

## **Global divergence from WHO treatment guidelines for neonatal and paediatric sepsis**

### ***Introduction***

An estimated 3.0 million neonatal and 1.2 million paediatric cases of sepsis occur annually worldwide<sup>1</sup>. The World Health Organization (WHO) recommends gentamicin with either ampicillin or benzylpenicillin as first-line treatment, and ceftriaxone as second-line, for infants and children<sup>2</sup>. Although there is currently no strong evidence that these guidelines are inadequate<sup>3</sup>, many sepsis pathogens may be resistant to these antibiotics<sup>4</sup>. National guidelines for antibiotic treatment of neonatal and paediatric sepsis often differ from WHO recommendations<sup>5</sup>. The extent to which sepsis treatment worldwide is consistent with WHO guidelines is therefore unclear.

### ***Materials and Methods***

This analysis used combined data from the GARPEC (Global Antimicrobial Resistance, Prescribing and Efficacy in Neonates and Children) study and the Global Point Prevalence Survey on Antimicrobial Consumption and Resistance (year 2015) ([www.Global-PPS.com](http://www.Global-PPS.com)), both of which collected data on antimicrobial prescribing to hospitalised children and neonates. Detailed methods have been described elsewhere<sup>6,7</sup>. Briefly, point prevalence surveys (PPS) of antimicrobial prescribing were conducted in 297 voluntarily participating hospitals in 56 countries. Hospitals reported the numbers of children and neonates with an active antimicrobial prescription admitted on the day of the PPS, with details of the prescription (drug, dose, route of administration), indication (e.g. targeted or empiric, treatment or prophylaxis) and patient risk factors (e.g. co-morbidities). Denominators comprised all admitted children and neonates on the day of the PPS. All active antimicrobial prescriptions for all admitted neonates and children prescribed on a particular day were reported through an online system, irrespective of the patients' treatment history and how long they had been receiving the current prescription. Here, we summarise the antibiotics (excluding antifungal, antiviral and anti-tuberculosis medications) used in treatment of neonates (aged <30 days) and children (≥30 days and ≤18 years) with a recorded diagnosis of sepsis.

We report the percentage of neonates and children with sepsis who received a WHO-recommended first-line treatment. Amongst those receiving other treatments, the percentage receiving a WHO-recommended second-line treatment was calculated. Both were determined overall and separately for those recorded as receiving empiric treatment. Data are also presented separately for community- and hospital-acquired infections (CAI and HAI). The alternative regimens used (one or more antibiotics prescribed to the same child at the time of the PPS, irrespective of dose or route of administration) are described. Countries were stratified into high and low/middle income (HICs and LMICs) using World Bank classifications<sup>8</sup>.

### ***Results***

Information on antibiotic prescribing for neonates with sepsis was available from 41 countries and for children from 43 countries (Appendix Table 1). The countries contributing data on the largest numbers of patients were the UK (272), India (178) and South Africa (121).

#### *All antibiotics*

In total, 1422 antibiotic prescriptions were recorded for 824 neonates (median 2 prescriptions per neonate, range 1-3) and 1172 prescriptions for 786 children (median 1 per child, range 1-6). Monotherapy was used in 255/824 neonates (31.0%) and 457/786 children (58.1%), dual therapy in 540/824 neonates (65.5%) and 277/786 children (35.2%) and >2 antibiotics in 29/824 neonates (3.5%) and 52/786 children (6.6%). In HICs, the most commonly prescribed regimens were WHO-recommended first-line treatments for neonates and WHO-recommended second-line treatment for children. In LMICs, meropenem was the most frequently prescribed regimen for neonates and children (Figure 1).

Overall, 44 different monotherapies and 192 combination therapies were prescribed. In HICs, 20 different antibiotics were used as monotherapy and 66 combinations were prescribed for neonates; for children there were 29 monotherapies and 83 combinations. In LMICs, 19 different monotherapies and 59 combinations were prescribed to neonates, and 36 monotherapies and 72 combinations to children.

Overall, 185/824 (22.5%) neonates and 9/786 children (1.1%) received a WHO-recommended first-line treatment: 104 neonates and 7 children received ampicillin/gentamicin, while 81 neonates and 2 children received benzylpenicillin/gentamicin. Sample sizes in some countries were very small so country-specific estimates are not always possible; however, the percentage receiving a WHO-recommended first-line treatment was low in all countries (rarely >50% for neonates). Twelve neonates and two children received a WHO-recommended first-line treatment with a third antibiotic (usually cefotaxime). Additionally, two neonates and one child received gentamicin with ampicillin and a  $\beta$ -lactamase inhibitor.

