

European Surveillance of Antibiotic Consumption (ESAC) point prevalence survey 2008: paediatric antimicrobial prescribing in 32 hospitals of 21 European countries

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Background: Antimicrobials are the most common medicines prescribed to children, but very little is known about patterns of hospital paediatric antimicrobial prescribing. This study aimed at describing paediatric antimicrobial prescribing in European hospitals to identify targets for quality improvement.

Methods: The European Surveillance of Antibiotic Consumption (ESAC) project (www.esac.ua.ac.be) collected data during 2 calendar weeks between May and June 2008 in 32 hospitals of 21 European countries with paediatric departments, using a standardized method. The ESAC point prevalence survey included all inpatient beds and identified all patients who were receiving systemic antimicrobials on the day of the survey or had received antimicrobial surgical prophylaxis on the previous day.

Results: Of 1799 children, 583 (32%) received one or more antimicrobials (range 17%–100%). The indications were therapeutic in 71%, prophylactic in 26% and both indications in 3% of patients. The parenteral route was used in 82% of therapeutic indications and in 63% of prophylactic indications. Third-generation cephalosporins were the most prescribed antimicrobials for therapeutic indications (18%). A high proportion of treated children received antimicrobial combinations (37%). The most commonly treated diagnosis site was the respiratory tract for both therapeutic use (30%) and prophylaxis (25%). The duration of surgical prophylaxis was >1 day in 67%.

Conclusions: Targets identified for quality improvement of antimicrobial use in children included excessive use of antimicrobial combinations and a high proportion of parenteral antimicrobials, both of which require further investigation. Surgical prophylaxis for >1 day should also be curbed in order to achieve quality improvement.

Keywords: antimicrobial use, drug consumption, Europe

Introduction

Antimicrobials are among the most commonly prescribed drugs in both hospitals and the community. The link between antimicrobial use and the emergence of bacterial resistance has been clearly established and represents a major public health problem.^{1,2} The emergence of antibiotic resistance leads to increases in length of stay, mortality and, subsequently, the cost of healthcare.³ Several studies have reported on antimicrobial prescribing in hospitalized children,^{4–15} but there is no validated programme for monitoring antimicrobial prescribing in children admitted to hospitals.¹⁶ This is predominantly because

the established surveillance programmes in hospitals have focused on adults, even though children are very high users of antimicrobials. The investigation of antimicrobial use in children is crucial because they are an excellent environment for the selection of resistant bacterial pathogens after recent antimicrobial use.¹⁷ In hospitals, the risk of the emergence and the transmission of bacterial resistance are dramatically increased because of the high incidence of patients treated with antimicrobials and close patient proximity.

Point prevalence surveys (PPSs) have been used to provide information about nosocomial infections and antimicrobial

use.^{4,9,10,12,13} Phase III of the European Surveillance of Antibiotic Consumption (ESAC) project (www.esac.uu.ac.be), grant-funded by the European Centre for Disease Prevention and Control (ECDC), collects data on antimicrobial consumption in ambulatory care and hospital settings from 34 European countries. The ESAC Hospital Care Subproject developed a standardized method for PPS (the ESAC PPS) on antimicrobial use in European hospitals from different healthcare systems in 2006.¹⁸

The aims of this study were: (i) to describe antimicrobial prescribing in paediatric units in 2008 at 32 hospitals from 21 European countries using the standardized ESAC PPS; (ii) to assess the prescribed daily dose (PDD) in children; and (iii) to identify targets for quality improvement of antimicrobial prescribing in paediatric patients.

Methods

Data source and study population

Data were extracted from the 50 hospitals of the ESAC PPS 2008 database. The ESAC national representatives were invited to recruit one or several hospitals to participate in the ESAC PPS in 2008. In this report, the analyses were restricted to hospitals with paediatric units: 32 hospitals in 21 European countries (Austria, Belgium, Bulgaria, Switzerland, Cyprus, Czech Republic, Estonia, France, Greece, Croatia, Hungary, Ireland, Israel, Italia, Lithuania, Latvia, Malta, Portugal, Russia, Slovenia and the UK).

Submission of data was done using a web-based application developed and validated by the ESAC project.¹⁸ This application allowed automatic reporting for the participating hospitals. Additionally, a personal digital assistant (PDA) could be used for data entry. The software for the PDA was developed by the ESAC management team.

