Use of the WHO Access, Watch, and Reserve classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries

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Summary

Background Improving the quality of hospital antibiotic use is a major goal of WHO's global action plan to combat antimicrobial resistance. The WHO Essential Medicines List Access, Watch, and Reserve (AWaRe) classification could facilitate simple stewardship interventions that are widely applicable globally. We aimed to present data on patterns of paediatric AWaRe antibiotic use that could be used for local and national stewardship interventions.

Methods 1-day point prevalence survey antibiotic prescription data were combined from two independent global networks: the Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children and the Global Point Prevalence Survey on Antimicrobial Consumption and Resistance networks. We included hospital inpatients aged younger than 19 years receiving at least one antibiotic on the day of the survey. The WHO AWaRe classification was used to describe overall antibiotic use as assessed by the variation between use of Access, Watch, and Reserve antibiotics, for neonates and children and for the commonest clinical indications.

Findings Of the 23 572 patients included from 56 countries, 18 305 were children (77·7%) and 5267 were neonates (22·3%). Access antibiotic use in children ranged from 7·8% (China) to 61·2% (Slovenia) of all antibiotic prescriptions. The use of Watch antibiotics in children was highest in Iran (77·3%) and lowest in Finland (23·0%). In neonates, Access antibiotic use was highest in Singapore (100·0%) and lowest in China (24·2%). Reserve antibiotic use was low in all countries. Major differences in clinical syndrome-specific patterns of AWaRe antibiotic use in lower respiratory tract infection and neonatal sepsis were observed between WHO regions and countries.

Interpretation There is substantial global variation in the proportion of AWaRe antibiotics used in hospitalised neonates and children. The AWaRe classification could potentially be used as a simple traffic light metric of appropriate antibiotic use. Future efforts should focus on developing and evaluating paediatric antibiotic stewardship programmes on the basis of the AWaRe index.

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Introduction

Antimicrobial resistance is a rapidly emerging global public health crisis. In response, the World Health Organization has published a global action plan on antimicrobial resistance,[1] one of the aims of which is to optimise the use of antimicrobials. Knowledge gaps about the global use of antibiotics need to be addressed to inform the implementation and monitoring of antimicrobial stewardship activities. In 2014, WHO recommended improved surveillance of antibiotic use as one of its key strategies.[2] Children are high users of antibiotics, but very little progress has been made with developing paediatric antibiotic stewardship programmes. One of the difficulties with developing such programmes is that the defined daily dose method used in adult antibiotic surveillance is not suitable for use in neonates and children, who have widely variable bodyweights.[3,4] In March, 2017, the WHO Essential Medicines List (EML) Working Group classified antibiotics in the EML for Children (EMLc) into three groups: Access, Watch, and Reserve.[5] The Access group contains generally narrow-spectrum antibiotics recommended as first and second choice for most common clinical infection syndromes. The Watch group contains generally broader spectrum antibiotic classes corresponding to the highest priority agents on the list of critically important antimicrobial drugs for human medicine.[6] The Reserve group consists of last-resort antibiotics for targeted use in multidrug-resistant infections. These groups are collectively known as the AWaRe classification,[7] and traffic light colour codes have been suggested to indicate the different categories:

Research in context

Evidence before this study

Data on patterns of antibiotic use in the paediatric population are mainly from high-income countries, whereas data from low-income and middle-income countries are scarce. We searched MEDLINE and Embase with the terms "point prevalence survey", "antibiotic", "pediatric", "children", and "neonate", with age restriction (0–18 years) and no language restrictions; results were restricted to those published before April 14, 2018. A total of 17 relevant articles were included, of which one study was done through the European Surveillance of Antimicrobial Consumption project, 12 studies through the Antimicrobial Resistance and Prescribing in European Children network, and two were Indian studies from the Global Antimicrobial Resistance, Prescribing and Efficacy in Neonates and Children network. One study was done in Italian children's hospitals, collecting data from patients hospitalised for more than 48 h by reviewing medical charts. A multicentre point prevalence survey (PPS) was done to assess inappropriate antibiotic use in hospitalised children in Turkey. These studies reported antibiotic prescribing patterns by means of the Anatomical Therapeutic Chemical classification. In March, 2017, the WHO Essential Medicines List for Children (EMLc) was updated and released a new antibiotic classification: Access, Watch, and Reserve (known as the AWaRe classification). We could identify no previous antibiotic use studies that applied the AWaRe classification in the inpatient paediatric population.

Added value of this study

We combined PPS data from three different study groups that all used similar methods. We applied the AWaRe classification to assess total and condition-specific patterns of antibiotic use for neonates and children in the hospital setting. Our study has shown the substantial variations of overall AWaRe antibiotics use in this population. Previous antibiotic stewardship programmes have used the defined daily dose system as the main tool to monitor patterns of antibiotic use. However, defined daily dose is complex and requires specialist knowledge of pharmacological and therapeutic systems. Additionally, defined daily dose cannot be applied to measure antibiotic use in the paediatric population owing to the wide variation in weights in hospitalised children. This study suggests that the AWaRe classification might be a simpler metric, and it could potentially be used in hospital antibiotic stewardship activities to monitor or compare antibiotic use between and within hospitals. Furthermore, the AWaRe classification could be a simple easy to understand indicator for clinicians and policy makers to identify issues of inappropriate antibiotic use and develop more specific guidance for antibiotic stewardship activities.

Implications of all the available evidence

We have shown that it is feasible to combine global PPSs originating from different study partners and subsequently categorise both overall and condition-specific patterns of antibiotic use by the AWaRe classification. Limitations include specific issues with the PPS methodology and the survey being biased towards long-stay patients when doing repeated PPS. Additionally, antibiotics not listed on the EMLc are not classified into an AWaRe category. Further refinement of the categories is required to take into account global patterns of use and formally evaluate this new method in stewardship programmes.

Access antibiotics (green), Watch antibiotics (amber), and Reserve antibiotics (red).