Amongst those not receiving a WHO-recommended first-line treatment, 9/639 neonates (1.4%) and 102/777 (13.1%) children received the recommended second-line treatment, ceftriaxone. Twenty neonates and 44 children received ceftriaxone with one or two additional antibiotics, usually ceftriaxone with gentamicin (10 neonates and 7 children). Five further children were recorded as receiving "ceftriaxone combinations", of whom four additionally received ofloxacin.

#### *Empiric antibiotics*

1246 patients (670 neonates, 576 children) were receiving antibiotics for empiric use only (of the remainder, 322 were receiving targeted treatment only, 37 both empiric and targeted, information was unavailable for 5 patients). 179/670 neonates (26.7%) and 7/576 (1.2%) children received a WHO-recommended first-line treatment (Appendix Figure 1). Overall, ampicillin/gentamicin (101/670,

15.1%) and benzylpenicillin/gentamicin (78/670, 11.6%) were the most commonly prescribed empiric regimens for neonates. Amongst the remainder, 8/491 neonates (1.6%) and 80/569 children (14.1%) were receiving ceftriaxone (WHO-recommended second-line treatment), the most commonly prescribed regimen for empiric treatment of children. Amongst those receiving empiric treatment only, 108 different antibiotic regimens (mono- or combination therapy) were recorded for neonates and 137 for children, including WHO-recommended first- and second-line treatments.

#### *CAI and HAI*

Indication was recorded as CAI for 347 neonates and 360 children, and as HAI for 380 neonates and 384 children (a further four neonates and three children were recorded as having both HAI and CAI; information was unavailable for 93 neonates and 39 children). Amongst neonates, 136/347 (39.2%) with CAI received a WHO-recommended first-line treatment, compared to 17/380 (4.5%) of those with HAI. Ceftriaxone alone was prescribed to 4 neonates with CAI and 4 with HAI. Of 360 children with CAI, 6 (1.7%) received a WHO-recommended first-line treatment and 91 (25.3%) received the recommended second-line treatment. For HAI, 2/384 children (0.5%) received WHO-recommended first-line treatment and 10/384 children (2.6%) received second-line treatment.

#### **Discussion**

There is substantial variation in the treatment of neonatal and paediatric sepsis amongst the HICs and LMICs included in the GARPEC and Global-PPS studies. Although the WHO-recommended first-line (gentamicin/ampicillin or gentamicin/benzylpenicillin) and second-line (ceftriaxone) treatments <sup>2</sup> were the most commonly prescribed overall, most patients were not receiving these treatments. This was true even for empiric treatment, which is influenced by expected, rather than confirmed, resistance.

The appropriateness of any treatment for sepsis depends on factors including local epidemiology and resistance. For example, the predominant causes of community-acquired paediatric sepsis were *Neisseria meningitidis*, *Streptococcus pneumoniae* and Group A streptococcus in European countries <sup>9</sup> and Enterobacteriaceae in African countries <sup>10</sup>. The different antibiotic susceptibilities of these organisms must be considered in guidelines and clinical practice. Context-specific approaches, such as weighted incidence syndromic combination antibiograms (WISCAs) <sup>11</sup>, may be helpful, although not necessarily straightforward to implement. Robust antimicrobial stewardship programmes are needed globally to ensure consistency with appropriate guidelines.

Clinicians may have valid reasons for prescribing alternative antibiotics, including adherence to local or national guidelines (potentially differing from WHO recommendations), a high risk of resistance to the WHO-recommended treatments, limited updated guidance on how to treat sepsis due to resistant organisms, or lack of availability of recommended antibiotics. The high use of meropenem in LMICs may partly reflect high levels of resistance to the recommended antibiotics amongst common sepsis pathogens <sup>4</sup>. Additionally, similar antibiotics such as cefotaxime may be used instead of ceftriaxone,

or amoxicillin instead of ampicillin, in specific circumstances; our analysis does not allow for such flexibility. WHO recommendations have recently changed <sup>12</sup>, but those used in the analysis applied at the time of data collection. Our data suggest that there is no global consensus on which drugs to use to treat neonatal or paediatric sepsis.

Our study provides data on antibiotic treatment of neonatal and paediatric sepsis in 43 diverse countries. The large number of patients included has enabled us to stratify by country income and HAI versus CAI, and to assess the subgroup of patients receiving empiric treatment. Limitations of the PPS design <sup>6</sup> include absence of information on treatment history, so it is unknown whether patients not receiving WHO-recommended treatments had received them previously. Cross-sectional studies measure prevalence of prescribing, with bias towards longer treatment courses, potentially over-representing those for whom previous treatments have failed. Without data on resistance or patient outcomes, we cannot assess the appropriateness of prescribing for individuals or effectiveness of different regimens. Reporting of sepsis was based on physician assessment rather than a formal case definition. Finally, the contributing hospitals are not representative of hospitals worldwide, by region or by country, particularly in LMICs. Several were tertiary centres with an interest in research; clinicians here might be expected to be particularly aware of guidelines but may also see complex patients who may require non-standard treatments.