Data collection

The survey was carried out during a maximum of 2 calendar weeks between 20 May and 30 June 2008 using a simplified version of the 2006 ESAC PPS protocol.¹⁸ Hospitals recruited clinical staff familiar with reading patient notes (infection disease specialist, microbiologist, pharmacist or infection control nurse) to perform the survey. The survey could be completed by a single person or by a number of clinical personnel.

All children who were present in the hospital at least 24 h before the survey and present at 8 am on the day of the survey were included in the survey. The following information was collected for children who were receiving antimicrobials on the day of the survey: age; gender; and antimicrobial agent according to the anatomical therapeutic chemical (ATC) classification system¹⁹ (dose per administration, number of doses per day and route of administration). Furthermore, the targeted anatomical site according to a list of diagnosis groups and indication, including both therapeutic use and prophylaxis, were also collected. For surgical patients, administration of prophylactic antimicrobials in the previous 24 h was recorded, in order to code the duration of prophylaxis as: one dose; 1 day; or more than 1 day.

Quantification of antimicrobial use

Antimicrobial prescriptions, including antibacterials for systemic use (J01), antifungals (J02), rifampicin (J04AB02, excluding anti-tuberculosis indication), oral vancomycin and colistin (A07AA09-10) and oral and rectal metronidazole (P01AB01), were grouped at ATC level 4. Patients who had received more than one antimicrobial were considered as being on combination therapy. The mean PDD of individual antimicrobials

for the respective route of administration was calculated for the most frequently used drugs. The PDD was defined as the observed dose received by each patient. Due to the extremely large differences in dosing in paediatrics, ranging from pre-term neonates to teenagers, the PDD was stratified into five age groups (1, 0–11 months; 2, 12–23 months; 3, 2–4 years; 4, 5–9 years; 5, ≥ 10 years).

Data analysis

Data were analysed using SAS 9.1 (SAS Institute, Cary, NC, USA). The results were analysed at the patient level. Separate analyses were carried out for patients receiving therapeutic and prophylactic antimicrobials.

Results

Antimicrobial overview

From the 32 ESAC PPS 2008 hospitals, there were a total of 69 paediatric units, of which 28 were medical, 26 were intensive care and 15 were surgical wards. Of 1799 eligible children, 583 (32%) received one or more antimicrobial(s). The proportion of patients receiving antibacterials ranged from 17% to 100% in hospitals. The median age was 2 years, with 317 (54%) being males. Medical wards included the highest proportion of all the treated children, 316 (54%), followed by intensive care 172 (30%) and surgical wards 95 (16%). The average number of antimicrobials per patient was higher in intensive care (mean 1.6; range 1.0–2.3) than in medicine (mean 1.4; range 1.0–3.0) or surgery (mean 1.4; range 1.0–2.0).

Of the 839 antimicrobials prescribed, antibacterials for systemic use (J01) represented 96% of all prescriptions. Overall, 17 substances accounted for 75% of the total use (DU75%). These included only two oral antibiotics (sulfamethoxazole and trimethoprim, and amoxicillin and enzyme inhibitor). The indications for children receiving antimicrobials were therapeutic in 71% ($n=412$), prophylaxis in 26% ($n=154$) and both indications in the remaining 3% ($n=17$).

Prophylactic antimicrobial use

The parenteral route was more commonly used than the oral route for prophylactic antimicrobials (parenteral, 63%; oral, 37%) (Table 1). Antimicrobial combinations represented 37% of prophylaxis. The respiratory tract (25%) was the most common site for prophylaxis. The completely undefined site represented 20% of overall prophylactics.

The pattern of antimicrobial use varied between surgical and medical prophylaxis (Figure 1). Of the 171 prophylactic antimicrobials, 113 (66%) were prescribed for medical prophylaxis and 58 (34%) for surgical prophylaxis.

For surgical prophylaxis, the duration was more than 1 day in 67% of children whilst single doses were used in 8%. Prophylaxis was generally prolonged for more than 1 day for all sites. For instance, it was longer than 1 day in all CNS and in 78% of urinary tract prophylaxis cases. In surgical prophylaxis, combinations of penicillins with β -lactamase inhibitors (J01CR) and first-generation cephalosporins (J01DB) were the more common drug classes (26% and 15%, respectively).