Standardised data collection is necessary to better understand contemporary antibiotic use among neonates and children worldwide and support the development of simple, globally applicable paediatric antibiotic stewardship programmes. Data on antibiotic use in children are mainly from high-income countries (HICs) and remain scarce from low-income and middle-income countries (LMICs).[1] WHO's global action plan highlighted a need for antimicrobial resistance surveillance networks and centres to collaborate to create or strengthen coordinated regional and global surveillance.[2] In this Article, we report on such a collaborative approach, combining paediatric data collected in HICs and LMICs from the Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children (GARPEC) network and the Global Point Prevalence Survey on Antimicrobial Consumption and Resistance (Global-PPS) network. Specifically, this study aimed to describe antibiotic use in hospitalised neonates and children by combining data from the Global-PPS and GARPEC networks and establish the feasibility of applying the new WHO AWaRe classification to classify specific antibiotic use for total and clinical infection syndrome in this population.

Methods

Data sources

Data were obtained from the GARPEC and Global-PPS networks. Both of these datasets come from point prevalence surveys (PPSs) of antibiotic use in hospitalised neonates and children. The PPS method has been used extensively to measure antimicrobial use in hospitalised adults and children.[8–10] In both networks, participating centres contributed data voluntarily and received no financial incentives. This study was considered a clinical audit. Each participating hospital received local ethics approval if required. All data were anonymised without patient identifiers.

Data collection procedures

In 2015, a 1-day pilot PPS was done over 2 months in 11 countries that were part of the GARPEC network

(Americas: three countries, four hospitals; Africa: one country, one hospital; Eastern Mediterranean: one country, one hospital; Europe: two countries, two hospitals; Western Pacific: two countries, four hospitals; South-East Asia: two countries, three hospitals). Following the pilot PPS study, four full-scale 1-day GARPEC PPSs were done between February, 2016, and February, 2017: February–March, 2016, May–June, 2016, September–October, 2016, and December, 2016–February, 2017. In total, 116 hospitals from 24 countries participated in at least one wave of the PPSs between 2015 and 2017 (Europe: ten countries, 34 hospitals; Americas: three countries, 39 hospitals; Western Pacific: five countries, 25 hospitals; Africa: three countries, five hospitals; South-East Asia: two countries, 12 hospitals; Eastern Mediterranean: one country, one hospital). Patient demographics (age, gender, bodyweight), comorbidity, antimicrobial agents, dose, frequency, route of administration, empirical or targeted treatment, and reasons for treatment were collected. Information on gestational age and birthweight were collected for neonates. The information collected in the pilot study was similar to that of the main waves of PPSs. GARPEC-data were collected via REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA), a web-based application through which participating centres entered data online. All data were anonymised and linked only to an identification number unique to each participating centre. Additionally, 31 hospitals in the Sharing Antimicrobial Reports for Pediatrics Stewardship (SHARPS) project—a national antimicrobial stewardship collaboration between children's hospitals in the USA[11]—agreed to do a PPS using the GARPEC method and contribute their PPS data to the GARPEC network between June, 2016, and July, 2017.

A pilot Global-PPS was done between October and November, 2014. By means of a standardised surveillance method, detailed data on hospitalised adults, neonates, and children receiving an antimicrobial on the day of the survey were collected between January and September, 2015, from 335 hospitals in 53 countries: Europe (24 countries; 214 hospitals); Africa (five countries; 12 hospitals), Asia (16 countries; 57 hospitals), the Americas (six countries; 43 hospitals), and Oceania (two countries; nine hospitals). A web-based application was used for data entry, validation, and reporting designed by the University of Antwerp. Further details have been published elsewhere.[10]

For more on the **web-based application** see www.global-pps.com

We combined the GARPEC-PPS, SHARPS-PPS, and Global-PPS paediatric data for analysis. We only present variables that were collected in all datasets, including patient demographics, antibiotic use (type, route of administration, frequency of use), type of treatment (empirical or targeted treatment), and diagnosis. Neonates were defined as aged 30 days or younger and children were aged between 30 days and younger than 19 years. Antibiotic drugs were coded on the basis of the WHO Anatomical Therapeutic Chemical (ATC) classification system.[12] We included antibiotics classified as antibacterials for systemic use (ATC code: J01). Prescriptions for antifungal (ATC code: J02), antiviral (ATC code: J05), and drugs for tuberculosis (ATC code: J04) treatment were

Africa
5 countries; 12 hospitals; 906 prescriptions

Ceftriaxone	109 (12·0%)
Gentamicin	91 (10·0%)
Ampicillin	69 (7·6%)
Sulfamethoxazole–trimethoprim	66 (7·3%)
Amoxicillin	58 (6·4%)
Metronidazole	50 (5·5%)
Cefuroxime	48 (5·3%)
Amoxicillin and inhib	44 (4·9%)
Meropenem	41 (4·5%)
Ciprofloxacin	34 (3·8%)
Vancomycin	25 (2·8%)
Cloxacillin	23 (2·5%)
Cefotaxime	23 (2·5%)
Amikacin	23 (2·5%)
Ertapenem	20 (2·2%)
Azithromycin	19 (2·1%)
Benzylpenicillin	15 (1·7%)
Clindamycin	13 (1·4%)
Chloramphenicol	13 (1·4%)
Erythromycin	12 (1·3%)
Sulfamoxole-trimethoprim	11 (1·2%)
Piperacillin and inhib	10 (1·1%)

Americas
6 countries; 63 hospitals; 13 610 prescriptions

Sulfamethoxazole–trimethoprim	1510 (11·1%)
Ceftriaxone	1329 (9·8%)
Vancomycin	1284 (9·4%)
Piperacillin and inhib	865 (6·4%)
Cefepime	844 (6·2%)
Clindamycin	810 (6·0%)
Cefazolin	746 (5·5%)
Metronidazole	641 (4·7%)
Meropenem	570 (4·2%)
Amoxicillin	443 (3·3%)
Azithromycin	431 (3·2%)
Ampicillin	370 (2·7%)
Erythromycin	363 (2·7%)
Ceftazidime	323 (2·4%)
Amoxicillin and inhib	321 (2·4%)
Tobramycin	296 (2·2%)
Ciprofloxacin	283 (2·1%)
Ampicillin and inhib	276 (2·0%)
Gentamicin	223 (1·6%)
Amikacin	192 (1·4%)
Levofloxacin	173 (1·3%)

