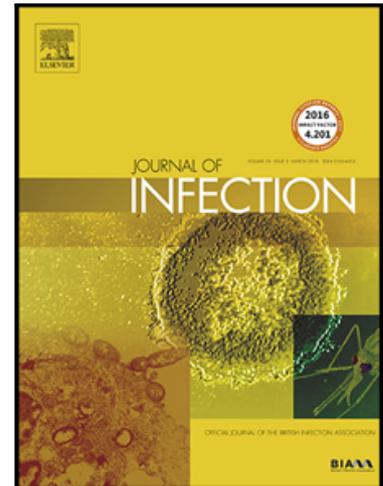


Journal Pre-proof

Impact of hospital antibiotic use on patient-level risk of death among 36,124,372 acute and medical admissions in England

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PII: S0163-4453(21)00648-4
DOI: <https://doi.org/10.1016/j.jinf.2021.12.029>
Reference: YJINF 5372



To appear in: *Journal of Infection*

Accepted date: 17 December 2021

Please cite this article as: Eric P Budgell , Tim Davies , Tjibbe Donker ,
Susan Hopkins Writing – review & editing , David Wyllie , Tim E A Peto , Martin Gill ,
Martin J Llewelyn , A. Sarah Walker , Impact of hospital antibiotic use on patient-level risk of
death among 36,124,372 acute and medical admissions in England, *Journal of Infection* (2021), doi:
<https://doi.org/10.1016/j.jinf.2021.12.029>

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Highlights

- English hospitals seek 1% annual reductions in their antibiotic use
- Antibiotic use per occupied bed-day at English hospitals varies by up to 15-fold
- Adjusting for case-mix, this does not impact on mortality risk for medical patients
- High antibiotic-using hospitals could be safely benchmarked against low users
- Benchmarking against lower-using hospitals could reduce use by up to 1/3

Impact of hospital antibiotic use on patient-level risk of death among 36,124,372 acute and medical admissions in England

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ABSTRACT

Objectives: Initiatives to curb hospital antibiotic use might be associated with harm from under-treatment. We examined the extent to which variation in hospital antibiotic prescribing is associated with mortality risk in acute/general medicine inpatients. Methods: This ecological analysis examined Hospital Episode Statistics from 36,124,372 acute/general medicine admissions (≥ 16 y) to 135 acute hospitals in England, 01/April/2010-31/March/2017. Random-effects meta-regression was used to investigate whether heterogeneity in adjusted 30-day mortality was associated with hospital-level antibiotic use, measured in defined-daily-doses (DDD)/1,000 bed-days. Models also considered

DDDs/1,000 admissions and DDDs for narrow-spectrum/broad-spectrum antibiotics, parenteral/oral, and local interpretations of World Health Organization Access, Watch, and Reserve antibiotics. Results: Hospital-level antibiotic DDDs/1,000 bed-days varied 15-fold with comparable variation in broad-spectrum, parenteral, and Reserve antibiotic use. After extensive adjusting for hospital case-mix, the probability of 30-day mortality changed -0.010% (95% CI: -0.064,+0.044) for each increase of 500 hospital-level antibiotic DDDs/1,000 bed-days. Analyses of other metrics of antibiotic use showed no consistent association with mortality risk. Conclusions: We found no evidence that wide variation in hospital antibiotic use is associated with adjusted mortality risk in acute/general medicine inpatients. Using low-prescribing hospitals as benchmarks could help drive safe and substantial reductions in antibiotic consumption of up-to one-third in this population.

Keywords (MeSH terms): Antimicrobial Stewardship; Anti-Bacterial Agents; Electronic Health Records; Secondary care; Mortality

INTRODUCTION

Antibiotic overuse puts individual patients[1] and whole populations[2] at risk of antimicrobial resistance (AMR). AMR infections cause higher mortality, longer hospital admissions, and increased costs of care[3]. Reducing unnecessary antibiotic use is therefore essential to reduce the selective pressure for resistance[4,5] and avoid other harms including adverse drug events[6], toxicity[7–9], changes to the gut microbiome[10,11], and increased susceptibility to infections such as *Clostridioides difficile*[12–15]. The urgency of this problem is reflected in many national plans to tackle AMR, with 26/30 countries in Europe and North America having established or planned targets to reduce antimicrobial use in humans[16], including the UK which aims to reduce antimicrobial use by 15% between 2019-2024[17].

In England's National Health Service (NHS), primary care antibiotic stewardship initiatives focusing on decisions to start antibiotics have been successful in reducing antibiotic overuse[18], but in hospital practice, prescribers must balance the risks of harm posed by under-treating an infection and those of prolonged or excessively-broad spectrum antibiotic use[19]. For patients with life-threatening infections, even modest treatment delays can increase mortality risk[20], and diagnostic uncertainty means it is often necessary to administer broad-spectrum antibiotics empirically while waiting for additional clinical, microbiological, or radiographic information.

For these reasons, controlling antibiotic overuse in hospitals depends on early antibiotic initiation followed by the review of prescriptions after 24-72 hours to re-evaluate whether continued therapy is appropriate[21]. Different healthcare systems operationalise this approach in different ways, including through "antibiotic timeouts" in the United States[22] and "Start Smart then Focus" in England[21]. Although 20-30% of prescriptions may be safely stopped at review[23], stop and review dates are poorly documented[24] and opportunities to stop early or "de-escalate" – i.e. switch from parenteral to oral antibiotics, or to agents with a narrower spectrum of activity – are often missed[25–28]. In NHS hospitals antibiotic consumption has continued to increase year-on-year[18] despite the introduction of financial incentives to reduce overuse[29].

