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Using a simple Point-Prevalent Survey to define appropriate antibiotic prescribing in hospitalised children across United Kingdom

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Short running title: antibiotic use in hospitalised children

Article summary

Strengths of this study

- First study that gives an insight into antibiotic prescribing in paediatric acute settings in the UK using quality indicators recommended nationally by the UK Department of Health.
- We used a simple rigorous and standardised point prevalence method that could provide the baseline for future benchmarking to monitor national strategies for optimal antimicrobial prescribing in children.
- We identified appropriate prescribing in hospitalised children in UK adjusting for case mix using patient-level data.

Limitations

- The Point Prevalence Survey methodology is a cross sectional study with no longitudinal data.
- No consensus exists for measuring antibiotic prescribing in children as DDD/100 inpatients is not validated for this population.

ABSTRACT

- **Background** – The National Health Service England, Commissioning for Quality and Innovation for antimicrobial resistance (CQUIN AMR) aims to reduce the total antibiotic consumption and the use of certain broad-spectrum antibiotics in secondary care. However, robust baseline antibiotic use data are lacking for hospitalised children. In this study, we aim to describe and compare the prescription pattern of antibiotics across paediatric units in the UK and to identify inappropriate prescribing areas for improvement using CQUIN AMR guidance.
- **Method** - We conducted a cross sectional study using a point prevalence survey (PPS) in 61 paediatric units across the UK. The standardised study protocol from the Antimicrobial Resistance and Prescribing in European Children (ARPEC) project was used. All inpatients under 18 years of age present in the participating hospital the day of the study were included except neonates.
- **Results** – A total of 1247 (40.9%) of 3047 children hospitalised on the day of the PPS were on antibiotics. The proportion of children receiving antibiotics showed a wide variation between both district general and tertiary hospitals, with 36.4% (Confidence Interval 95% [CI95] 33.4-39.4) and 43.0% (CI95, 40.9-45.1) of children prescribed antibiotics respectively. The proportion of children on antibiotic therapy for medical and surgical prophylaxis was very high (24.1%, CI 21.8-26.4) with parenteral administration being the main prescribed route for antibiotics (>60% of the prescriptions for both type of hospitals). General paediatrics units were surprisingly high prescribers of critical broad-spectrum antibiotics, i.e. carbapenems and piperacillin-tazobactam.
- **Conclusions** - We identified areas of improvement for appropriate children antibiotic prescribing in relation to current national stewardship efforts in the UK. Repeated PPS with further linkage to resistance data need to be part of the antibiotic stewardship strategy to tackle the issue of suboptimal antibiotic use in hospitalised children.

INTRODUCTION

The increasing levels of antimicrobial resistance (AMR) are strongly correlated with inappropriate use of antibiotics. [1 2] Recent United Kingdom (UK) and international reports have advocated the critical need to monitor and control the use of existing antibiotics since the number of new classes of antibiotics has dramatically decreased over last 40 years. [3-5] Antimicrobial Stewardship Programmes (ASP), defined as comprehensive quality improvement activities for optimising antimicrobial prescribing and minimising resistance, have been widely adopted in adult care settings, [6 7] but still remain limited in children's units. [8 9] The heterogeneity in age and weight of children, as well as the lack of standardised method to quantify antibiotic use in paediatrics, increases the challenge of determining and benchmarking the appropriateness of prescribing within or between children institutions; [10-12] and children are often excluded from comparative studies on antibiotic use. [13 14]

The National Health Service England, Commissioning for Quality and Innovation for antimicrobial resistance (AMR CQUIN) 2016/17, aims to reduce by 1% or more per year the total antibiotic consumption and the use of certain broad-spectrum antibiotics considered as critical antibiotics, (carbapenems and piperacillin-tazobactam), in secondary care. [15-17] However, robust baseline antibiotic use data, so far developed for adults, are lacking for hospitalised children while they are key to measure the impact of the proposed strategies and to identify room for improvement. Two international study have proposed to describe and compare the use of antimicrobials in children across Europe and worldwide using various quality indicators, [18 19] but no comparable detailed information on antibiotic use in hospitalised children in UK is available.

The aim of our study is to describe and compare the prescription pattern of antibiotics across paediatric units in the UK collected in a cross-sectional point prevalence survey (PPS) carried out as part of the Antibiotic Resistance and Prescribing in European Children (ARPEC) project. [20 21] We also proposed to use the simple PPS to apply AMR CQUIN quality indicators to identify

inappropriate prescribing and areas for improvement, and provide a benchmarking baseline to measure the impact of the current and future national strategies.

METHODS

Study design and settings

Detailed antimicrobial prescribing data were collected for all inpatients under 18 years-old present in a participating hospital's paediatric and neonatal wards at 8am since at least midnight. Data were collected on paper forms, anonymously entered, validated and reported online through the ARPEC-PPS program. Antimicrobial agents were analysed in accordance with the Anatomical Therapeutic Chemical (ATC) Classification (World Health Organisation Collaborative Centre for Drug Statistics Methodology, 2013). [22] The full method is described elsewhere by Versporten et al. [21]

Data extraction

For this study, we extracted and analysed data from 61 paediatric units in the UK which participated in the ARPEC-PPS organised in March-April 2011 (feasibility survey), September-November 2011 (worldwide pilot ARPEC-PPS) [21] and October-December 2012 (full worldwide ARPEC-PPS). [19] All inpatients under 18 years of age admitted to a paediatric ward were included. We excluded neonates from neonatal units and/or under 28 days of age. We analysed antibacterials for systemic use (ATC J01).

Data analysis

Descriptive analysis

Demographic data, underlying chronic conditions, current diagnosis, hospital-acquired infections versus community-acquired infections, therapeutic versus prophylactic prescribing, and antibiotic type, dosing and route of administration were analysed and compared between 44 District

General Hospitals, which provide secondary care, and 17 Tertiary Referral Hospitals, which provide tertiary or specialised care.

Metrics for measuring antibiotic use

We compared two different metrics of antibiotic prescribing within and between hospitals: (i) The proportion of children on antibiotics (prevalence rate) with 95% confidence intervals (CIs); (ii) The Defined Daily Doses per 100 inpatients (DDD/100 inpatients), as recommended in the AMR CQUIN. [17 23] Antibiotic consumption in grams was converted into DDD using the 2013 release of the ATC Classification. [22] The denominator "inpatients" was defined in this study as the sum of inpatients in the hospital at 8:00am.

Quality indicators for national benchmarking between UK hospitals

We explored the different inpatient antibiotic prescribing quality indicators proposed by CQUIN NHS England for antimicrobial resistance. [17]

1. The total amount of antibiotics prescribed using both metrics, the proportion of children receiving antibiotics and DDD/100 inpatients in different age bands. A funnel plot was used to graphically compare antibiotic prescribing between hospitals, to adjust for different hospital sizes and to identify outliers.[24] This takes account of the variable number of cases by institution by plotting the proportion of children on antibiotics against the sample size for each hospital using a binomial distribution and 95% CI (~2 standard deviation). We also displayed antibiotic prescribing in DDD/100 inpatients for each hospital, as well as the median and interquartile range for each age band.
2. The use of the carbapenems and the use of piperacillin-tazobactam, which are both considered critically important antibiotics against extended-spectrum beta-lactamase producing Gram negative bacteria. [3] The proportions of children on carbapenems and piperacillin-tazobactam, as well as the amount of these drugs prescribed in DDD/100

inpatients, were monitored and compared between institutions after adjusting for hospital type (district general hospitals versus tertiary referral hospitals) and presence of underlying disease.

Statistical analyses

We conducted comparative analyses to determine the balance between district general hospitals and tertiary referral hospitals using tests of proportions (e.g., Chi-square analysis, Fishers exact test), and tests of central tendency (e.g., ANOVA, sign rank). Mean total daily doses were compared by unpaired two-sample t-test. All p-values were based on two-tailed test with p-value<0.05 for significance. Statistical analysis was performed using STATA version 12 (STATA Corp, College Station, Texas).

Ethics

The responsible UK Research Ethics Committee was approached to establish the need for a formal evaluation. Written confirmation was provided that within the UK framework a fully anonymised point prevalence survey constituted surveillance and that formal review by the Research Ethics Committee was not required.