Eastern Mediterranean
6 countries; 10 hospitals; 817 prescriptions

Ceftriaxone	198 (24·2%)
Vancomycin	69 (8·5%)
Metronidazole	60 (7·3%)
Cefotaxime	55 (6·7%)
Amikacin	47 (5·8%)
Piperacillin and inhib	39 (4·8%)
Meropenem	38 (4·7%)
Azithromycin	28 (3·4%)
Ampicillin	27 (3·3%)
Gentamicin	26 (3·2%)
Clindamycin	25 (3·1%)
Sulfamethoxazole–trimethoprim	24 (2·9%)
Cefuroxime	21 (2·6%)
Amoxicillin	19 (2·3%)
Penicillins combination	15 (1·8%)
Ciprofloxacin	13 (1·6%)
Teicoplanin	12 (1·5%)
Imipenem and inhib	11 (1·4%)
Clarithromycin	11 (1·4%)

Europe
28 countries; 160 hospitals; 7092 prescriptions

Ceftriaxone	714 (10·1%)
Amoxicillin and inhib	646 (9·1%)
Sulfamethoxazole–trimethoprim	481 (6·8%)
Piperacillin and inhib	395 (5·6%)
Cefuroxime	343 (4·8%)
Meropenem	333 (4·7%)
Gentamicin	303 (4·3%)
Cefotaxime	289 (4·1%)
Metronidazole	263 (3·7%)
Vancomycin	260 (3·7%)
Amoxicillin	254 (3·6%)
Azithromycin	242 (3·4%)
Amikacin	234 (3·3%)
Cefazolin	218 (3·1%)
Ciprofloxacin	205 (2·9%)
Ceftazidime	205 (2·9%)
Ampicillin	194 (2·7%)
Clarithromycin	156 (2·2%)
Teicoplanin	121 (1·7%)
Trimethoprim	103 (1·5%)
Flucloxacillin	102 (1·4%)
Tobramycin	89 (1·3%)
Clindamycin	89 (1·3%)
Colistin	80 (1·1%)
Ampicillin and inhib	72 (1·0%)

South-East Asia
2 countries; 10 hospitals; 995 prescriptions

Ceftriaxone	153 (15·4%)
Meropenem	99 (10·0%)
Amoxicillin and inhib	89 (8·9%)
Cefotaxime	79 (7·9%)
Amikacin	74 (7·4%)
Metronidazole	50 (5·0%)
Vancomycin	35 (3·5%)
Sulfamethoxazole–trimethoprim	34 (3·4%)
Piperacillin and inhib	33 (3·3%)
Cefoperazone combination	30 (3·0%)
Colistin	25 (2·5%)
Ciprofloxacin	25 (2·5%)
Amoxicillin	25 (2·5%)
Ofloxacin	24 (2·4%)
Cefazolin	23 (2·3%)
Cefuroxime	19 (1·9%)
Ceftazidime	19 (1·9%)
Azithromycin	19 (1·9%)
Cefixime	12 (1·2%)
Levofloxacin	11 (1·1%)
Ampicillin	10 (1·0%)
Piperacillin	9 (0·9%)

Western Pacific
7 countries; 44 hospitals; 3863 prescriptions

Azithromycin	455 (11·8%)
Ceftriaxone	333 (8·6%)
Latamoxef	258 (6·7%)
Sulfamethoxazole–trimethoprim	234 (6·1%)
Meropenem	207 (5·4%)
Amoxicillin and inhib	197 (5·1%)
Erythromycin	179 (4·6%)
Piperacillin and inhib	166 (4·3%)
Cefoperazone combination	164 (4·3%)
Vancomycin	136 (3·5%)
Ceftizoxime	130 (3·4%)
Cefazolin	114 (3·0%)
Cefuroxime	113 (2·9%)
Cefotiam	74 (1·9%)
Cefotaxime	64 (1·7%)
Mezlocillin	62 (1·6%)
Cefepime	61 (1·6%)
Imipenem and inhib	48 (1·2%)
Ceftazidime	48 (1·2%)
Mezlocillin–sulbactam	45 (1·2%)
Linezolid	45 (1·2%)
Cefmenoxime	44 (1·1%)
Gentamicin	42 (1·1%)
Ampicillin	42 (1·1%)
Metronidazole	40 (1·0%)
Ceftriaxone comb.	39 (1·0%)
Amoxicillin	37 (1·0%)
Cefoperazone	35 (0·9%)
Ampicillin and inhib	34 (0·9%)
Flucloxacillin	29 (0·8%)

Access group antibiotics Watch group antibiotics Reserve group antibiotics Unclassified antibiotics

Figure 1: **Regional patterns of AWaRe antibiotic prescribing to children by drug utilisation 90%**
AWaRe=Access, Watch, and Reserve. inhib=inhibitor.