The issues of clinical urgency and diagnostic uncertainty which make limiting antibiotic overuse in hospitals challenging for clinicians also make attempts to define inappropriate use inherently subjective[30]. Another way to approach this problem is through "benchmarking", whereby low-prescribing organisations are used to drive improvements[31–33]. Previous studies have reported wide variation in both recommended antibiotic prescribing duration[34] and total antibiotic

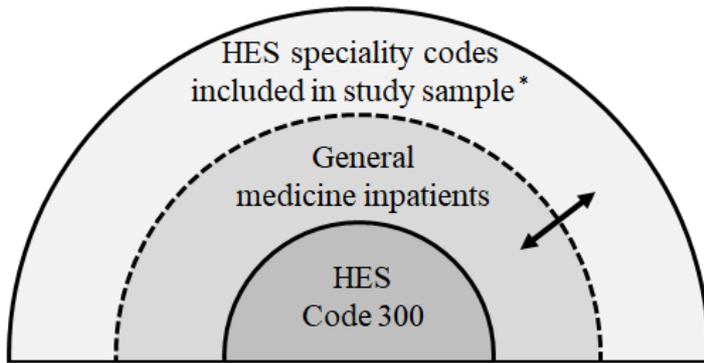
consumption[35,36] among acute hospitals. However, simple comparisons of hospital-level consumption data largely fail to account for case-mix, and in hospitals with more acute patients, systematic under-treatment might be expected to harm patients. Antibiotic stewardship leads at acute hospitals in England have also expressed concern about the safety of a target-driven antibiotic reduction strategy[26]. As a result, many hospitals are benchmarked against their own historical performance rather than externally, and only relatively small reduction targets are sought, such as the 1% year-on-year reduction target used in the NHS Standard Contract with hospital Trusts[37]. Examination of the possibility that substantially driving down antibiotic use could compromise clinical outcomes is needed to reassure practitioners and the public that substantially reducing antibiotic use could be safe.

This study therefore aimed to determine the extent to which variation in antibiotic prescribing was associated with risk of death and hospital readmission in acute/general medicine inpatients in England. Whilst observational analysis can never prove safety, were reduced antibiotic treatment associated with harm, this should be identifiable from case-mix adjusted observational data.

PATIENTS AND METHODS

Data sources

Health Episode Statistics (HES) Admitted Patient Care (APC) data was obtained through NHS Digital's Data Access Request Service (DARS). The HES APC data captures all emergency, planned, and day-case admissions requiring an NHS hospital bed in England, but excludes outpatient visits and Accidents & Emergency (A&E) attendances, which are stored in separate HES databases not accessed in this study[38]. The configuration of acute medical services varies widely across hospitals and general medical patients may be treated under several different adult specialties, with coding practices varying by hospital Trust [39]. The study population was therefore defined using multiple consultant specialty codes (Figure 1). This definition was selected to align with the most commonly used HES specialty codes used to admit adult general medicine inpatients. All inpatient spells and episodes were requested for patients with any eligible admission, in order to calculate hospital exposure. A binary measure of death within 14 and 30 days of admission (all cause, in/out of hospital) was obtained through linkage with data from the Office of National Statistics (ONS), performed in advance by NHS Digital.

Figure 1: Study sample

*Admissions were included if the speciality under which attending consultants were contracted (HES field: mainspef) or worked (HES field: tretspef) included any of the following HES codes in the first or second episode: acute/general medicine (300), gastroenterology (301), endocrinology (302), haematology (303), diabetic medicine (307), cardiology (320), acute internal medicine (326), respiratory/thoracic medicine (340), infectious diseases (350), neurology (400), rheumatology (410), and geriatric medicine (430). Given the variation in coding practices among hospitals, admission codes in general medicine (300) are likely only a subset of general medicine inpatients (perfect specificity, but less than perfect sensitivity). By contrast, the wider set of admission codes used to define this study sample is likely to have very high sensitivity but at the cost of reduced specificity. The extent of the reduction in specificity will vary by hospital depending on local coding practices.

Information on NHS hospital-level antibiotic consumption was obtained from pharmacy dispensing records provided by IQVIA (formerly Quintiles and IMS Health, Inc)[40] through Public Health England (PHE) and measured in defined-daily-doses (DDDs), which enable standardised comparisons of antibiotic use and are defined by the World Health Organisation (WHO) as the average maintenance dose per day for a drug used for its main indication in adults[41]. Data included both inpatient and outpatient prescribing and was only available at the hospital Trust-level (not by specialty) from April/2014. Bed-days by hospital Trust were obtained from PHE[42] and admissions by hospital Trust were obtained from NHS Digital[43].

Data Cleaning

The HES data extract included 88,718,419 hospital admissions (“spells”) from 15,708,476 patients admitted between 1/April/2009-31/March/2017. Data cleaning steps are outlined in Appendix Figure S1. The merging and splitting of NHS hospital Trusts over time was accounted for by updating provider codes so they were current at March/2017 (Appendix Table S1)[44]. This left admissions from 188 NHS hospital Trusts, defined as spells with a provider code of treatment beginning with “R”, thereby excluding primary care Trusts, independent providers and NHS treatment centres[45]. To improve model stability, 49 hospital Trusts with fewer than 50,000 admissions between April/2010-March/2017 were excluded, as were four specialist hospital Trusts which lacked admissions in general medicine, leaving 135 acute hospital Trusts for which antibiotic data was merged (subsequently denoted “hospitals”).

All data processing was carried out in Stata/MP 16 with data held on NHS servers located at the Oxford University Hospitals NHS Trust. We followed the RECORD statement[46] for routinely collected observational health data (Appendix Table S2).

Primary analysis

The primary ecological analysis employed a meta-regression[47] on hospital-level summary data to compare outcomes in acute/general medicine inpatients with hospital-level antibiotic use. This involved deriving confounding-adjusted relative risks of death (all-cause, in/out of hospital) within 30 days of admission using Poisson regression with a robust variance adjustment by patient[48]. Models included admissions between April/2010-March/2017, with prior data used only to calculate previous hospital exposure. A separate model was fit to each hospital (135 models) to allow each potential confounder to have a different impact on the outcome in each hospital, including the same factors in each model regardless of statistical significance. These multivariate models included an *a priori* list of 16 admission factors used to adjust for case-mix in previous analyses (Table 1) and nine interaction terms that improved model fit by lowering the Bayesian information criterion (BIC) of a single multivariate model applied to all hospitals (with hospital as a main effect)[49]. Continuous factors were truncated at the 2.5th, 95th, or 99th percentiles to reduce the influence of outliers, and natural cubic splines were used to account for non-linear effects if they lowered the BIC of a model containing hospital as a factor; the number of knots was chosen based on BIC (Appendix Figure S2). Marginal effects were then derived at the reference level of all model covariates[50].