RESULTS

Patient demographics

A total of 1247 (40.9%) of 3047 surveyed UK paediatric inpatients were receiving antimicrobials. Overall 1348 indications were recorded for 1247 inpatients with a total of 1858 antibiotic prescriptions. The median age of exposed children was 2 years (IQR=0.083-8). More than two-thirds of inpatients were recruited from tertiary care centres, and from General Paediatric and Paediatric Surgery wards (**Supplemental Table**).

Age differences by speciality were seen among children on antibiotics. For general paediatrics, the median age of exposed children was 2 years (IQR=0.75-6), for surgery 5 years (IQR=1.25-11), for paediatric intensive care units (PICU) 0.71 years (IQR=0.08-3), for haematology-oncology-transplant 6 years (IQR=2-11) and for other medical specialties 3 years (IQR=0.75-9).

Total use of antibiotics

Proportion of children on antibiotics

Table 1 shows that the proportion of children on antibiotics and the number of prescribed antibiotics was significantly higher in tertiary hospitals (43.0%, CI95% 40.9-45.1, 40 different prescribed antibiotics) than in district general hospitals (36.4%, CI95% 33.4-39.4, 30 different prescribed antibiotics, p-value=0.001). About two-thirds of inpatients in intensive or specialist care wards (PICU and haematology-oncology-transplant) were prescribed antibiotics in high specialist care areas compared to about one third in general paediatrics and surgery. Multiple antibiotics were also used more frequently in children admitted to PICU (77/145, 53.1%, CI95% 45.0-61.2) and haematology-oncology-transplant units (63/92; 68.5%, CI95% 59.0-78.0) compared to children in paediatric surgery (93/214; 43.5%, CI95% 36.8-50.1) and general paediatrics (199/554, 35.9%, CI 95% 31.9-39.9).

Among all children receiving antibiotics, 60.9% (CI95% 57.5-64.4) of children had an underlying disease compared with 39.1% (CI95% 34.7-43.4) of previously healthy children. Exposed children were more likely to be younger (69.5% exposed below 7 years of age compared to 30.5% at 7 years and older).

Of 1348 indications, a diagnosis of lower respiratory, urinary tract, skin and soft tissue, bone or joint infection, pyrexia and gastrointestinal infection was recorded in 42.2% (CI 38.1-46.3) compared to 18.2% (CI 13.4-23.0) with a diagnosis of severe infections, i.e. sepsis, catheter-related bloodstream infection, central nervous system infection or febrile neutropenia. For exposed children, treatment for community-acquired infections (CAI) was almost 4 times more common

(59.1%, CI 55.7-62.5) than for healthcare-associated infection (15.7%, CI 10.8-20.6). Finally, the proportion of children on antibiotic therapy for medical and surgical prophylaxis was high (24.1%, CI 21.8-26.4).

Proportion of prescriptions for parenteral administration versus oral

Parenteral was the main prescribed route for administrating antibiotics, with more than 60% of the prescriptions in district general hospitals and tertiary referral hospitals. Parenteral antibiotics were highly prescribed in PICU (81.6% of the prescriptions), for previous healthy children (70.1% of the prescriptions), for surgical infections (89.8% of the prescriptions) and for sepsis, central nervous system infections and febrile neutropenia (96.4% of the prescriptions).

Figure 1 shows the funnel plot of the proportion of children on antibiotic for each institution. Hospitals with a proportion outside the funnel plot's 2 standard deviation control limits are considered to be potential outliers. 7/61 institutions were identified as potential "high prescribers", 2 district general hospitals (88 children on antibiotics) and 5 tertiary referral hospitals (365 children on antibiotics). For the 2 district general hospitals, all children on antibiotics were from general paediatric wards with 45.5% (n=40) of them having an underlying disease; for the 5 tertiary hospitals, a high proportion of children on antibiotics (n=110, 30.1%) were from haematology/oncology/transplant units and PICU, with a total of 71.2% (n=365) of children having an underlying disease.

Table 1: Proportion of children prescribed antibiotics in paediatric acute care settings across the United Kingdom (years 2011, 2012)

	N patients treated with antibiotic	Proportion of children on antibiotic % (CI95)	N antibiotic prescriptions (Total of different prescribed antibiotics)	Parenteral administration n (% of prescriptions)
District general hospitals (n=958 Patients)	349	36.4 (33.4-39.4)	479 (30)	291 (60.8)
Tertiary referral hospitals (n=2089 Patients)	898	43.0 (40.9-45.1)	1379 (40)	861 (62.4)
General Paediatric n=1477	554	37.5 (35.0-40.0)	791 (37)	467 (59.0)
PICU- n=226	145	64.2 (57.9-70.5)	228 (27)	186 (81.6)
Paediatric Surgery n=597	214	35.8 (32.0-39.6)	321 (29)	223 (69.5)
Haematology-Oncology-Transplant n=144	92	63.9 (56.1-71.7)	156 (24)	77 (49.4)
Others n=603	242	40.1 (36.2-44.0)	362 (31)	199 (55.0)
Total (n patients = 3047)	1247	40.9 (39.2-42.6)	1858 (41)	
	N patients treated with antibiotic (N=1247)	Proportion among total children on antibiotics % (CI95)	N antibiotic prescriptions (Total of different prescribed antibiotics)	Parenteral administration n (% of prescriptions)
No underlying disease	487	39.1 (34.7-43.4)	689 (30)	483 (70.1)
Underlying disease	760	60.9 (57.5-64.4)	1169 (41)	669 (57.2)
Aged <1 year	347	27.8 (23.1-32.6)	500 (29)	337 (67.4)
Aged 1-6 years	520	41.7 (37.5-46.0)	734 (31)	413 (56.3)
Aged 7-11 years	174	14.0 (8.8-19.1)	259 (32)	159 (61.4)
Aged > 12 years	206	16.5 (11.4-21.5)	363 (36)	243 (66.9)
	N indications for antibiotics (N=1348)	Proportion % (CI95)	N antibiotic prescriptions (Total of different prescribed antibiotics)	Parenteral administration n (% of prescriptions)
Surgical infection	74	5.5 (0.3-10.7)	137 (15)	123 (89.8)
Surgical prophylaxis	92	6.8 (1.7-11.9)	123 (17)	95 (77.2)
Medical prophylaxis	233	17.3 (12.4-22.16)	285 (29)	25 (8.8)
Sepsis/CRBSI/CNS/febrile neutropenia*	246	18.2 (13.4-23.0)	385 (22)	371 (96.4)
URTI*	73	5.4 (0.2-10.6)	90 (14)	42 (46.7)
LRTI/UTI/SSTI/Joint-Bone/Pyrexia/GITI*	569	42.2 (38.1-46.3)	764 (35)	458 (60.0)
Other/unknown	61	4.6 (0.0-9.7)	74 (22)	38 (51.4)
Community-Acquired Infection	797	59.1 (55.7-62.5)	1121 (34)	774 (69.1)
Hospital-Acquired Infection	211	15.7 (10.8-20.6)	298 (28)	240 (80.5)
Other (prophylaxis or unknown)	340	25.2 (20.6-29.8)	439 (34)	138 (31.4)
Total	1348		1858 (41)	

*CRBSI=Catheter-Related bloodstream Infection; CNS= Central Nervous System; URTI=Upper Respiratory Tract Infection; LRTI= Lower Respiratory Tract Infection; UTI=Urinary Tract Infection; SSTI=Skin and Soft Tissue Infection; GITI=Gastro Intestinal Tract Infection

Total usage of antibiotics in children in DDD/100 inpatients

Table 2 illustrates the total usage of antibiotics in DDD/100 inpatients for each age category per type of hospital and specialty. The total amount of antibiotics used is slightly higher in tertiary hospitals than in district general hospitals (37.8 versus 30.7 DDD/100 inpatients), except for children aged 1-6 years-old. The use of antibiotics is about twice as common in haematology-oncology-transplant units compared to other specialties, especially for patients above 12 years-old. For patients below 1 year-old, the use of antibiotics is substantially higher in PICU compared to other specialties.