For medical prophylaxis, the top two classes were combinations of sulphonamides and trimethoprim (J01EE) and 'other

Table 1. Characteristics of patients receiving therapeutic and prophylactic antimicrobials in paediatric units in 32 European hospitals

Characteristics	Therapeutic use		Prophylactic use	
	n	%	n	%
Number of antimicrobials				
1 antimicrobial	272	63.4	107	62.6
2–3 antimicrobials	148	34.5	59	34.5
>3 antimicrobials	9	2.1	5	2.9
Route of administration				
oral	85	18.2	66	37.5
parenteral	383	81.8	110	62.5
Diagnosis				
respiratory	127	29.6	42	24.6
systemic ^a	67	15.6	13	7.6
ear, nose, throat	60	14.0	10	5.8
gastrointestinal	48	11.2	31	18.1
urology	41	9.6	16	9.4
skin, soft tissue, bone and joint	35	8.2	9	5.3
CNS	22	5.1	8	4.7
undefined ^b	17	4.0	34	19.9
eye	6	1.4	1	0.6
central vascular system	5	1.2	5	2.9
gynaecology, obstetric	1	0.2	2	1.2

The total number of patients receiving antimicrobials was different for each characteristic; a patient could receive both therapeutic and prophylactic antimicrobials and both oral and parenteral antimicrobials. ^aSystemic corresponds to bacteraemia (not endocarditis) and systemic inflammatory response with no clear anatomical site. ^bCompletely undefined site with no systemic inflammation.

aminoglycosides’ (J01GB) (referring to all aminoglycosides with the exception of streptomycins; 22% and 20%, respectively). However, ‘other aminoglycosides’ were often used in combination with penicillins with extended spectrum (J01CA). This dual therapy represented 17% of all medical prophylaxis.

Therapeutic antimicrobial use

The parenteral route was used in 82% of infections. The proportion of antimicrobial combinations prescribed for infection represented 37% of all prescriptions and was similar to prophylaxis. Respiratory tract infections (30%; Table 1), systemic infections (16%) and ear, nose and throat infections (14%) accounted for approximately 60% of all diagnoses for infections. The completely undefined site represented only 4% of all diagnoses.

The top three antimicrobial classes were third-generation cephalosporins (J01DD, 18%), ‘other aminoglycosides’ (J01GB, 14%) and penicillins with extended spectrum (J01CA, 10%) (Figure 2). Of all antimicrobial combinations, ‘other aminoglycosides’ and extended-spectrum penicillins (J01CA) was the most common (n=20, 13%). Children with respiratory tract infections were most commonly treated with monotherapy using third-generation cephalosporins (J01DD, 13%), macrolides (J01FA, 11%) or second-generation cephalosporins (J01DC, 11%). Treatment of systemic infections included antimicrobial combinations in 65% of cases, the most frequently used being the combination of penicillins with either aminoglycosides (21%) or cephalosporins (16%).

PDDs

The six most frequently used therapies were ampicillin, amoxicillin and enzyme inhibitor, cefuroxime, ceftriaxone, sulfamethoxazole and trimethoprim, and gentamicin. The PDD increased with age,