Table 1: Admission Characteristics of 36,124,372 Acute/General Medical Inpatient Admissions in 135 Acute Care NHS Hospital Trusts, England, April 2010 to March 2017

Characteristic		Admissions (N=36,124,372)
Age (years) ⁱ	Median (IQR)	66 (51-78)
Charlson Comorbidity Index ⁱ	Median (IQR)	0 (0-7)
Index of multiple deprivation (IMD) ⁱⁱ	Median (IQR)	18.5 (10.5-32.2)
Overnight admissions in past year ⁱ	Median (IQR)	0 (0-1)
	0	20,684,824 (57.3%)
	1-3	12,626,901 (35.0%)
	4-6	2,032,847 (5.6%)
	7+	779,800 (2.2%)
Any complex overnight admission in past year (>1 consultant episode, excluding episodes in A&E or rehabilitation)	No ⁱⁱⁱ	27,299,336 (75.6%)
	Yes	8,825,036 (24.4%)
Sex	Female ⁱⁱⁱ	18,197,325 (50.4%)
	Male	17,927,047 (49.6%)
Ethnic category	White ⁱⁱⁱ	30,270,021 (83.8%)
	Asian	1,728,243 (4.8%)
	Black	874,178 (2.4%)
	Mixed/other	640,043 (1.8%)
	Unknown	2,611,887 (7.2%)
Patient classification	Ordinary admission ⁱⁱⁱ	20,663,007 (57.2%)
	Day-case admission	13,559,311 (37.5%)
	Regular day attender	1,902,054 (5.3%)
Admission source	Usual/other residence ⁱⁱⁱ	34,680,673 (96.0%)
	NHS general ward / other care provider	1,443,699 (4.0%)
Admission method	Accident and emergency (A&E) ⁱⁱⁱ	14,477,420 (40.1%)
	Elective / non-emergency	17,218,343 (47.7%)
	Emergency via GP or other	4,428,609 (12.3%)
Immunosuppression	No ⁱⁱⁱ	35,119,372 (97.2%)
	Yes	1,005,000 (2.8%)
Admission time of week	Weekday ⁱⁱⁱ	30,719,593 (85.0%)
	Weekend	5,404,779 (15.0%)
Admission specialty	General medicine ⁱⁱⁱ	19,144,018 (53.0%)
	Gastroenterology	4,991,951 (13.8%)
	Clinical Haematology	4,441,171 (12.3%)
	Cardiology	2,456,490 (6.8%)
	Geriatric Medicine	1,878,069 (5.2%)
	Other	3,212,673 (8.9%)
Admission financial year (April-March)	2010	4,532,650 (12.5%)
	2011	4,712,543 (13.0%)

Characteristic		Admissions (N=36,124,372)
	2012	4,939,621 (13.7%)
	2013	5,124,951 (14.2%)
	2014	5,383,865 (14.9%)
	2015	5,634,144 (15.6%)
	2016 ⁱⁱⁱ	5,796,598 (16.0%)
Admission month	January ⁱⁱⁱ	3,137,513 (8.7%)
	February	2,922,611 (8.1%)
	March	3,170,887 (8.8%)
	April	2,890,364 (8.0%)
	May	2,975,721 (8.2%)
	June	2,951,925 (8.2%)
	July	3,043,793 (8.4%)
	August	2,937,379 (8.1%)
	September	2,962,424 (8.2%)
	October	3,088,645 (8.6%)
	November	3,040,081 (8.4%)
	December	3,003,029 (8.3%)
5 most prevalent Clinical Classifications Software (CCS) diagnosis groups (abbreviated, out of 29)	Nonspecific chest pain ⁱⁱⁱ	4,649,241 (12.9%)
	Cancer related	3,848,695 (10.7%)
	Headache / other nervous system disorders	2,520,624 (7.0%)
	Regional enteritis and ulcerative colitis	2,288,317 (6.3%)
	Other gastrointestinal disorders	2,062,927 (5.7%)
Five largest hospital Trusts	Barts Health NHS Trust	655,728 (1.8%)
	Heart of England NHS Foundation Trust	600,781 (1.7%)
	University Hospitals of Leicester NHS Trust	592,378 (1.6%)
	King's College Hospital NHS Foundation Trust	577,624 (1.6%)
	Pennine Acute Hospitals NHS Trust	563,816 (1.6%)
Five smallest hospital Trusts	Yeovil District Hospital NHS Foundation Trust	103,543 (0.3%)
	George Eliot Hospital NHS Trust	94,417 (0.3%)
	East Cheshire NHS Trust	93,900 (0.3%)
	Weston Area Health NHS Trust	89,741 (0.2%)
	Wye Valley NHS Trust	86,567 (0.2%)

ⁱ Truncated at the 99th percentile to improve model stability. Median age was used as reference in regression models. Overnight admissions in past year was included in adjusted models as a continuous covariate; categories are shown here only for information.

ⁱⁱ Higher IMD scores indicate greater deprivation (range: 0.53–87.8), and median IMD score was used as the reference in regression models.

ⁱⁱⁱ Reference category in regression models.

Finally, random effects meta-regression was used to investigate whether heterogeneity in the adjusted probability of death (one estimate per hospital) was associated with hospital-level antibiotic use, measured in DDDs/1,000 bed-days. We carefully reviewed spaghetti plots of quarterly changes in antibiotic use for all 135 Trusts and found antibiotic use was largely stable over time. DDD estimates were therefore calculated as the annual mean of antibiotic data from April/2014 to March/2017. Multiple other metrics of antibiotic use were considered, including inpatient/outpatient DDDs, narrow-spectrum/broad-spectrum DDDs, parenteral/oral DDDs, DDDs for piperacillin/tazobactam and meropenem, and DDDs for PHE-interpretations of WHO Access, Watch, and Reserve (AWaRe) antibiotics[51] (Appendix Table S3). The minor PHE amendments to AWaRe classifications reflected which antibiotics NHS hospitals should be prioritizing for human use. Meta-regression models adjusted for hospital size measured in terciles of either bed-days[42] or admissions[43], depending on whether DDDs was measured per bed-days or per admissions. An interaction between DDDs and hospital size was assessed and retained where the heterogeneity $p < 0.01$.

