none declared

MS – none declared

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494 **Table 1.** Reports and guidance documents issued by various governments and
495 societies between 2006 and 2011
496

Year	Report
2006	Antimicrobial prescribing policy and practice in Scotland: recommendations for good antimicrobial practice in acute hospitals[32]
2006	The Health Act 2006: Code of Practice for the Prevention and Control of Healthcare Associated Infections[33]
2006	2006 Essential Steps to Safe, Clean Care: Reducing Healthcare-Associated Infections[34]
2007	The Best Medicine: The Management of Medicines in Acute and Specialist Trusts[35]
2007	Saving Lives: reducing infection, delivering clean and safe care (Antimicrobial Prescribing)[36]
2007	Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship[37]
2007	Specialist Advisory Committee on Antimicrobial Resistance (SACAR) Antimicrobial Framework[38]
2008	*Clostridium difficile* infection: how to deal with the problem[17]
2008	Clean, Safe Care: Reducing Infections and Saving Lives[39]
2008	High Quality care for all NHS Next Review Stage Review Final Report[40]
2009	The Health and Social Care Act 2008: Code of Practice for health and adult social care on the prevention and control of infections and related guidance[41]
2011	Start SMART then FOCUS[6]
2013	UK 5-year Antimicrobial Resistance Strategy[42]