Table 2: Total usage of antibiotics in DDD/ 100 inpatients in paediatric acute care settings across the United Kingdom, year 2011-2012

	DDD/100 inpatients				
	Aged <1yr	**Aged 1-6yrs**	**Aged 7-11yrs**	**Aged >12yrs**	**Total**
District general hospitals n=958	3.2	12.3	6.0	9.2	30.7
Tertiary referral hospitals n=2089	4.0	10.5	7.1	16.2	37.8
General Paediatric n=1477	3.9	11.9	4.7	12.8	33.4
PICU- n=226	7.5	12.7	6.4	10.9	37.5
Paediatric Surgery n=597	2.1	9.0	10.7	15.7	37.6
Haematology-oncology-transplant n=144	0.45	14.2	14.0	31.7	60.3
Others n=603	4.3	9.7	6.3	11.9	32.2
Total	32.9	64.8	118.3	207.5	35.5

The total prescribed antibiotics in DDD/100 inpatients per age band is shown **Figure 2**. A wide range of antibiotic use is observed among the 61 centres for patients aged between 12-18 years-old, whereas the three other groups show greater homogeneity between institutions in antibiotic usage. The total prescribed antibiotics is harmonised between district general hospitals and tertiary referral hospitals across the four age groups.

Carbapenems and piperacillin-tazobactam

Table 3 shows that among children receiving at least one antibiotic, the proportion of children on carbapenems was significantly higher in tertiary hospitals than in district general hospitals (respectively, n=54, 6.0% versus n=7, 2.0%, p-value=0.003). The same results were observed for the total amount of DDD/100 inpatients. Less than half of the children on carbapenems had at least one underlying disease recorded for district general hospitals, while more than 9 out of 10 had an underlying disease for tertiary hospitals. In district general hospitals, the general paediatric wards were the main prescribers of carbapenems as an empirical treatment, whereas in tertiary hospitals, about 43% of the prescriptions were targeted and PICU were the main prescribers. The amount of piperacillin-tazobactam in DDD/100 inpatients was also surprisingly 2-fold higher in district general hospitals than in tertiary hospitals. However, the proportion of children on piperacillin-tazobactam among all the children on antibiotics was much higher in tertiary hospitals. In district general hospitals, most of the patients were prescribed piperacillin-tazobactam in paediatric general wards, as an empirical treatment when they had at least one underlying disease, whereas, in tertiary hospitals, piperacillin-tazobactam was prescribed in haematology-oncology-transplant wards in presence of an underlying disease.

Table 3: Total usage of carbapenems and piperacillin-tazobactam in paediatric acute care settings across the United Kingdom, year 2011-2012

	Carbapenems		Piperacillin-tazobactam	
	District general hospitals (349 children on antibiotics)	Tertiary referral hospitals (898 children on antibiotics)	District general hospitals (349 children on antibiotics)	Tertiary referral hospitals (898 children on antibiotics)
Total DDD/100 inpatients	36.4	56.0	39.7	20.0
Total children n (%)*	7 (2.0)	54 (6.0)	14 (4)	68 (7.6)
General Paediatric n children (%)**	6 (85.7)	14 (25.9)	11 (78.6)	9 (13.2)
PICU n children (%)	1 (14.3)	17 (31.5)	0	12 (17.6)
Paediatric Surgery n children (%)	0	6 (11.1)	3 (21.4)	7 (10.3)
Haematology-oncology-transplant n children (%)	0	10 (18.5)	0	19 (27.9)
Others n children (%)	0	7 (13.0)	0	21 (30.9)
Underlying disease versus previously healthy children n children (%)**	3 (42.9)	49 (90.7)	12 (85.7)	67 (98.5)

**% among the total number of children on antibiotics per type of hospitals*

**% among the total number of children on antibiotics per type of hospitals*
***% among the number of children on carbapenems or piperacillin-tazobactam*

DISCUSSION

We describe a unique inpatient antibiotic prescribing dataset from 61 paediatric units across the UK. Our results identified areas of potential improvement for appropriate prescribing at the patient-level adjusting for risk factors (age, underlying diseases, infections, specialties), using the paediatric point prevalence method developed by the ARPEC project. Our results provide the baseline for future benchmarking to monitor national strategies for optimal antimicrobial prescribing in children, particularly the CQUIN NHS England scheme 2015/16 for AMR.

A total of 1247 out of 3047 surveyed admitted children were on antibiotics in this study. The proportion of children receiving antibiotics showed a wide variation between district general hospitals and tertiary referral hospitals, but also a wide variation within both groups of hospitals. The presence of case-mix and specialities, such as haematology-oncology-transplant and PICU, may be responsible for some of the differences observed in prescribing. Figure 1 highlighted that a total of 7/61 (11.5%) institutions, mainly the haematology-oncology-transplant and PICU units of the tertiary hospitals, were identified as potential "high prescribers". However, potential "high prescribers" in general district hospitals were only general paediatric units with less than half of the patients having an underlying diseases.

We also highlighted the considerable volume of antibiotics prescribed for surgical and medical prophylaxis accounting for 22.0% of all antibiotic prescriptions. Similarly to adult antimicrobial stewardship programmes, the reason, duration and need for prophylaxis should be assessed through antimicrobial stewardship programmes across paediatric units in the UK. [25]

The total usage of antibiotics in DDD/100 inpatients per age group showed a higher consumption in haematology-oncology-transplant units compared to the other specialties, except for under 1 year-old receiving antibiotics on PICU. Children admitted to haematology-oncology-transplant units or to PICU were more likely to receive a combination of antibiotics than general and surgery paediatric patients, which may directly impact exposure measured in DDD/1000 inpatients.

Carbapenems and piperacillin-tazobactam, were mainly prescribed empirically, and to children with underlying conditions in tertiary hospitals. These results are expected and will serve as a benchmark in future evaluations. However, we did not predict that general paediatric units were high prescribers for these two drugs in both district general and tertiary hospitals. With the spread of extended-spectrum-beta-lactamase producing Enterobacteriaceae in adults [26] but also in paediatrics over last decade, [27] and the increase of small outbreaks of multidrug resistant organisms in UK paediatric hospitals, [28] the prescribing pattern for these critical drugs may change in the future and needs to be better monitored, especially in the general paediatric units for previously healthy children.

There remains a lack of consensus regarding the optimal metric to assess paediatric antimicrobial use, which is an important limitation. The use of DDD/100 inpatients (DDD being defined as the amount of antibiotic prescribed for a 70kg average adult weight for its main indication) proposed by CQUIN AMR is not a perfect measure, especially in children with a wide range of weights (from 5kg in a 3 months-old to over 100kg in obese adolescents). As DDD is weight and dose-dependent, [29] we decided to compare overall drug exposure using DDD/100 inpatients per age bands as proposed by Porta et al.[23] Despite DDD/100 inpatients being advocated by the WHO Collaborating Centre for Drug Statistics and Methodology, “days of therapy” could have advantages over DDD measures, because the impact of variation in absolute dose is limited for this metric. [11 29] However, longitudinal studies or access to electronic-prescribing systems for each hospital in the UK would be required to calculate this, which may not be realistic in the near future. [30] For now, DDD/100 inpatients can still be used to monitor changes in same units over time as long as case mix stays similar.

In conclusion, we identified areas of improvement for appropriate children antibiotic prescribing in relation to current national stewardship efforts in the UK. Repeated PPS [31] need to be part of the paediatric antibiotic stewardship strategy in order to identify prescribing trends over

time, to evaluate the efficacy of antimicrobial stewardship programmes and to tackle the issue of suboptimal antibiotic use, especially on antibiotic dosing.[32] International standardised PPS with further linkage between antibiotic prescribing and resistance will be critical to characterise appropriate use of antibiotics in hospitalised children globally and to propose guidance on the management of paediatric infections taking into account resistance profiles.

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COMPETING INTERESTS

No competing interest to declare.