Sensitivity analyses

In sensitivity analyses, a more narrow definition of general medicine was used, where all spells had a HES main specialty code or treatment specialty code of 300 in the first or second consultant episode. As outlined in Figure 1, this definition is likely to have perfect specificity but varying sensitivity among hospitals due to local variations in coding practices. Since antibiotic data was only available from April/2014, a separate sensitivity test restricted the study sample to admissions between 01/April/2014-31/March/2017.

Secondary analyses

Secondary outcomes included death within 14 days of admission (all cause, in/out of hospital) and non-elective re-admission to hospital within 30 days of discharge (regardless of re-admission speciality). Analyses of re-admission were restricted to patients discharged alive more than 30 days before 31/March/2017. Without death date, deaths outside hospital could not be treated as competing events for re-admission. Poisson models for each binary outcome adjusted for the same admission characteristics and interaction terms and this was followed by random effects meta-regression as previously described.

Scope for achieving antibiotic prescribing reductions

We considered the impact of reducing hospital antibiotic use to the 25th, 10th and 5th centiles among hospitals, by examining the proportion of DDDs that could be safely avoided if high-using hospitals were able to replicate the prescribing practices of lower using hospitals (Appendix Figure S3).

Ethics

This study is an analysis of de-identified routine electronic health record data. The original study protocol was approved by the Health and Social Care Information Centre (now NHS Digital), whose guidance at the time was that the use of non-identifiable data did not require Research Ethics Committee review. Analyses were conducted in accordance with the Declaration of Helsinki and national and institutional standards.

RESULTS

Primary analysis

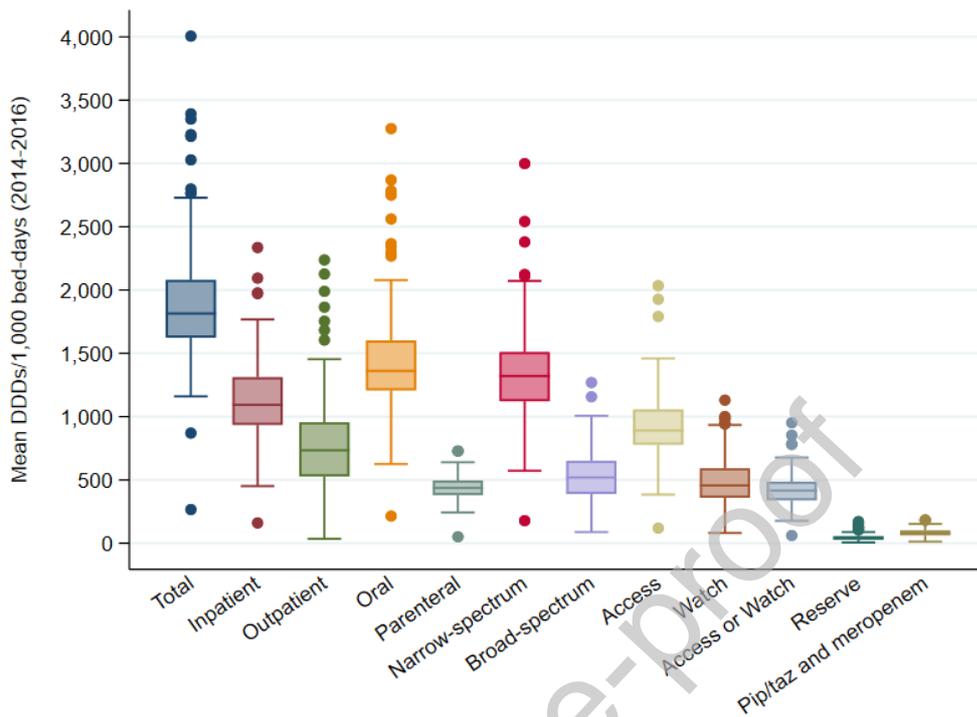
The final analytic cohort contained 36,124,372 acute/general medicine admissions from 12,320,069 patients between April/2010 and March/2017 inclusive, with median of two admissions (IQR: 1-3) per patient. Admissions increased year-on-year (Table 1). The largest and smallest hospitals received 655,728 admissions and 86,567 admissions respectively (Appendix Table S4). Median age was 66 years (IQR: 51-78), the most prevalent admission characteristics were female sex (50.4%), ethnically white (83.8%), admission on a weekday (85.0%), a low median Charlson Comorbidity Index (0, IQR: 0-7), low median IMD score (18.5, IQR: 10.5-32.2), and a Clinical Classifications Software (CCS) diagnosis group indicating non-specific chest pain (12.9%) (Appendix Table S5).

In primary analyses, which adjusted for all the factors in Table 1, the adjusted probability of 30-day mortality varied three-fold by hospital (0.58-1.75%; median: 1.12%, IQR: 0.96-1.28%). Antibiotic consumption measured as mean total DDDs/1,000 bed-days (2014-2016) varied 15-fold across hospitals (median: 1,814; IQR: 1,624-2,080; range: 266-4,006), with a 13-fold difference when expressed as DDDs/1,000 admissions (median: 4,132; IQR: 3,604-4,766; range: 584-7,494). Wide variation was also observed for other antibiotic metrics (Figure 2). Ten antibiotics accounted for the majority prescribed (63.36-85.10%) at every acute hospital, but there was also considerable variation in the use of individual agents (Appendix Figure S4).