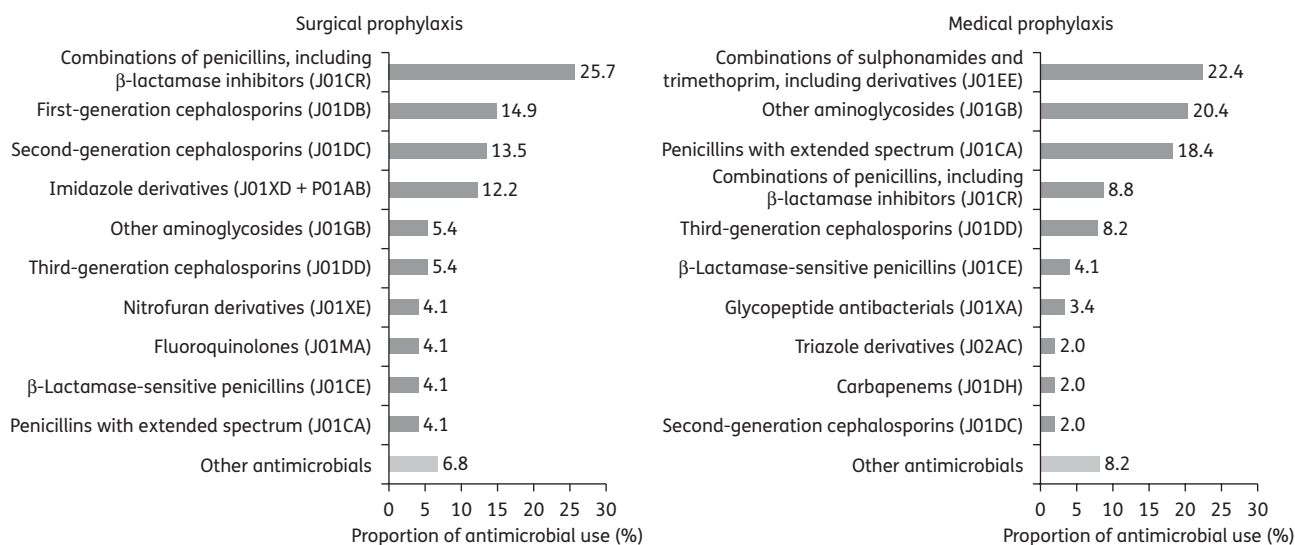


Figure 1. Proportion of antimicrobial prophylactic use in paediatric units for the 10 most frequently used groups at ATC level 4.

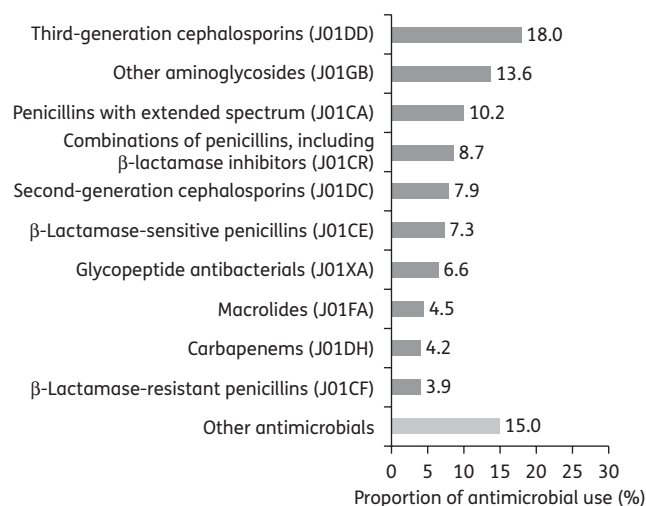


Figure 2. Proportion of antimicrobial therapeutic use in paediatric units for the 10 most frequently used groups at ATC level 4.

as shown in Table 2, with a ratio (oldest children/youngest children) ranging from 5-fold for ceftriaxone to 21-fold for gentamicin.

Discussion

Approximately one-third of paediatric patients were on antimicrobials, with considerable differences between hospitals. These variations could be explained by the characteristics of hospital care systems, which differ across countries, and by the case mix.²⁰ Hospitals with similar patient populations could have different prescribing patterns, influenced by local antibiograms and formularies. Therefore, data are intended for auditing

trends of use within the same institution, not for benchmarking between hospitals.

Several targets for quality improvement were identified. The first performance indicator was the high proportion of parenteral antimicrobials, especially for therapeutic indications, since this is associated with vascular line infections, inconvenience to patients, prolonged hospital stay and increased costs.²¹ A number of factors partially explain this high rate of parenteral use. These include: life-threatening infections (e.g. systemic infections and CNS infections) requiring intravenous therapy; drugs available exclusively for parenteral use (e.g. the aminoglycosides, one of the most used classes); and the fact that neonates and younger infants are unable to take oral medications. Although a number of factors could partially explain this high rate of parenteral use, individual hospitals should develop effective strategies to use oral instead of parenteral antimicrobials whenever possible (e.g. after the critical phase of infection is over switching to oral therapy has become the mainstay of antibiotic therapy for the majority of patients).²²

The second performance indicator identified was the high proportion of antimicrobial combinations. Several reasons could be advanced to justify the use of antimicrobial combinations, including: prevention of the emergence of resistant organisms (e.g. efficacy of combinations to prevent mutational resistance in the treatment of tuberculosis); polymicrobial infections (e.g. intraperitoneal and pelvic infection caused by mixed aerobic and anaerobic organisms); initial therapy; and synergism.²³ Despite this, there is clear evidence to prefer monotherapy because combination therapy may have important negative effects, such as drug interactions, increased cost and adverse effects. In our study, the appropriate use of antimicrobial combinations was not assessed. However, an example of misuse was the number and type of antimicrobial combinations used in surgical prophylaxis (24%). Most frequently this included an overlap of anti-anaerobic cover with metronidazole added to a penicillin with enzyme inhibitor. Analysing the type of