CONTRIBUTORSHIP STATEMENT

MG, KD, JAB, AV, HG and MS had substantial contributions to the conception and the design of the work; MG, KD, SV, JAB, SP, EM, AR, HL, SVP, JB, AV, MH, HG, MS participated in the acquisition, and interpretation of data for the work; The data management was done by AV and MG and the data analysis by MG. MG, KD, SV and MS drafted the work and MG, KD, SV, JAB, SP, EM, AR, HL, SVP, JB, AV, MH, HG, MS revised it critically for important intellectual content; and all the

authors, i.e. MG, KD, SV, JAB, SP, EM, AR, HL, SVP, JB, AV, MH, HG, MS gave the final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA SHARING

No additional data available. The additional unpublished data on antimicrobial prescribing for neonates and children are currently being published within the ARPEC project.

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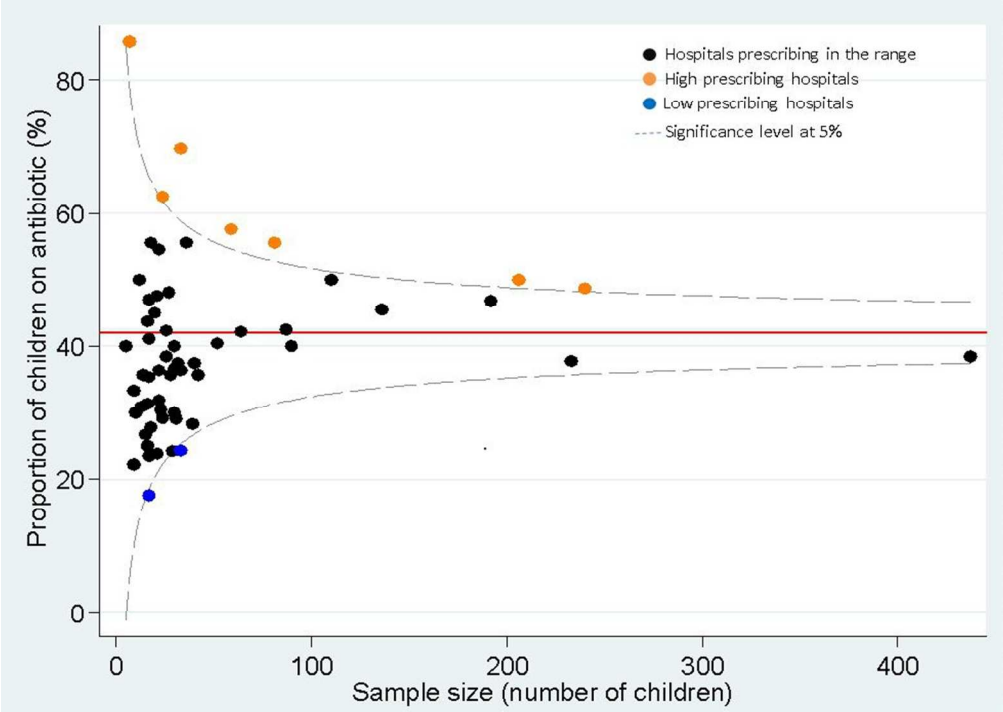
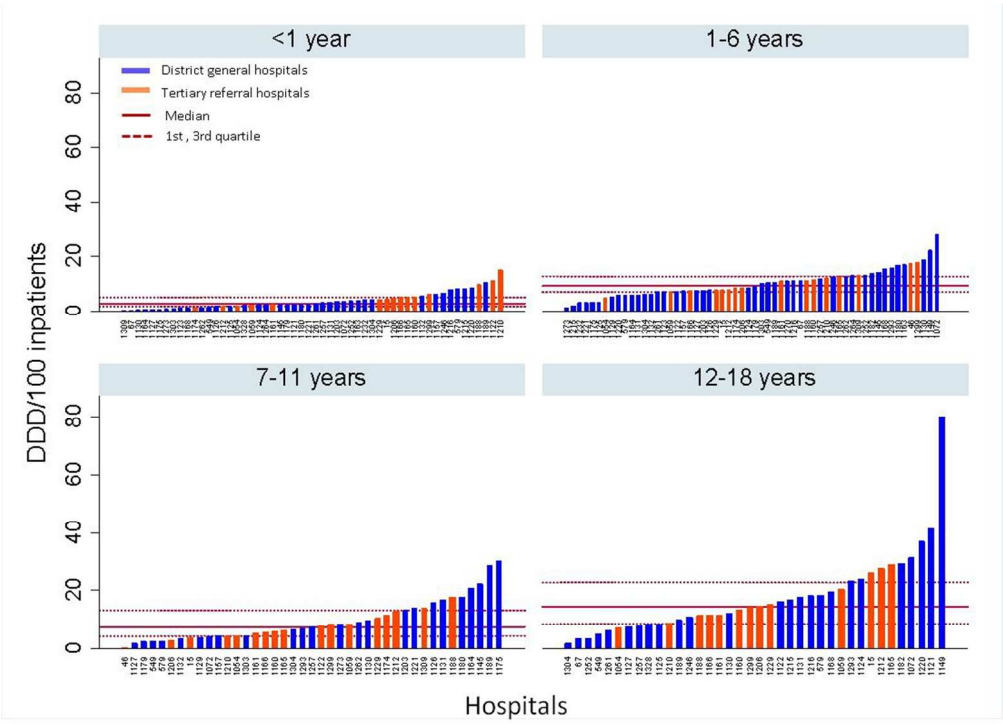
Licence for Publication statement



Funnel plot comparing hospital prescribing in United Kingdom using proportion of children on antibiotics

258x183mm (96 x 96 DPI)



Total prescribed antibiotics (DDD/100 inpatients) per age class and type of hospital across United Kingdom during the point prevalence survey in 2011-1012

291x211mm (96 x 96 DPI)

	N patients (%)	N beds	Bed occupancy
District general hospitals	958 (31.4)	1604	59.7%
Tertiary referral hospitals	2089 (68.6)	2542	82.2%
General Paediatric	1477 (48.5)	2235	66.1%
PICU - Paediatric Intensive Care Unit	226 (7.4)	265	85.3%
Paediatric Surgery	597 (19.6)	789	75.7%
Haematology-oncology-transplant	144 (4.7)	195	73.8%
Others	603 (19.8)	662	91.1%
Total (N centres = 61)	3047	4146	73.5%

166x71mm (150 x 150 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Done page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Done page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Done page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Done pages 4-5
Methods		
Study design	4	Present key elements of study design early in the paper Done page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Done page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Done page 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Done page 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Done page 6
Bias	9	Describe any efforts to address potential sources of bias Done page 6-7
Study size	10	Explain how the study size was arrived at Done pages 5 and 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Done pages 6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Done page 7
		(*b*) Describe any methods used to examine subgroups and interactions Done pages 6-7
		(*c*) Explain how missing data were addressed No missing data
		(*d*) If applicable, describe analytical methods taking account of sampling strategy NA
		(*e*) Describe any sensitivity analyses NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Done page 7
		(b) Give reasons for non-participation at each stage All participants eligible participated at the Point Prevalence Survey
		(c) Consider use of a flow diagram Not necessary here because all the patients eligible were included in the analyses
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Done page 7
		(b) Indicate number of participants with missing data for each variable of interest Done Table 1 and page 7
Outcome data	15*	Report numbers of outcome events or summary measures Done table 1-2 and 3

		pages 8-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Done table 1-2-3
		(*b*) Report category boundaries when continuous variables were categorized Done table 1-2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses NA
Discussion		
Key results	18	Summarise key results with reference to study objectives Done p14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Done p15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Done page 15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results Done pages 15-16
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Done page 17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Using a simple Point-Prevalent Survey to define appropriate antibiotic prescribing in hospitalised children across the United Kingdom

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Using a simple Point-Prevalent Survey to define appropriate antibiotic prescribing in hospitalised children across the United Kingdom

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Short running title: antibiotic use in hospitalised children

ABSTRACT

- **Background** – The National Health Service England, Commissioning for Quality and Innovation for antimicrobial resistance (CQUIN AMR) aims to reduce the total antibiotic consumption and the use of certain broad-spectrum antibiotics in secondary care. However, robust baseline antibiotic use data are lacking for hospitalised children. In this study, we aim to describe, compare and explain the prescription patterns of antibiotics within and between paediatric units in the UK and to provide a baseline for antibiotic prescribing for future improvement using CQUIN AMR guidance.
- **Method** - We conducted a cross sectional study using a point prevalence survey (PPS) in 61 paediatric units across the UK. The standardised study protocol from the Antimicrobial Resistance and Prescribing in European Children (ARPEC) project was used. All inpatients under 18 years of age present in the participating hospital the day of the study were included except neonates.