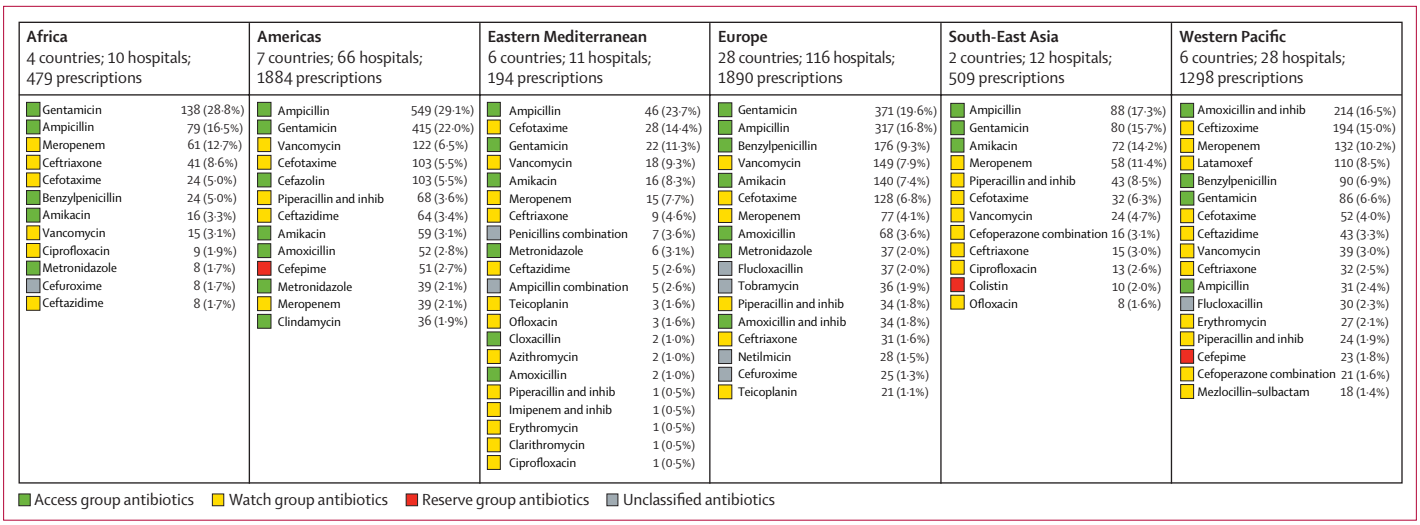

Figure 2: **Regional patterns of AWaRe antibiotic prescribing to neonates by drug utilisation 90%**
AWaRe=Access Watch, and Reserve. inhib=inhibitor.

	Children (>1 month)	Neonates (≤30 days)
Bacterial lower respiratory tract infection	21·3%	12·5%
Prophylaxis for medical problems	17·0%	8·1%
Prophylaxis for surgical disease	9·4%	6·5%
Other	7·0%	5·2%
Sepsis	6·0%	28·3%
Febrile neutropenia or fever	5·1%	..
Gastrointestinal tract infections	4·9%	4·2%
Skin or soft tissue infections*	4·7%	2·7%
Urinary tract infections	3·8%	..
Upper respiratory tract infections	3·3%	..
Newborn prophylaxis for newborn risk factors	..	12·8%
CNS infections	..	4·3%
Newborn prophylaxis for maternal risk factors	..	4·2%

*Includes surgical site infection and burns.

Table: **Most frequently reported clinical indications for antibiotic prescribing in children and neonates**

excluded, as were antibiotics for topical use. Diagnoses were recorded slightly differently in the two datasets and were reviewed and unified by a paediatric infectious diseases consultant (JB). The mapped diagnoses are presented in the appendix.

See Online for appendix

Antibiotics were classified as Access, Watch, and Reserve on the basis of the EMLc (appendix).[7] Some antibiotics for specific clinical indications are listed by WHO in both the Access and Watch groups; these were classified as Watch antibiotics in our analyses. Antibiotics not included in any of the Access, Watch, and Reserve groups were defined as unclassified. This group includes all antibiotics not listed on the EMLc such as second-generation cephalosporins (ATC code: J01DC) and combinations of antimicrobials (ATC code: J01RA).

Statistical analysis

Descriptive analyses were done separately for neonates and children. We described patterns of antibiotic use by using drug utilisation 90%, defined as the number of antibiotics that accounted for 90% of the total of antibiotics prescribed.[13] The proportion of antibiotic use in each AWaRe category was calculated as the total number of Access, Watch, or Reserve prescriptions during the survey divided by the total number of antibiotic prescriptions, stratified by country and WHO region.

We then applied the AWaRe classification to treatment of the two most common clinical diagnoses, lower respiratory tract infection in children and sepsis in neonates.[8,9] Prescriptions with missing data on patient demographics (eg, age and gender) were excluded from the analyses. Countries with a total number of prescriptions below the 25th percentile were included in the analyses but excluded from the graph presentations. Data management and analyses were done by means of Stata SE software version 14.0.

Role of the funding source

The sponsors of this study had no role in the study design, data collection, data analysis, data interpretation, or drafting of the manuscript. The corresponding author has full access to the final GARPEC dataset and access to a subset of completely anonymised Global-PPS data at institutional, ward, and patient level. The corresponding author has full responsibility for the decision to submit for publication.

Results

A total of 23 572 patients were included from 56 countries, of whom 18 305 (77·3%) were children and 5267 (22·3%) neonates. A full list of included countries and hospitals is given in the appendix. The majority of participating

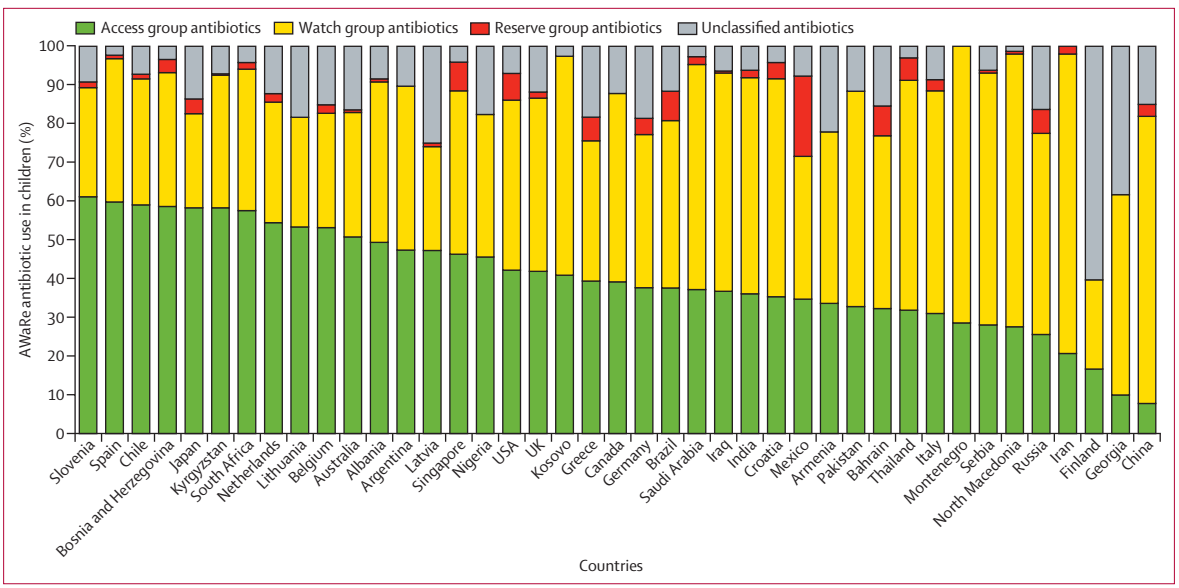

Figure 3: **Percentage of total antibiotic use in children by WHO AWaRe classification by country**
Only countries with prescriptions >25th percentile are included. AWaRe=Access, Watch, and Reserve.