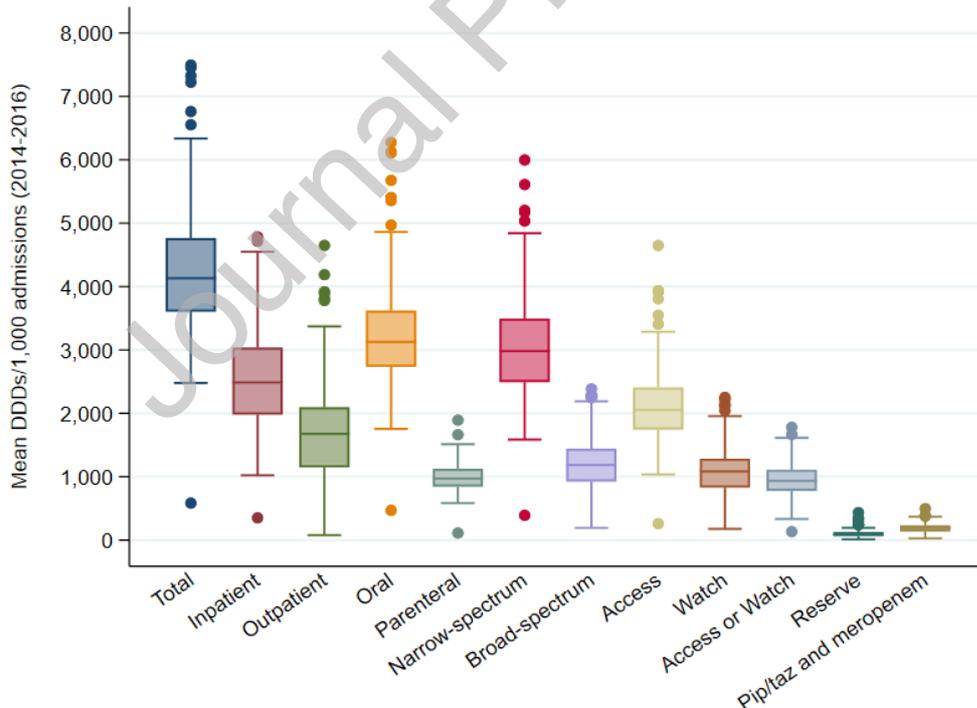
Meta-regression estimates are displayed in Figure 3 and Appendix Table S6, with associations between selected antibiotics and 30-day mortality in Figure 4 and Appendix Figure S5. In 22/24 meta-regression models we found evidence of no association between the adjusted probability of death and hospital-level antibiotic use; the two models with some evidence of association identified effects in opposite directions.

Figure 2: Mean Antibiotic Defined-Daily-Doses Consumed Among 135 NHS Acute Care Hospital Trusts (April 2014 – March 2017)

2a) Mean total DDDs per 1,000 bed-days*



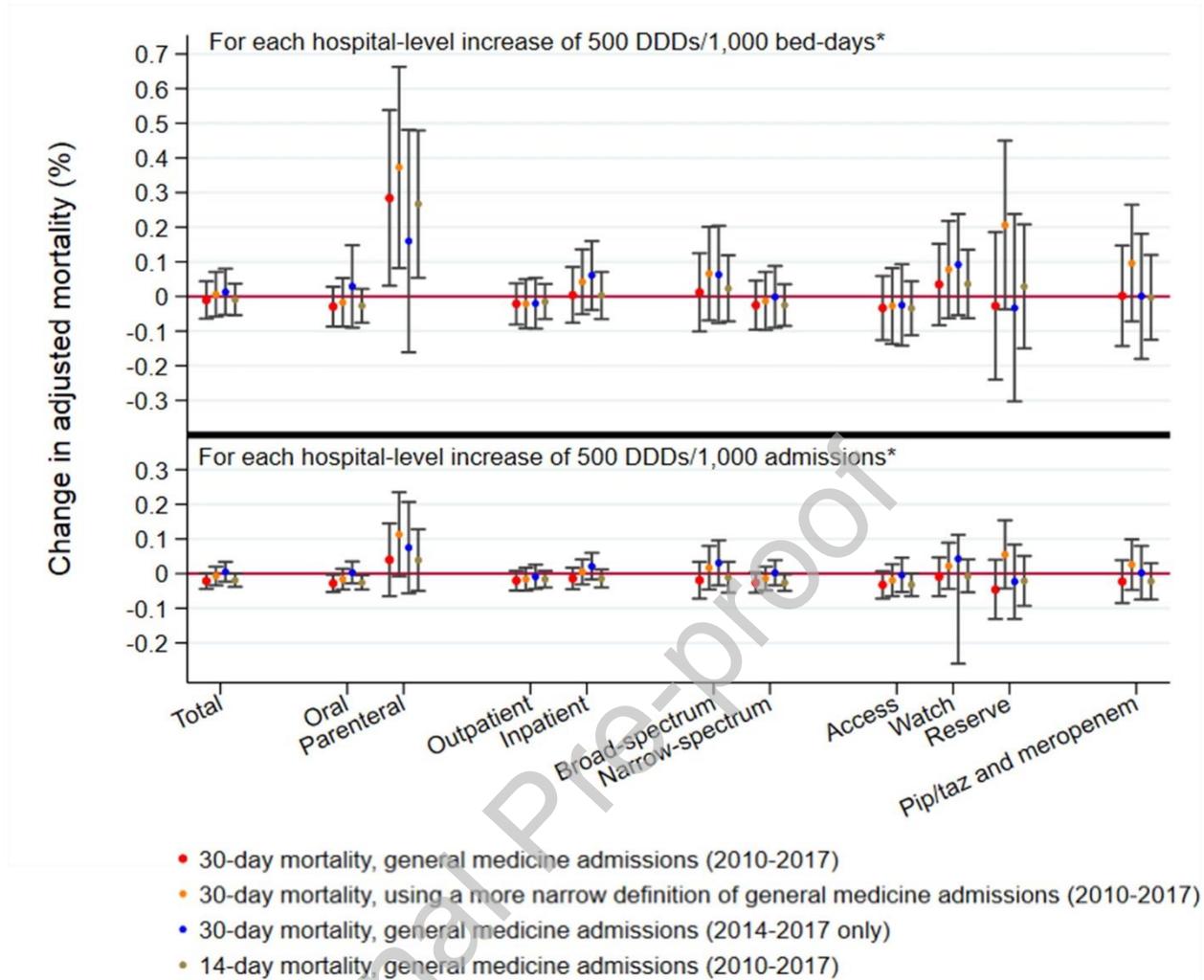
2b) Mean total DDDs per 1,000 admissions*



* Each box represents the interquartile range of the distribution and is subdivided by a horizontal line representing the median. The ends of the whiskers display the most extreme DDD estimate within 1.5 IQR of the nearest quartile, while even more extreme outliers are displayed as isolated points.