- **Results** – A total of 1247 (40.9%) of 3047 children hospitalised on the day of the PPS were on antibiotics. The proportion of children receiving antibiotics showed a wide variation between both district general and tertiary hospitals, with 36.4% (Confidence Interval 95% [CI95] 33.4-39.4) and 43.0% (CI95, 40.9-45.1) of children prescribed antibiotics respectively. About a quarter of children on antibiotic therapy received either a medical or surgical prophylaxis with parenteral administration being the main prescribed route for antibiotics (>60% of the prescriptions for both type of hospitals). General paediatrics units were surprisingly high prescribers of critical broad-spectrum antibiotics, i.e. carbapenems and piperacillin-tazobactam.
- **Conclusions** - We provide a robust baseline for antibiotic prescribing in hospitalised children in relation to current national stewardship efforts in the UK. Repeated PPS with further linkage to resistance data need to be part of the antibiotic stewardship strategy to tackle the issue of suboptimal antibiotic use in hospitalised children.

Article summary

Strengths and limitations of this study

- We used a simple, rigorous, validated and standardised point prevalence method to provide the baseline for antimicrobial prescribing in hospitalised children to assess current and future national strategies in the UK. .
- Data were collected from a large sample of hospitalised children on antibiotics (n=1247) including a wide variety of different hospitals (61 institutions) across the UK, wards and patients characteristics.
- Data were collected at the patient-level providing information on the paediatric antimicrobial prescribing in secondary care adjusted on the case-mix.
- Only volunteer hospitals were including in this cross sectional study leading to potential selection biases and limited temporal relationship between antimicrobial prescribing and covariates.

- No consensus exists for measuring antibiotic prescribing in children as DDD/100 inpatients is not a validated measure for this population.

INTRODUCTION

The increasing levels of antimicrobial resistance (AMR) are strongly correlated with inappropriate use of antibiotics. [1 2] Recent United Kingdom (UK) and international reports have advocated the critical need to monitor and control the use of existing antibiotics since the number of new classes of antibiotics has dramatically decreased over last 40 years. [3-5] Antimicrobial Stewardship Programmes (ASP), defined as comprehensive quality improvement activities for optimising antimicrobial prescribing and minimising resistance, have been widely adopted in adult care settings, [6 7] but still remain limited in children's units. [8 9] The heterogeneity in age and weight of children, as well as the lack of standardised method to quantify antibiotic use in paediatrics, increases the challenge of determining and benchmarking the appropriateness of prescribing within or between children institutions; [10-12] and children are often excluded from comparative studies on antibiotic use. [13 14]

The National Health Service England, Commissioning for Quality and Innovation for antimicrobial resistance (AMR CQUIN) 2016/17, aims to reduce by 1% or more per year the total antibiotic consumption and the use of certain broad-spectrum antibiotics considered as critical antibiotics, (carbapenems and piperacillin-tazobactam), in secondary care. [15-17] However, robust baseline antibiotic use data, so far developed for adults, are lacking for hospitalised children while they are key to measure the impact of the proposed strategies and to identify room for improvement. Two international study have proposed to describe and compare the use of antimicrobials in children across Europe and worldwide using various quality indicators, [18 19] but no comparable detailed information on antibiotic use in hospitalised children in UK is available.

The aim of our study is to describe, compare and explain the prescription pattern of antibiotics across paediatric units in the UK collected in a cross-sectional point prevalence survey (PPS) carried out as part of the Antibiotic Resistance and Prescribing in European Children (ARPEC) project. [20 21] We also proposed to use the simple PPS to apply AMR CQUIN quality indicators to

provide a baseline of antibiotic prescribing in children to measure the impact of the current and future national strategies.

METHODS

Study design and settings

Detailed antimicrobial prescribing data were collected for all inpatients under 18 years-old present in a participating hospital's paediatric and neonatal wards at 8am since at least midnight. Data collection included a wide variety of different hospitals, wards and patient characteristics to be as representative as possible of hospitalised children in the UK. Data were collected on paper forms, anonymously entered, validated and reported online through the ARPEC-PPS program. Information on surgical prophylaxis was captured for the previous 24 hours. Antimicrobial agents were analysed in accordance with the Anatomical Therapeutic Chemical (ATC) Classification (World Health Organisation Collaborative Centre for Drug Statistics Methodology, 2013). [22] To facilitate the data collection on underlying diagnosis (defined as a pre-existing comorbidity in addition to the diagnosis of infection for which patients are prescribed antibiotics) and reason for treatment with antibiotics, predefined lists of grouped items were used.[23] The full method is described elsewhere by Versporten et al. [21]

Data extraction

For this study, we extracted and analysed data from 61 paediatric units in the UK which participated in the ARPEC-PPS organised in March-April 2011 (feasibility survey), September-November 2011 (worldwide pilot ARPEC-PPS) [21] and October-December 2012 (full worldwide ARPEC-PPS). [19] All inpatients under 18 years of age admitted to a paediatric ward were included. We excluded infants on neonatal units and those on children's wards aged under 28 days of age. We analysed antibacterials for systemic use (ATC J01).

Data analysis

Descriptive analysis

Demographic data, presence or not of an underlying chronic condition, current diagnosis, hospital-acquired infections versus community-acquired infections, therapeutic versus prophylactic prescribing, and antibiotic type, dosing and route of administration were analysed and compared between 44 District General Hospitals, which provide secondary care, and 17 Tertiary Referral Hospitals, which provide tertiary or specialised care.

Metrics for measuring antibiotic use

We compared two different metrics of antibiotic prescribing within and between hospitals: (i) The proportion of children on antibiotics (prevalence rate) with 95% confidence intervals (CIs); (ii) The Defined Daily Doses per 100 inpatients (DDD/100 inpatients), as recommended in the AMR CQUIN. [17 24] Antibiotic consumption in grams was converted into DDD using the 2013 release of the ATC Classification. [22] The denominator "inpatients" was defined in this study as the sum of inpatients in the hospital at 8:00am.

Quality indicators for national benchmarking between UK hospitals

We explored the different inpatient antibiotic prescribing quality indicators proposed by CQUIN NHS England for antimicrobial resistance. [17]

1. The total amount of antibiotics prescribed using both metrics, the proportion of children receiving antibiotics and DDD/100 inpatients in different age bands. A funnel plot was used to graphically compare antibiotic prescribing between hospitals, to adjust for different hospital sizes and to identify outliers.[25] This takes account of the variable number of cases by institution by plotting the proportion of children on antibiotics against the sample size for each hospital using a binomial distribution and 95% CI (~2 standard deviation). We also

displayed antibiotic prescribing in DDD/100 inpatients for each hospital, as well as the median and interquartile range for each age band.

2. The use of the carbapenems and the use of piperacillin-tazobactam, which are both considered critically important antibiotics against extended-spectrum beta-lactamase producing Gram negative bacteria. [3] The proportions of children on carbapenems and piperacillin-tazobactam, as well as the amount of these drugs prescribed in DDD/100 inpatients, were monitored and compared between institutions after adjusting for hospital type (district general hospitals versus tertiary referral hospitals) and presence of underlying disease.

Statistical analyses

We conducted comparative analyses to determine the balance between district general hospitals and tertiary referral hospitals using tests of proportions (e.g., Chi-square analysis, Fishers exact test), and tests of central tendency (e.g., ANOVA, sign rank). Mean total daily doses were compared by unpaired two-sample t-test. All p-values were based on two-tailed test with p-value<0.05 for significance. Statistical analysis was performed using STATA version 12 (STATA Corp, College Station, Texas).

Ethics

The responsible UK Research Ethics Committee was approached to establish the need for a formal evaluation. Written confirmation was provided that within the UK framework a fully anonymised point prevalence survey constituted surveillance and that formal review by the Research Ethics Committee was not required.