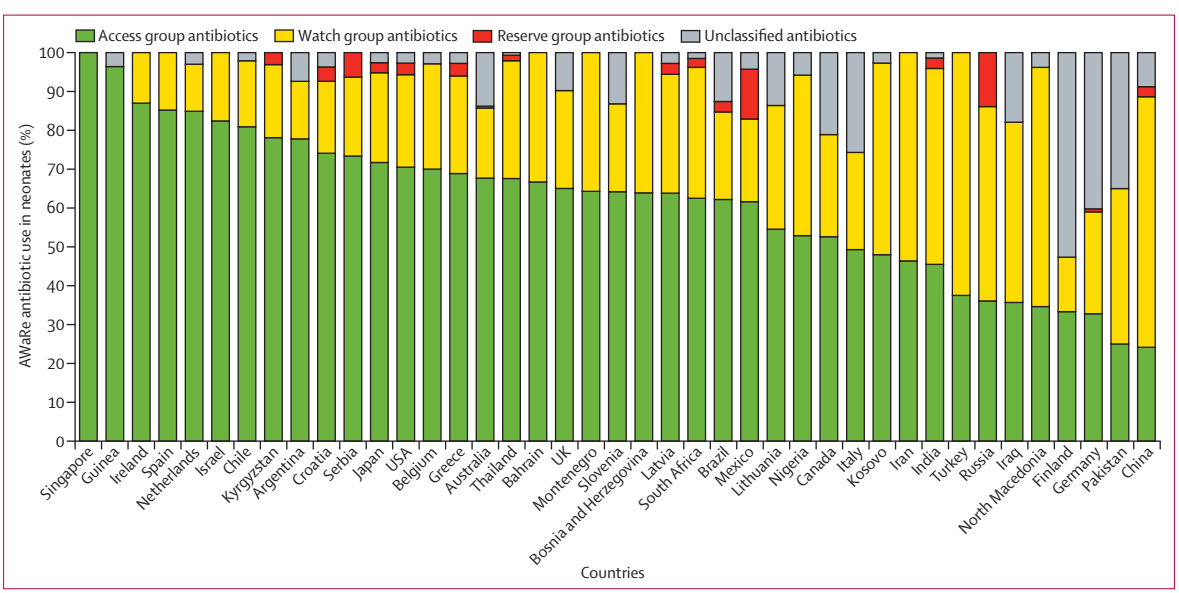

Figure 4: **Percentage of total antibiotic use in neonates by WHO AWaRe classification by country**
Only countries with prescriptions >25th percentile are included. AWaRe=Access, Watch, and Reserve.

centres were from HICs (29 of 56), with 19 from upper-middle-income countries and eight from lower-middle-income countries. Figure 1 shows the variation between WHO regions in antibiotic prescribing to children. Ceftriaxone was the most commonly prescribed antibiotic to hospitalised children in Africa, the Eastern Mediterranean, Europe, and South-East Asia. Sulfamethoxazole–trimethoprim was the most commonly prescribed to children in the Americas and azithromycin in the Western Pacific region (figure 1). Gentamicin and ampicillin were commonly prescribed to hospitalised neonates in most regions (Africa, the Americas, the Eastern Mediterranean, Europe, and South-East Asia; figure 2). In the Western Pacific region, the use of amoxicillin and β-lactamase inhibitor, ceftizoxime, and meropenem were high among hospitalised neonates (figure 2). Overall, lower respiratory tract infection, prophylaxis for medical problems, and prophylaxis for surgical disease were the most common diagnoses for children receiving antibiotics (table). Sepsis, newborn prophylaxis for newborn risk factors, and lower respiratory tract infection were the most common diagnoses for neonates.