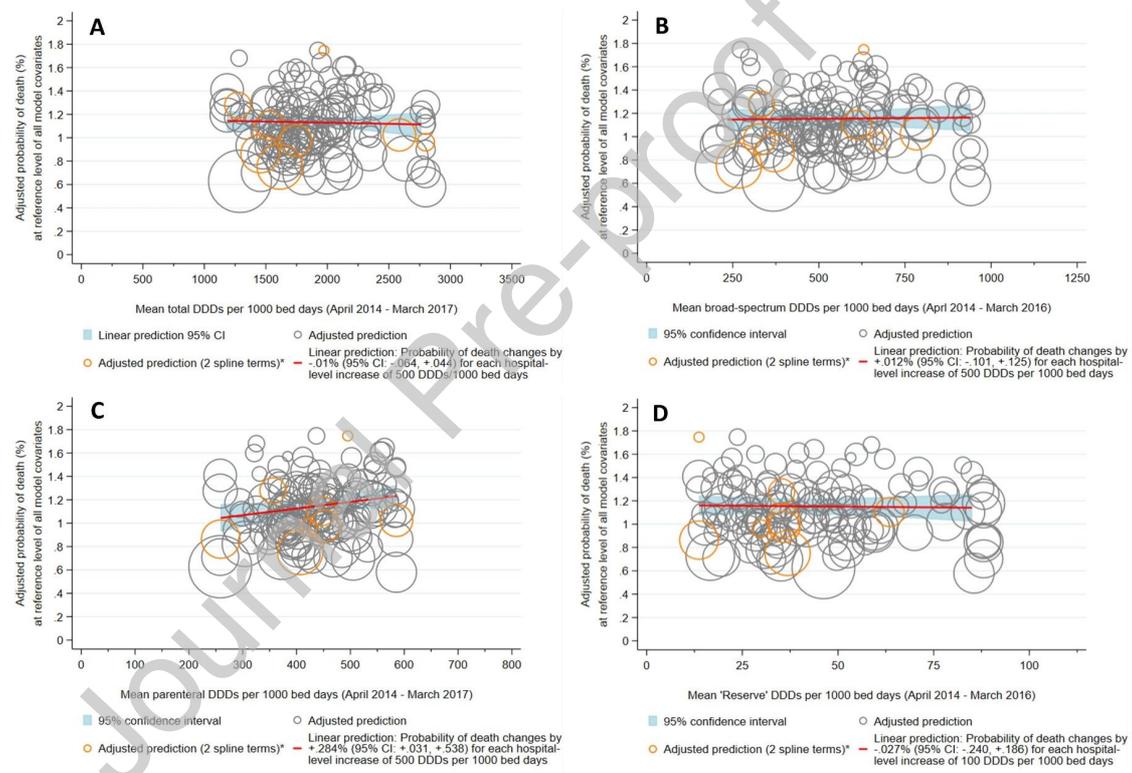
“Pip/taz” refers to piperacillin/tazobactam. Some antibiotics may be considered Access or Watch depending on indication, so they have been included as their own separate category.

Figure 3: Random Effects Meta-Regression of the Association Between the Adjusted Probability of Death (In/Out of Hospital) and Different Metrics of Hospital-level Antibiotic Use



* Point estimates above the null (red line) suggest increasing hospital-level antibiotic use is associated with harm (increased mortality risk), or conversely that decreasing hospital-level antibiotic use is associated with clinical benefit (reduced mortality risk). Estimates below the null suggest increasing antibiotic use is associated with clinical benefit, or conversely that decreasing antibiotic use is associated with clinical harm. The associations displayed for Reserve antibiotics and piperacillin/tazobactam (“pip/taz”) and meropenem are for a unit increase of 100 DDDs rather than 500 DDDs. Some antibiotics (not shown) may be considered either Access or Watch (depending on indication) and have been analysed as their own separate category in Appendix Tables S6–S10 alongside the categories shown here.

Figure 4: Random Effects Meta-Regression of the Association Between the Adjusted Probability of Death Within 30 Days of Admission (In/Out of Hospital) and Hospital-level Antibiotic Use



- A) Mean total DDDs/1,000 bed-days
- B) Mean broad-spectrum DDDs/1,000 bed-days
- C) Mean parenteral DDDs/1,000 bed-days
- D) Mean “Reserve” DDDs/1,000 bed-days

* Marginal effects were derived from 135 separate (hospital-specific) models, represented here as circles sized according to the precision of the estimate (inverse of the within-hospital variance). Most (127/135) hospital-specific multivariate models included four spline terms (for age, Charlson Comorbidity Index, IMD score, and overnight admissions in the past year), however models for eight hospitals would only converge with two spline terms (age and overnight admissions in the past year). Antibiotic use was truncated below the 2.5th percentile and above the 95th percentile. Probability estimates were truncated above the 99th percentile. Associations displayed here can be found in Appendix Table S6.

Sensitivity analyses

Using a narrower definition of general medicine resulted in an adjusted probability of 30-day mortality that varied between 0.59-2.10% across hospitals (median: 1.11%, IQR: 0.96-1.33%). In 23/24 meta-regression models there was no evidence of association between the adjusted probability of death and hospital-level antibiotic use (Figure 3 and Appendix Table S7). In one model there was a small increase in the adjusted probability of death of +0.373% (95% CI: +0.082,+0.663; p=0.012) for each increase of 500 parenteral DDDs/1,000 bed-days.

Restricting the study sample to admissions between April/2014-March/2017 inclusive (i.e., the period with overlapping antibiotic data) yielded adjusted probability of death estimates that were highly correlated (Spearman's ρ : 0.851, $p < 0.0001$) and similar in magnitude to those in the primary analysis and showed no evidence of association with hospital-level antibiotic use, regardless of how antibiotic use was measured (Figure 3 and Appendix Table S8).