RESULTS

Patient demographics

A total of 1247 (40.9%) of 3047 surveyed UK paediatric inpatients were receiving antimicrobials. Overall 1348 indications were recorded for 1247 inpatients with a total of 1858 antibiotic prescriptions. The median age of exposed children was 2 years (IQR=0.083-8). More than two-thirds of inpatients were recruited from tertiary care centres, and from General Paediatric and Paediatric Surgery wards (**Supplemental Table**).

Age differences by speciality were seen among children on antibiotics. For general paediatrics, the median age of exposed children was 2 years (IQR=0.75-6), for surgery 5 years (IQR=1.25-11), for paediatric intensive care units (PICU) 0.71 years (IQR=0.08-3), for haematology-oncology-transplant 6 years (IQR=2-11) and for other medical specialties 3 years (IQR=0.75-9).

Total use of antibiotics

Proportion of children on antibiotics

Table 1 shows that the proportion of children on antibiotics and the number of prescribed antibiotics was significantly higher in tertiary hospitals (43.0%, CI95% 40.9-45.1, 40 different prescribed antibiotics) than in district general hospitals (36.4%, CI95% 33.4-39.4, 30 different prescribed antibiotics, p-value=0.001). About two-thirds of inpatients in intensive or specialist care wards (PICU and haematology-oncology-transplant) were prescribed antibiotics in high specialist care areas compared to about one third in general paediatrics and surgery. Multiple antibiotics were also used more frequently in children admitted to PICU (77/145, 53.1%, CI95% 45.0-61.2) and haematology-oncology-transplant units (63/92; 68.5%, CI95% 59.0-78.0) compared to children in paediatric surgery (93/214; 43.5%, CI95% 36.8-50.1) and general paediatrics (199/554, 35.9%, CI 95% 31.9-39.9).

Among all children receiving antibiotics, 60.9% (CI95% 57.5-64.4) of children had an underlying disease compared with 39.1% (CI95% 34.7-43.4) of previously healthy children. Exposed

children were more likely to be younger (69.5% exposed below 7 years of age compared to 30.5% at 7 years and older).

Of 1348 indications, a diagnosis of lower respiratory, urinary tract, skin and soft tissue, bone or joint infection, pyrexia and gastrointestinal infection was recorded in 42.2% (CI 38.1-46.3) compared to 18.2% (CI 13.4-23.0) with a diagnosis of severe infections, i.e. sepsis, catheter-related bloodstream infection, central nervous system infection or febrile neutropenia. For exposed children, treatment for community-acquired infections (CAI) was almost 4 times more common (59.1%, CI 55.7-62.5) than for healthcare-associated infection (15.7%, CI 10.8-20.6). Finally, about a quarter of children on antibiotic therapy received either medical (17.3%) or surgical (6.8%) prophylaxis.

Proportion of prescriptions for parenteral administration versus oral

Parenteral was the main prescribed route for administrating antibiotics, with more than 60% of the prescriptions in district general hospitals and tertiary referral hospitals. Parenteral antibiotics were highly prescribed in PICU (81.6% of the prescriptions), for previous healthy children (70.1% of the prescriptions), for surgical infections (89.8% of the prescriptions) and for sepsis, central nervous system infections and febrile neutropenia (96.4% of the prescriptions).

Figure 1 shows the funnel plot of the proportion of children on antibiotic for each institution. Hospitals with a proportion outside the funnel plot's 2 standard deviation control limits are considered to be potential outliers. 7/61 institutions were identified as potential "high prescribers", 2 district general hospitals (21 children on antibiotics) and 5 tertiary referral hospitals (322 children on antibiotics). For the 2 district general hospitals, all children on antibiotics were from general paediatric wards, aged under 7 years old for 76.2% of them (mainly aged between 1-6), with 52.4% of them having an underlying disease and 80.1% with a common bacterial infection (LRTI, UTI, SSTI, joint bone tissue infection). For the 5 tertiary hospitals, a high proportion of children on antibiotics (30.1%) were from haematology/oncology/transplant units and PICU, with a total of

71.4% of children having an underlying disease and 22.7% of them presenting with a severe infection (Sepsis/CRBSI/CNS/febrile neutropenia) while 21.1% were on medical prophylaxis. 73.9% of the children were aged below 7 years old (35.4% <1 and 38.5% between 1-6).

Table 1: Proportion of children prescribed antibiotics in paediatric acute care settings across the United Kingdom (years 2011, 2012)

	N patients treated with antibiotic	Proportion of children on antibiotic % (CI95)	N antibiotic prescriptions (Total of different prescribed antibiotics)	Parenteral administration n (% of prescriptions)
District general hospitals (n=958 Patients)	349	36.4 (33.4-39.4)	479 (30)	291 (60.8)
Tertiary referral hospitals (n=2089 Patients)	898	43.0 (40.9-45.1)	1379 (40)	861 (62.4)
General Paediatric n=1477	554	37.5 (35.0-40.0)	791 (37)	467 (59.0)
PICU- n=226	145	64.2 (57.9-70.5)	228 (27)	186 (81.6)
Paediatric Surgery n=597	214	35.8 (32.0-39.6)	321 (29)	223 (69.5)
Haematology-Oncology-Transplant n=144	92	63.9 (56.1-71.7)	156 (24)	77 (49.4)
Others n=603	242	40.1 (36.2-44.0)	362 (31)	199 (55.0)
Total (n patients = 3047)	1247	40.9 (39.2-42.6)	1858 (41)	
	N patients treated with antibiotic (N=1247)	Proportion among total children on antibiotics % (CI95)	N antibiotic prescriptions (Total of different prescribed antibiotics)	Parenteral administration n (% of prescriptions)
No underlying disease	487	39.1 (34.7-43.4)	689 (30)	483 (70.1)
Underlying disease	760	60.9 (57.5-64.4)	1169 (41)	669 (57.2)
Aged <1 year	347	27.8 (23.1-32.6)	500 (29)	337 (67.4)
Aged 1-6 years	520	41.7 (37.5-46.0)	734 (31)	413 (56.3)
Aged 7-11 years	174	14.0 (8.8-19.1)	259 (32)	159 (61.4)
Aged > 12 years	206	16.5 (11.4-21.5)	363 (36)	243 (66.9)
	N indications for antibiotics (N=1348)	Proportion % (CI95)	N antibiotic prescriptions (Total of different prescribed antibiotics)	Parenteral administration n (% of prescriptions)
Surgical infection	74	5.5 (0.3-10.7)	137 (15)	123 (89.8)
Surgical prophylaxis	92	6.8 (1.7-11.9)	123 (17)	95 (77.2)
Medical prophylaxis	233	17.3 (12.4-22.16)	285 (29)	25 (8.8)
Sepsis/CRBSI/CNS/febrile neutropenia*	246	18.2 (13.4-23.0)	385 (22)	371 (96.4)
URTI*	73	5.4 (0.2-10.6)	90 (14)	42 (46.7)
LRTI/UTI/SSTI/Joint-Bone/Pyrexia/GITI*	569	42.2 (38.1-46.3)	764 (35)	458 (60.0)
Other/unknown	61	4.6 (0.0-9.7)	74 (22)	38 (51.4)
Community-Acquired Infection	797	59.1 (55.7-62.5)	1121 (34)	774 (69.1)
Hospital-Acquired Infection	211	15.7 (10.8-20.6)	298 (28)	240 (80.5)
Other (prophylaxis or unknown)	340	25.2 (20.6-29.8)	439 (34)	138 (31.4)
Total	1348		1858 (41)	

*CRBSI=Catheter-Related bloodstream Infection; CNS= Central Nervous System; URTI=Upper Respiratory Tract Infection; LRTI= Lower Respiratory Tract Infection; UTI=Urinary Tract Infection; SSTI=Skin and Soft Tissue Infection; GITI=Gastro Intestinal Tract Infection

Total usage of antibiotics in children in DDD/100 inpatients

Table 2 illustrates the total usage of antibiotics in DDD/100 inpatients for each age category per type of hospital and specialty. The total amount of antibiotics used is slightly higher in tertiary hospitals than in district general hospitals (37.8 versus 30.7 DDD/100 inpatients), except for children aged 1-6 years-old. The use of antibiotics is about twice as common in haematology-oncology-transplant units compared to other specialties, especially for patients above 12 years-old. For patients below 1 year-old, the use of antibiotics is substantially higher in PICU compared to other specialties.