Table 2. Distribution of PDDs for the six most frequently used antimicrobials in paediatric units stratified by age

Antimicrobials	Number of therapies	DDD (g)	PDD (g), median (IQR)				
			0–11 months	12–23 months	2–4 years	5–9 years	≥10 years
Gentamicin (P)	76	0.24	0.01 (0.01–0.03)	0.07 (0.06–0.07)	0.07 (0.06–0.09)	0.15 (0.15–0.22)	0.21 (0.16–0.24)
Ceftriaxone (P)	59	2	0.40 (0.23–0.50)	0.75 (0.56–1.00)	1.00 (0.90–1.00)	1.45 (1.00–1.50)	2.00 (2.00–3.00)
Ampicillin (P)	54	2	0.34 (0.20–0.45)	0.54 (0.36–0.96)	1.00 (0.60–1.00)	2.90 (2.60–3.20)	4.00 ^a
Cefuroxime (P)	52	3	0.44 (0.18–0.55)	1.50 (1.20–1.50)	0.80 (0.75–0.84)	2.00 (1.50–3.90)	2.25 (1.50–4.25)
Sulfamethoxazole and trimethoprim (O)	46	1.92	0.15 (0.14–0.24)	0.24 (0.15–0.24)	0.48 (0.24–0.48)	0.25 (0.10–0.48)	0.96 (0.24–1.72)
Amoxicillin and enzyme inhibitor (P)	43	3	0.33 (0.20–0.66)	0.80 (0.60–0.90)	1.20 (1.20–2.36)	2.60 (1.82–3.00)	3.60 (3.00–3.60)
Amoxicillin and enzyme inhibitor (O)	23	1	0.23 (0.15–0.26)	0.38 (0.28–0.47)	0.99 (0.19–1.37)	1.00 (0.90–1.35)	1.75 (1.05–1.80)

Route of administration: P, parenteral; O, oral.

The interquartile range (IQR) corresponds to the 25th percentile and the 75th percentile. Therefore, half of the distribution is between these percentiles.

The DDD (defined daily dose) is a standardized unit defined by the WHO for the main indication in an adult of 70 kg.

^aSample size too small to give the percentiles.

combinations used for infections, nearly a quarter of the combination therapies included what seemed to be non-clinically relevant combinations (e.g. penicillin with extended spectrum plus a third-generation cephalosporin).

The third performance indicator identified was a duration of surgical prophylaxis of more than 24 h. While prolonged antibiotic prophylaxis showed no improvement in preventing the risk of infection, the ecological risk is pertinent.²⁴ A previous study performed in France in children and adults using the ESAC PPS showed that 50% of antimicrobial prophylaxis was not in line with local guidelines.²⁵ Similarly, a recent multicentre survey in four tertiary neonatal intensive care units in the USA showed frequent inappropriately prolonged post-surgical use of antimicrobials (>48 h).¹⁴ These data show that even in the most documented evidence-based area of practice, which recommends a surgical antimicrobial prophylaxis duration of less than 24 h, clinicians tend to overprescribe, and this is a global phenomenon not exclusive to Europe.

In this study it was confirmed that the PDD increased with age and weight. Thus, further studies focusing on antimicrobial use in children could define standardized paediatric daily doses for different paediatric age groups and neonates separately. This study found that, for children ≥ 10 years old, the PDD for four antimicrobials was similar to or higher than the defined daily dose (DDD). These results add to the evidence from other studies that the DDD does not correspond to the PDD for many classes of antimicrobials in adults.^{26,27}

Finally, it is important to highlight the fact that the sample size may not be representative of European paediatric units. Nevertheless, surveillance of antimicrobial use at the hospital level is the first step in auditing, identifying and improving on the current situation with respect to inappropriate prescribing.

The ESAC PPS offers a standardized instrument that can identify targets for quality improvement of antimicrobial use in children. The use of the ESAC PPS in a larger sample of paediatric units in Europe could help to define standardized units for antimicrobial prescription in the different age groups in children.²⁸

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Transparency declarations

None to declare.

Disclaimer

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