Secondary analyses

The adjusted probability of 14-day mortality (in/out of hospital) varied from 0.38-1.40% across hospitals (median: 0.79%, IQR: 0.65-0.93%) at the reference level of all model factors. Most (20/24) metrics of antibiotic use showed no evidence of association with 14-day mortality, while the remaining estimates showed both positive and negative associations (Figure 3 and Appendix Table S9). The adjusted probability of non-elective re-admission to hospital within 30 days of discharge varied between 7.07-13.59% across hospitals (median: 10.16%, IQR: 9.34-10.86%) at the reference level of all model factors. Some (14/24) metrics of antibiotic use suggested re-admission risk increased with greater hospital-level antibiotic use, while the remainder (10/24) showed no evidence of association with re-admission risk (Appendix Table S10).

Scope for achieving antibiotic prescribing reductions

If hospitals with antibiotic use above the 25th percentile (1,624 DDDs/1,000 bed-days; 101 hospitals), 10th percentile (1,454 DDDs/1,000 bed-days; 121 hospitals), or 5th percentile (1,282 DDDs/1,000 bed-days; 128 hospitals) reduced their consumption to this level, total DDD use would decline by 21.6% (from 51,732,671 to 40,558,491 DDDs), 27.0% (from 58,838,197 to 42,953,040 DDDs), or 34.4% (from 61,250,673 to 40,153,594 DDDs), respectively. With antibiotic use measured in DDDs/1,000 admissions, reducing consumption to the 25th percentile (3,604 DDDs/1,000 admissions), 10th percentile (3,198 DDDs/1,000 admissions), or 5th percentile (2,992 DDDs/1,000 admissions) would drop total DDD use by 23.2%, 28.4%, and 31.8%, respectively.

DISCUSSION

We found very wide variation in the quantity of antibiotics being consumed across NHS acute hospitals, which is consistent with previous reports[36], including a systematic review of antibiotic consumption in 3130 (primarily European) hospitals which found a 40-fold difference among studies[35]. By calculating the confounding-adjusted probability of death among general medicine inpatients in each hospital we have been able to control extensively for case-mix and found no evidence that variation in antibiotic use is associated with 14 or 30-day mortality. This finding is consistent across different measures of antibiotic consumption and in multiple sensitivity analyses focusing on sub-populations. These results suggest further opportunities for antibiotic reduction at hospitals without negatively impacting patient outcomes. Rather than set an arbitrary threshold for what reduction in use could be achieved, we considered the impact of reducing hospital antibiotic use

to the 25th, 10th and 5th centiles among hospitals. Depending on the threshold, our models indicate that system-wide reductions of up to one-third of DDDs could be achieved safely if high-using hospitals could replicate prescribing practices of lower using hospitals.

Our study has not addressed how some Trusts achieve similar patient outcomes with much lower antibiotic consumption. This needs further exploration but it is likely that the quality of antibiotic prescription reviews is a major factor. Safe control of antibiotic overuse in hospital depends on balancing the need to initiate prompt effective therapy when bacterial infection is present with early review and revision of antibiotic prescriptions in the light of clinical and diagnostic data[21,22]. This is challenging in clinical practice. We have reported previously that hospitals which do this well have lower rates of *C. difficile* infection[34], and interventions to increase stop rates at review are feasible in hospital settings[25]. It is to be expected that at hospitals where antibiotic prescription reviews are done well, fewer antibiotics would be used without compromising patient outcomes. Data from medical inpatients in Oxford showed substantial reductions in antibiotic use (of around 30%) can be achieved without adverse clinical outcomes when patients are admitted under an infectious diseases specialist versus other clinical teams[23]. This is in keeping with a growing body of evidence that reducing antibiotic treatment duration across a wide-range of clinical scenarios is a safe and effective way of controlling antibiotic overuse[52-56]. Our data indicate the magnitude of reductions that could be safely achieved, dwarfing the 1% year-on-year reductions required of NHS hospitals[37].

Our study has important limitations. Patient-level factors significantly associated with mortality risk such as baseline haematology and biochemistry test results and admission time of day are not available in HES[49]. Any residual bias arising because hospitals with more acutely unwell patients are likely to use more antibiotics and to have patients at greater risk of death could mean we fail to detect harm associated with low antibiotic use. Some of our analyses indicated greater use of parenteral antibiotics (per 1,000 bed-days) was associated with increased risk of death, which is consistent with residual confounding after adjustment. Nevertheless, the magnitude of differences in antibiotic use we have observed and the marginal impact on mortality means residual confounders would have to be exerting a very large effect to meaningfully change our inferences.

Although we find no consistent evidence that reduced antibiotic use is associated with increased risk of readmission to hospital, this result should be interpreted with caution. More than half of our analyses using different measures of antibiotic consumption indicated increased antibiotic use to be associated with greater risk of non-elective readmission. It may be that some hospitals which use more antibiotics also discharge more quickly, and there is evidence from the United States indicating patients discharged against medical advice have higher readmission rates[57]. Alternatively this may be because our model factors, selected *a priori* based on previous analyses to adjust for case-mix in mortality models[49], are not sufficient to control for confounding of the relationship between antibiotic use and readmission. While this does not undermine our fundamental observation that lower antibiotic use is not associated with case-mix adjusted mortality, it is a reminder that other, albeit less impactful harms, could be associated with undertreatment of infection and should be investigated.

We did not restrict our analysis to sub-populations of general medical inpatients with specific diagnoses for several reasons. The diagnosis (ICD-10) codes used to derive CCS group, Charlson comorbidity index, and immunosuppression status, are captured in HES by clinical coding departments using discharge summaries. This process is both standardised and audited but primarily serves administrative and reimbursement purposes and describes the main condition managed in an episode, which may be ruled out at a later date or be unrelated to the clinical indication for antibiotics. Diagnostic coding practices also vary by hospital, with coding depth and accuracy improving over time[38]. As a result, reliably identifying sub-populations based on these codes is challenging, with

varied and potentially unknown sensitivity and specificity.