Table 2: Total usage of antibiotics in DDD/ 100 inpatients in paediatric acute care settings across the United Kingdom, year 2011-2012

	DDD/100 inpatients			
	Aged <1yr	**Aged 1-6yrs**	**Aged 7-11yrs**	**Aged >12yrs**
District general hospitals n=958	3.2	12.3	6.0	9.2
Tertiary referral hospitals n=2089	4.0	10.5	7.1	16.2
General Paediatric n=1477	3.9	11.9	4.7	12.8
PICU- n=226	7.5	12.7	6.4	10.9
Paediatric Surgery n=597	2.1	9.0	10.7	15.7
Haematology-oncology-transplant n=144	0.45	14.2	14.0	31.7
Others n=603	4.3	9.7	6.3	11.9
Total	32.9	64.8	118.3	207.5

The total prescribed antibiotics in DDD/100 inpatients per age band is shown **Figure 2**. A wide range of antibiotic use is observed among the 61 centres for patients aged between 12-18 years-old, whereas the three other groups show greater homogeneity between institutions in antibiotic usage. The total prescribed antibiotics is harmonised between district general hospitals and tertiary referral hospitals across the four age groups.

Carbapenems and piperacillin-tazobactam

Table 3 shows that among children receiving at least one antibiotic, the proportion of children on carbapenems was significantly higher in tertiary hospitals than in district general hospitals (respectively, n=54, 6.0% versus n=7, 2.0%, p-value=0.003). The same results were observed for the total amount of DDD/100 inpatients. Less than half of the children on carbapenems had at least one underlying disease recorded for district general hospitals, while more than 9 out of 10 had an underlying disease for tertiary hospitals. In district general hospitals, the general paediatric wards were the main prescribers of carbapenems as an empirical treatment, whereas in tertiary hospitals, about 43% of the prescriptions were targeted and PICU were the main prescribers. The amount of piperacillin-tazobactam in DDD/100 inpatients was also surprisingly 2-fold higher in district general hospitals than in tertiary hospitals. However, the proportion of children on piperacillin-tazobactam among all the children on antibiotics was much higher in tertiary hospitals. In district general hospitals, most of the patients were prescribed piperacillin-tazobactam in paediatric general wards, as an empirical treatment when they had at least one underlying disease, whereas, in tertiary hospitals, piperacillin-tazobactam was prescribed in haematology-oncology-transplant wards in presence of an underlying disease.

Table 3: Total usage of carbapenems and piperacillin-tazobactam in paediatric acute care settings across the United Kingdom, year 2011-2012

	Carbapenems		Piperacillin-tazobactam	
	District general hospitals (349 children on antibiotics)	Tertiary referral hospitals (898 children on antibiotics)	District general hospitals (349 children on antibiotics)	Tertiary referral hospitals (898 children on antibiotics)
Total DDD/100 inpatients	36.4	56.0	39.7	20.0
Total children n (%)*	7 (2.0)	54 (6.0)	14 (4)	68 (7.6)
General Paediatric n children (%)**	6 (85.7)	14 (25.9)	11 (78.6)	9 (13.2)
PICU n children (%)	1 (14.3)	17 (31.5)	0	12 (17.6)
Paediatric Surgery n children (%)	0	6 (11.1)	3 (21.4)	7 (10.3)
Haematology-oncology-transplant n children (%)	0	10 (18.5)	0	19 (27.9)
Others n children (%)	0	7 (13.0)	0	21 (30.9)
Underlying disease versus previously healthy children n children (%)**	3 (42.9)	49 (90.7)	12 (85.7)	67 (98.5)

**% among the total number of children on antibiotics per type of hospitals*

**% among the total number of children on antibiotics per type of hospitals*
***% among the number of children on carbapenems or piperacillin-tazobactam*

DISCUSSION

We describe a unique inpatient antibiotic prescribing dataset from 61 paediatric units across the UK. Our results identified areas of potential improvement for appropriate prescribing at the patient-level adjusting for risk factors (age, underlying diseases, infections, specialties), using the paediatric point prevalence method developed by the ARPEC project. Our results provide the baseline for future benchmarking to monitor national strategies for optimal antimicrobial prescribing in children, particularly the CQUIN NHS England scheme 2015/16 for AMR.

A total of 1247 out of 3047 surveyed admitted children were on antibiotics in this study. The proportion of children receiving antibiotics showed a wide variation between district general hospitals and tertiary referral hospitals, but also a wide variation within both groups of hospitals. The presence of case-mix and specialities, such as haematology-oncology-transplant and PICU, may be responsible for some of the differences observed in prescribing. Figure 1 highlighted that a total of 7/61 (11.5%) institutions, mainly the haematology-oncology-transplant and PICU units of the tertiary hospitals, were identified as potential "high prescribers". However, potential "high prescribers" in general district hospitals were only general paediatric units with less than half of the patients having an underlying disease.

We also highlighted a proportion of patients on medical prophylaxis (17.3%) similar to other countries (16.9% in Italy and 14.8% on average worldwide). [19 26] Medical prophylaxis appeared to be one of the most common indications for antibiotic prescribing in children (The reason, duration and need for prophylaxis should be further assessed for quality improvement through antimicrobial stewardship programmes across paediatric units in the UK, as it is in adult settings.[27]

The total usage of antibiotics in DDD/100 inpatients per age group showed a higher consumption in haematology-oncology-transplant units compared to the other specialties, except for under 1 year-old receiving antibiotics on PICU. Children admitted to haematology-oncology-transplant units or to PICU were more likely to receive a combination of antibiotics than general and surgical paediatric patients, which may directly impact exposure measured in DDD/1000 inpatients.

Carbapenems and piperacillin-tazobactam, were mainly prescribed empirically, and to children with underlying conditions in tertiary hospitals. These results are expected and will serve as a benchmark in future evaluations. However, we did not predict that general paediatric units were high prescribers for these two drugs in both district general and tertiary hospitals. With the spread of extended-spectrum-beta-lactamase producing Enterobacteriaceae in adults [28] but also in paediatrics over the last decade, [29] and the increase of small outbreaks of multidrug resistant organisms in UK paediatric hospitals, [30] the prescribing pattern for these critical drugs may change in the future and needs to be better monitored, especially in the general paediatric units for previously healthy children.

There remains a lack of consensus regarding the optimal metric to assess paediatric antimicrobial use, which is an important limitation. The use of DDD/100 inpatients (DDD being defined as the amount of antibiotic prescribed for a 70kg average adult weight for its main indication) proposed by CQUIN AMR is not a perfect measure, especially in children with a wide range of weights (from 5kg in a 3 months-old to over 100kg in obese adolescents). As DDD is weight and dose-dependent, [31] we decided to compare overall drug exposure using DDD/100 inpatients in age bands as proposed by Porta et al.[24] Despite DDD/100 inpatients being advocated by the WHO Collaborating Centre for Drug Statistics and Methodology, “days of therapy” could have advantages over DDD measures, because the impact of variation in absolute dose is limited for this metric. [11 31] However, longitudinal studies or access to electronic-prescribing systems for each hospital in the UK would be required to calculate this, which may not be realistic in the near future. [32] For now, DDD/100 inpatients could be used to monitor changes within units over time as long as the case mix remains the same. While we have strongly promoted this study to include a large number of paediatric centres from a wide variety of different hospitals, wards and patient characteristics across the UK, only volunteer centres were recruited, with the potential for selection biases. Finally, the PPS methodology provided limited evidence on the temporal relationship between the antimicrobial prescribing in children and the covariates of interest.