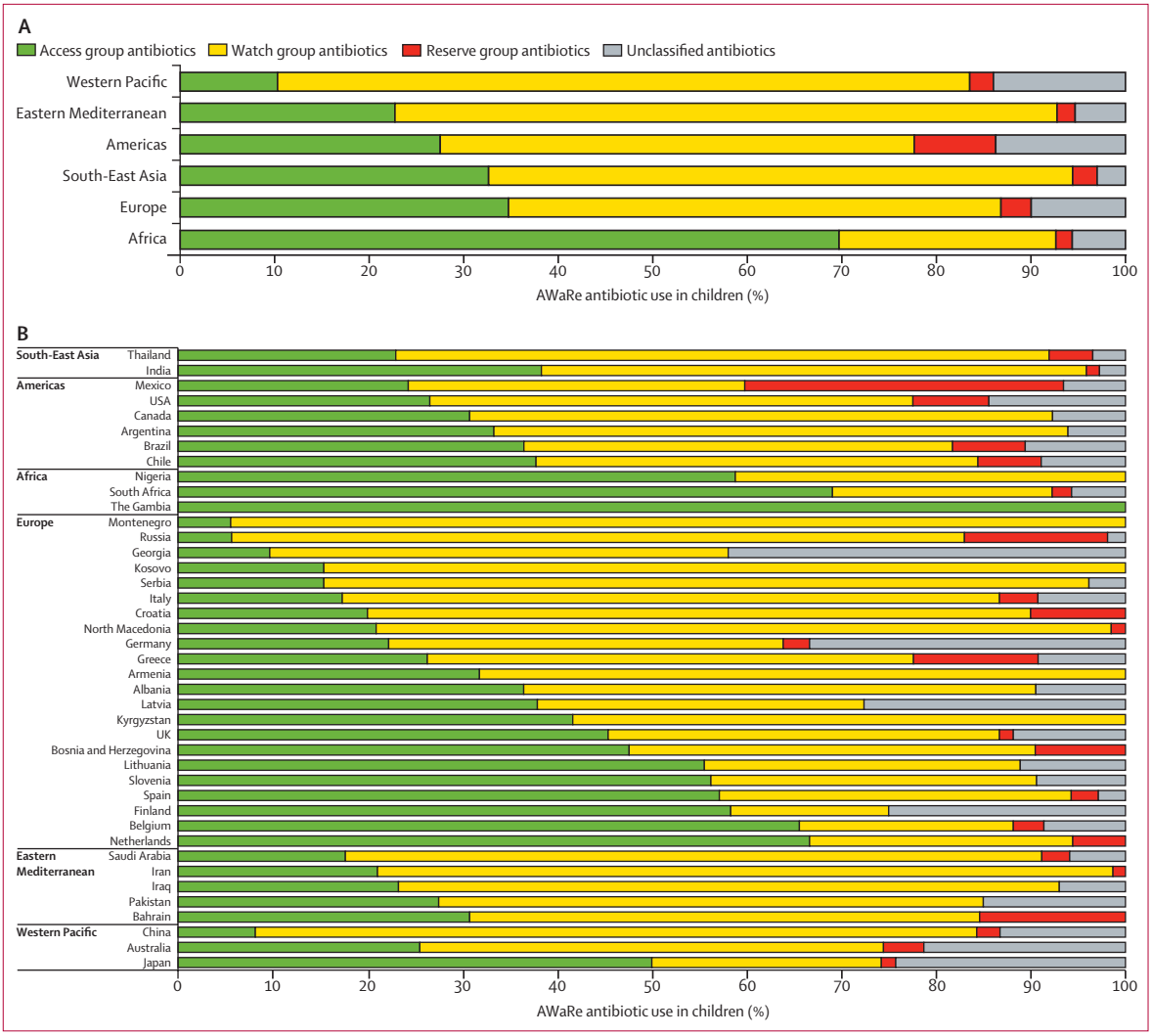

Figure 5: **Percentage of antibiotic use for children with lower respiratory tract infection**
(A) AWaRe classification and WHO region. (B) Percentage of antibiotic use for children with lower respiratory tract infection by AWaRe classification by WHO region and country. AWaRe=Access, Watch, and Reserve.

Figure 3 shows the overall percentage of AWaRe antibiotics in hospitalised children by country. Slovenia had the highest percentage of Access antibiotic use (61·2%), followed by Spain (59·8%) and Chile (59·0%). China had the lowest percentage of Access antibiotic use (7·8%) among the included countries. The percentage of Watch antibiotic use in children was high in Iran (77·3%), China (74·1%), Montenegro (71·4%), and Macedonia (70·4%). The specific Watch drugs used differed between these countries (eg, the most commonly prescribed Watch antibiotics were ceftriaxone in Iran and azithromycin in China). Reserve antibiotics comprised a minority of prescriptions in all countries, being highest in children in Mexico (20·7%). The Reserve antibiotics included mainly the fourth generation cephalosporin cefepime to treat lower respiratory tract infection, febrile neutropenia, fever, or sepsis. Several countries reported a high proportion of unclassified antibiotics use in children; this was highest in Finland (60·3%), Georgia (38·3%), Latvia (25·0%), and Armenia (22·1%). The most commonly used unclassified antibiotics were cefuroxime, oxacillin, flucloxacillin, tobramycin, and trimethoprim.

In neonates, Singapore had the highest prevalence of Access antibiotic use (100·0%) and China the lowest (24·2%; figure 4). Watch antibiotic prescribing to neonates was highest in China (64·5%) and no Watch antibiotics were reported in Guinea. Compared with Access and Watch antibiotics, Reserve antibiotic prescribing was low in hospitalised neonates. Russia (13·9%) and Mexico (12·8%) reported the highest use of Reserve antibiotics, mainly cefepime and daptomycin. Several countries had a high proportion of unclassified antibiotic use, including Finland (52·6%), Germany (40·2%), Pakistan (35·0%), Italy (25·7%), and Canada (21·1%).