Another important limitation of this study is that marginal effects were derived from outcomes in acute/general medicine admissions between 2010-2017, yet antibiotic data was not available at the specialty-level during this period or at all before April/2014. As a result, the share of DDDs attributable to general medical inpatients likely varies by hospital, though this drawback may be partially off-set by our broad definition of general medicine (Figure 1) and the fact that general medical inpatients are the largest consumers of non-prophylactic antibiotics in hospitals[58]. Also, sensitivity analyses restricting to April/2014-March/2017 yielded marginal effects that were very similar to those in the primary analysis and similarly found no evidence of association between 30-day mortality and hospital-level antibiotic use. The antibiotic data for 2014-2017 was received in January/2020; most hospitals' use was fairly stable over this period, supporting our comparison of average effects.

While the use of DDDs enables standardised comparisons of hospital antibiotic use without the need for patient-level data, it also has drawbacks[59]. For example, to reduce the selective pressure for resistance, antibiotic policies may recommend combinations of narrow-spectrum agents rather than one broad-spectrum agent. This would increase DDDs for treatment of the same indication, producing an apparent increase in antibiotic use. Local differences in the prevalence of AMR may also require some hospitals to use multiple agents to provide sufficient empiric coverage. Differences between prescribed doses and WHO's DDD reference values could also lead to overestimates or underestimates of antibiotic use, depending on local treatment guidelines. Unfortunately, linkage of clinical data with electronic prescribing data is not yet widely available in England.

Despite these limitations, electronic health record studies such as ours allow the impact of antibiotic therapy on patient outcomes to be assessed on a scale that cannot be achieved with other approaches. Where richer patient-level antibiotic data are available, investigations could analyse inappropriate prescribing, additional outcomes, and the use of alternate measures of antibiotic use that mitigate the limitations of DDDs, such as length of therapy (LOT) (days between first and last administered antibiotic inclusive) or days of therapy (DOT) (the sum of days between first and last administered antibiotic inclusive, with each antibiotic counted separately)[59].

Future observational work could also expand outcome measures to include other potential markers of harm, including length of stay or admission to intensive care. By using HES data we have not been able to assess potential benefits of lower antibiotic prescribing, such as declines in AMR or *C. difficile* infection. Such data would need to either be obtained from individual hospitals, or only analysed at a hospital-level (rather than within general medical inpatients) by using mandatory reported surveillance data.

CONCLUSION

We found no evidence that the wide variation in hospital antibiotic prescribing is associated with mortality risk in medical inpatients. Accordingly, risk-adjusted benchmarking of antibiotic use in hospitals could be used to drive safe and substantial reductions in antibiotic consumption. Further investigations should consider how some hospitals achieve low levels of antibiotic use. Understanding what explains these differences will facilitate the design of interventions that can be evaluated in randomised trials for unbiased inference. Although trials are costly and difficult to implement, the results of this study provide evidence to justify this further work.

FUNDING

This work was supported by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Reference Number RP-PG-0514-20015), and by Antibiotic Research UK (ANTRUK) grant number ANTSRG 02/2018. ASW is supported by the NIHR Biomedical Research Centre, Oxford. ASW and TEAP are NIHR Senior Investigators. The views expressed in this publication are those of the author(s) and not necessarily those of ANTRUK, the NHS, the NIHR, or the Department of Health. The funders had no role in the study design, data collection, analysis, interpretation of results, writing of the manuscript, or the decision to publish.

INFORMED CONSENT

Patient consent was waived as this study is an analysis of de-identified routine electronic health record data.

AUTHOR CONTRIBUTIONS

Conceptualization, E.P.B., T.E.A.P., M.J.L., and A.S.W.; Methodology, E.P.B., T.J.D, T.D., T.E.A.P., M.J.L., and A.S.W.; Software, E.P.B.; Validation, E.P.B.; Formal Analysis, E.P.B.; Investigation, E.P.B.; Resources, T.E.A.P. and A.S.W.; Data Curation, E.P.B., S.H. and A.S.W.; Writing – Original Draft Preparation, E.P.B.; Writing – Review & Editing, E.P.B, T.J.D, T.D., S.H., D.W., T.E.A.P., M.G., M.J.L., and A.S.W.; Visualization, E.P.B., T.E.A.P., M.J.L., and A.S.W.; Supervision, M.J.L. and A.S.W.; Project Administration, M.J.L. and A.S.W.; Funding Acquisition, E.P.B., T.E.A.P., M.J.L., and A.S.W.

DATA AVAILABILITY

A copy of the Health Episode Statistics (HES) Admitted Patient Care dataset used in this study can be requested from NHS Digital's Data Access Request Service (DARS) by using the same inclusion criteria and admission dates described in this study. NHS Digital can also be asked (via DARS) to link the requested HES data with death information from the Office of National Statistics (ONS). Antibiotic consumption data by NHS Trust can be requested from IQVIA Solutions UK Limited and its affiliates. Copyright: IQVIA Solutions UK Limited and its affiliates. All rights reserved. Use for sales, marketing or any other commercial purposes is not permitted without IQVIA Solutions UK Limited's express prior written consent.

CONFLICTS OF INTEREST

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf: EPB declares a grant from Antibiotic Research UK (ANTRUK) during the conduct of the study (grant number ANTSRG 02/2018). ASW reports grants from National Institutes of Health Research, UK, during the conduct of the study. TEAP reports grants from Wellcome Trust, the Medical Research Council, BBRC, Bill and Melinda Gates Foundation, and NIHR, outside the submitted work. All authors declare no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; all authors declare no other relationships or activities that could appear to have influenced the submitted work.

ACKNOWLEDGEMENTS

This work was supported by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Reference Number RP-PG-0514-20015), and by Antibiotic Research UK (ANTRUK) grant number ANTSRG 02/2018. ASW is supported by the NIHR Biomedical Research Centre, Oxford. ASW and TEAP are NIHR Senior Investigators. The views

expressed in this publication are those of the author(s) and not necessarily those of ANTRUK, the NHS, the NIHR, or the Department of Health.

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