In conclusion, we provide a robust baseline for antibiotic prescribing in hospitalised children in relation to current national stewardship efforts in the UK. Repeated PPS [33] need to be part of the paediatric antibiotic stewardship strategy in order to identify prescribing trends over time, to evaluate the efficacy of antimicrobial stewardship programmes and to tackle the issue of suboptimal antibiotic use, especially on antibiotic dosing.[34] International standardised PPS with further linkage between antibiotic prescribing and resistance will be critical to characterise appropriate use of antibiotics in hospitalised children globally and to propose guidance on the management of paediatric infections taking into account resistance profiles.

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COMPETING INTERESTS

No competing interest to declare.

CONTRIBUTORSHIP STATEMENT

MG, KD, JAB, AV, HG and MS had substantial contributions to the conception and the design of the work; MG, KD, SV, JAB, SP, EM, AR, HL, SVP, JB, AV, MH, HG, MS participated in the

acquisition, and interpretation of data for the work; The data management was done by AV and MG and the data analysis by MG. MG, KD, SV and MS drafted the work and MG, KD, SV, JAB, SP, EM, AR, HL, SVP, JB, AV, MH, HG, MS revised it critically for important intellectual content; and all the authors, i.e. MG, KD, SV, JAB, SP, EM, AR, HL, SVP, JB, AV, MH, HG, MS gave the final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA SHARING

No additional data available. The additional unpublished data on antimicrobial prescribing for neonates and children are currently being published within the ARPEC project.

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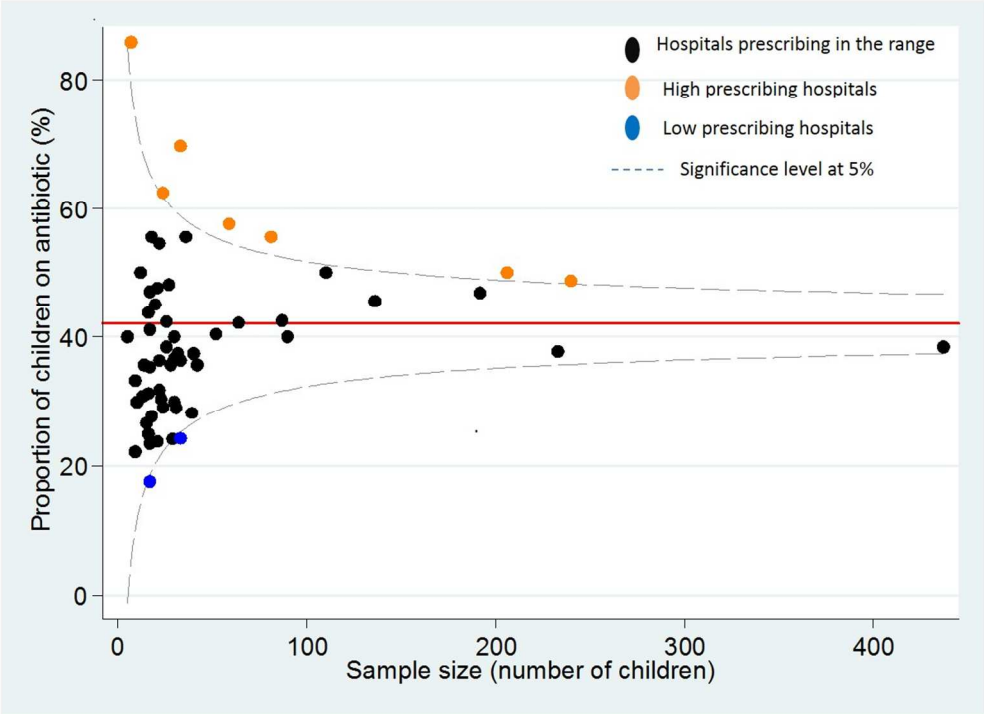
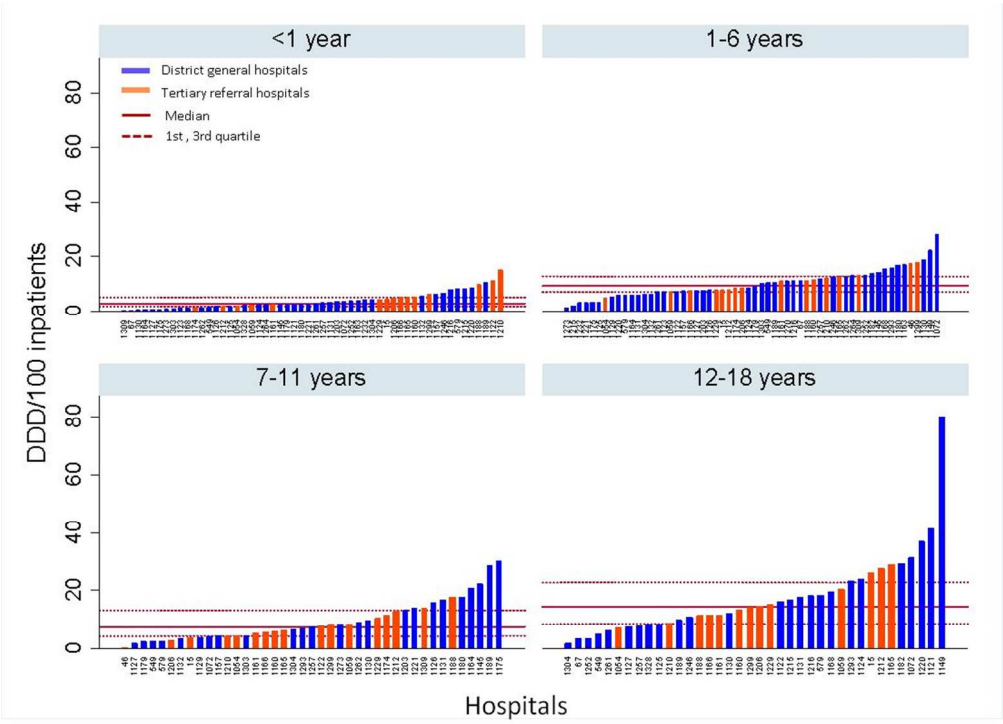


Funnel plot comparing hospital prescribing in United Kingdom using proportion of children on antibiotics

205x150mm (150 x 150 DPI)



Total prescribed antibiotics (DDD/100 inpatients) per age class and type of hospital across United Kingdom during the point prevalence survey in 2011-1012

233x168mm (120 x 120 DPI)

Supplemental table: Characteristics of paediatric hospital across the United Kingdom (during the two one-day point prevalence survey in 2011-12)

	N patients (%)	N beds	Bed occupancy
District general hospitals	958 (31.4)	1604	59.7%
Tertiary referral hospitals	2089 (68.6)	2542	82.2%
General Paediatric	1477 (48.5)	2235	66.1%
PICU - Paediatric Intensive Care Unit	226 (7.4)	265	85.3%
Paediatric Surgery	597 (19.6)	789	75.7%
Haematology-oncology-transplant	144 (4.7)	195	73.8%
Others	603 (19.8)	662	91.1%
Total (N centres = 61)	3047	4146	73.5%

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Done page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Done page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Done page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Done pages 4-5
Methods		
Study design	4	Present key elements of study design early in the paper Done page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Done page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Done page 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Done page 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Done page 6
Bias	9	Describe any efforts to address potential sources of bias Done page 6-7
Study size	10	Explain how the study size was arrived at Done pages 5 and 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Done pages 6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Done page 7
		(*b*) Describe any methods used to examine subgroups and interactions Done pages 6-7
		(*c*) Explain how missing data were addressed No missing data
		(*d*) If applicable, describe analytical methods taking account of sampling strategy NA
		(*e*) Describe any sensitivity analyses NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Done page 7
		(b) Give reasons for non-participation at each stage All participants eligible participated at the Point Prevalence Survey
		(c) Consider use of a flow diagram Not necessary here because all the patients eligible were included in the analyses
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Done page 7
		(b) Indicate number of participants with missing data for each variable of interest Done Table 1 and page 7
Outcome data	15*	Report numbers of outcome events or summary measures Done table 1-2 and 3

		pages 8-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Done table 1-2-3
		(*b*) Report category boundaries when continuous variables were categorized Done table 1-2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses NA
Discussion		
Key results	18	Summarise key results with reference to study objectives Done p14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Done p15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Done page 15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results Done pages 15-16
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Done page 17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.