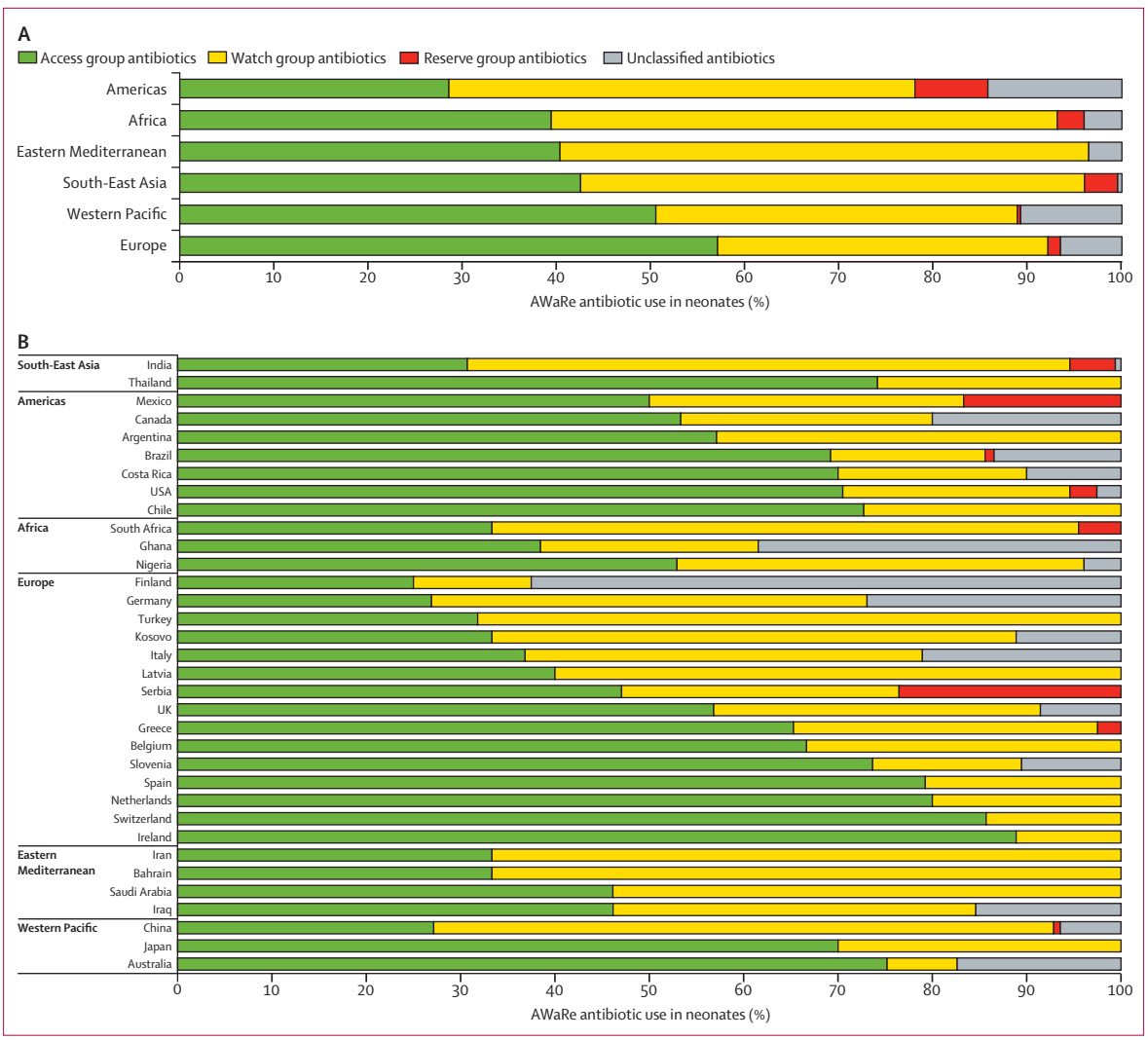

Figure 6: **Percentage of antibiotic use for neonatal sepsis**
(A) AWaRe classification and WHO region. (B) Percentage of antibiotic use for neonatal sepsis by AWaRe classification and WHO region and country. AWaRe=Access, Watch, and Reserve.

The percentage of children prescribed Access antibiotics for lower respiratory tract infection varied from 10·3% in the Western Pacific region to 69·7% in Africa (figure 5A). The percentage of children with lower respiratory tract infection prescribed Watch antibiotics varied from 22·9% in Africa to 73·2% in the Western Pacific. Variation in AWaRe antibiotic use was also observed between countries within the regions (figure 5B). In China, the use of Access antibiotics for lower respiratory tract infection treatment was very low (8·2%) compared with Australia (25·5%) and Japan (50·0%) in the Western Pacific region. In Africa, all children with lower respiratory tract infection received Access antibiotics for treatment in The Gambia. In Europe, Russia (5·7%) and Montenegro (5·6%) had the lowest percentage of Access antibiotic use; the highest percentage of Access antibiotic use was reported in the Netherlands (66·7%). Saudi Arabia had the lowest percentage of Access antibiotic use (17·7%) in the Eastern Mediterranean region. The high use of Watch antibiotics for childhood lower respiratory tract infection treatment in the Western Pacific region was owing to the high proportion of their use in China (76·1%). In the Americas, Canada reported a high percentage of Watch antibiotic use (61·5%) whereas Mexico had a high use of Reserve antibiotics (33·6%). Several European countries reported a high proportion of unclassified antibiotics use for lower respiratory tract infection treatment in children: Georgia (42·0%), Germany (33·3%), Latvia (27·5%), and Finland (25·0%).

Europe had the highest use of Access antibiotics (57·1%) for neonatal sepsis treatment and the Americas had the lowest use (28·6%; figure 6A). The proportion of Watch antibiotic use ranged from 35·1% (Europe)

to 56·1% (Mediterranean). The overall use of Reserve antibiotics was low, but was highest in the Americas (7·7%). The proportion of unclassified antibiotic use for neonates with sepsis was reported to be high in the Americas (14·2%) and low in the South-East Asia region (0·4%).

In the Americas, Chile reported the highest percentage of Access antibiotics (72·2%) and Mexico the lowest (50·0%; figure 6B). In the same region, Argentina reported high use of Watch antibiotics (42·9%) and Brazil the lowest use (16·4%). Mexico reported the highest use of Reserve antibiotics for neonatal sepsis treatment (16·7%), followed by the USA (2·9%) and Brazil (1·0%). In Africa, the use of Access antibiotics was low in South Africa (33·3%) and high in Nigeria (52·9%). In Ghana, the use of unclassified antibiotics was considerable (38·5%) compared with Nigeria (4·0%) and South Africa (0·0%). In Europe, Finland had the lowest percentage of Access antibiotic use for neonatal sepsis treatment (25·0%), mainly owing to the high use of unclassified antibiotics (62·5%). Only two European countries reported Reserve antibiotic use: Serbia (23·5%) and Greece (2·5%). In the South-East Asia region, Thailand reported high use of Access antibiotics for neonatal sepsis treatment (74·2%), whereas the use was lower in India (30·7%). In the Western Pacific region, China had the lowest use of Access antibiotics (27·1%) and Australia the highest (75·2%).

Discussion

To our knowledge this is the first global collaborative study of patterns of antibiotic use in hospitalised children that used the WHO AWaRe classification. We have observed substantial variation between countries in the use of Access, Watch, and Reserve antibiotics in neonates and children. In children, Access antibiotic use ranged from 7·8% in China to 61·2% in The Gambia; and Watch antibiotic use ranged from 23·0% in Finland to 77·3% in Iran. There was also substantial variation in patterns of antibiotic use for treatment of neonatal sepsis and paediatric lower respiratory tract infection.

No recognised standards exist for antibiotic prescribing at a population level that would enable us to define the appropriateness of antibiotic use for neonates and children. Therefore, comparisons between countries should be interpreted cautiously. Total amounts of antibiotic prescribing are recognised to vary substantially between and within countries even across Europe.[14] Important influences are disease burden, including the prevalence of infections caused by highly resistant bacteria; local health-care service issues (eg, infrastructure, staffing); and pricing and affordability of antibiotics. For example, the availability of some narrow-spectrum antibiotics, such as phenoxymethylpenicillin, is very low in many HIC and LMIC countries.[15,16] Patterns of antimicrobial resistance (particularly for conditions such as sepsis or urinary tract infections) are likely to be key drivers, but also difficult to identify when defining amounts of appropriate use of Access antibiotics. However, for some conditions, such as childhood lower respiratory tract infection, WHO guidance clearly recommends Access antibiotics (eg, amoxicillin) even in countries with high prevalence of pneumococcal resistance. Consequently, although opportunities exist to incorporate this AWaRe classification within paediatric antibiotic stewardship programmes, the situation is clearly more complex than simply increasing prescriptions for Access antibiotics. It might however be possible in the future to combine metrics from several data sources to improve estimates of appropriateness of antibiotic prescribing in this population.[17] A further challenge is that several commonly prescribed narrow-spectrum antibiotics (eg, second-generation cephalosporins, trimethoprim) are not included in the AWaRe classification as these antibiotics are not listed on the EMLc, resulting in a high proportion of unclassified antibiotic use for certain countries. The EML Working Group acknowledges the limitations of this new antibiotic classification and suggests further revision over time.[7]

Other studies have evaluated antibiotic use in children at the national or regional level.[8,9,18–30] Consistent with previous studies, lower respiratory tract infection and sepsis were the most common diagnoses in our study for children and neonates receiving antibiotics for treatment.[8,9] We found that the range of antibiotics used is much smaller in neonates than in children, which is also in line with previous studies.[8,9] This might be owing to the high use of the two key Access antibiotics, ampicillin and gentamicin, in line with the WHO recommendation for sepsis treatment in neonates. The most commonly prescribed antibiotic in children was ceftriaxone (third-generation cephalosporin), again in agreement with previous studies.[8,9] We observed a high proportion of Watch antibiotic use in Iranian children in our analysis. A multicentre PPS study in Iran has reported high use of third-generation antibiotics (ceftriaxone, cefotaxime, and ceftazidime) and vancomycin in children.[24] The consistency of our results with previous studies suggests that patterns of use have changed little over time, with little evidence of improvement in the quality of prescribing.

Several metrics have been developed in support of paediatric antibiotic stewardship programme interventions such as defined daily doses, day of treatment, length of treatment, and prescribed daily dose, but all of these are quite complex to measure and not easy to communicate back to prescribers. The AWaRe classification aims to provide an easily interpretable framework for broad assessment of patterns of narrow-spectrum and broad-spectrum antibiotic use. The patterns of use can be derived on the basis of the EMLc guidance for particular Access antibiotics for specific clinical conditions.[7]

The strength of this study lies in the collaboration between different research groups combining data, thus allowing a wide coverage of countries and regions.

The use of a simple, relatively cheap, cross-sectional PPS method allowed the collection of data in LMICs, where surveillance and stewardship programmes are not routinely available. However, although the PPS design has been extensively used to evaluate antibiotic use, it has some limitations.[8–10,20–30] It cannot capture treatment duration, switching patterns, or clinical outcomes, and is more likely to collect antibiotic data from long-stay hospital patients and longer treatment courses. The repeated PPS at different time periods might introduce bias in the case mix.[31] Furthermore, participating centres contributed data to the GARPEC and Global-PPS networks voluntarily, so our study might not be generalisable to the overall inpatient paediatric population. The data collection and data entry require clinicians and hospital staff to spend time going through medical notes and is clearly biased towards larger tertiary academic institutions in HICs (only one centre in a low-income country was included). Equally importantly, many participating centres did not collect data in all their neonatal or paediatric wards in their hospitals so the results might not be representative within hospitals. Additionally, we have not as yet investigated the variation of antibiotic use between hospitals in one country, and would not be able on the basis of available data to establish whether higher level factors, such as hospital infrastructure and resources, affect antibiotic use. Thus, more detailed country-specific analyses are required to further explore factors that affect antibiotic use between tertiary and district hospitals. There is also the possibility of an observer effect when doing repeated PPSs (GARPEC), whereby participation in the study causes changes in prescribing behaviour. However, our results were similar to previous studies of antibiotic use,[8,9] suggesting that any such biases were minimal. Finally, there might also be seasonal variations in antibiotic use that we have not assesed.[32,33]

The methods for antibiotic PPSs are now well established, whereby countries develop their own online tools at national level. However, it has proved easier to measure and monitor patterns of antibiotic use than to change them. Further work needs to focus on appropriate overall amounts of antibiotic use in both the community and hospital settings. However, condition-specific AWaRE metrics can show, for example, the marked variation in the overall proportion of children receiving Access antibiotics for lower respiratory tract infection, which cannot readily be explained on the basis of WHO guidelines. Risk adjustment models therefore need to be developed for different clinical conditions, focusing on both prevalence of underlying disease (HIV, malnutrition) and resistance profiles.[34] Furthermore, establishing whether the same variation in prescribing patterns according to AWaRe categories is also seen in the adult population is important. This study has shown that use of a simple PPS method is feasible to assess patterns of AWaRe antibiotic use in hospitalised children globally. National and international ambitions for the proportion of children in hospital treated with Access antibiotics could potentially be assessed by means of the AWaRe PPS method.

Contributors

YH, JB, and MS conceived the idea and contributed to the design of data collection tools for the GARPEC project. YY contributed to the data collection and management for Chinese hospitals. BRL and JN contributed to the design, conduct, data management, and analyses of the SHARP project. AV and HG contributed to the study design and conduct of the Global-PPS project. YH, CJ, JB, and AV contributed to the final dataset manipulation for the GARPEC, SHARPS, and Global-PPS projects. YH and CJ contributed to data management, analyses, and interpretation and writing of the manuscript. All authors were involved with drafting and essential revisions of the manuscript.

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Declaration of interests

We declare no competing interests.

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