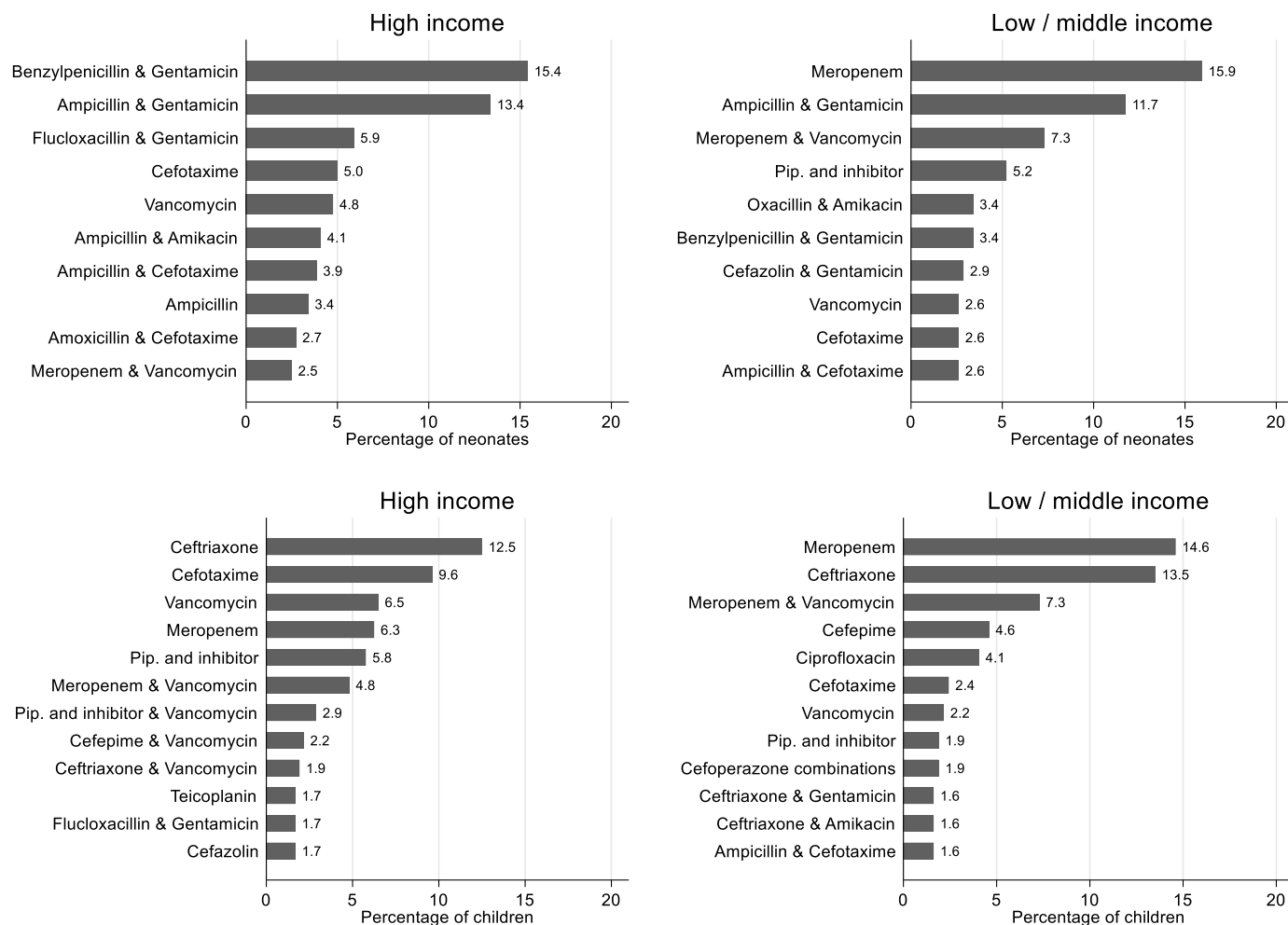
This analysis suggests that most neonates and children with sepsis do not receive the WHO-recommended first- or second-line treatments and a wide variety of antibiotics and antibiotic combinations are used globally. Future work should determine whether the treatments used are appropriate, accounting for the diversity of sepsis pathogens globally, and consider whether guidance should be updated to allow for varying patterns of antimicrobial resistance worldwide.

## References

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Figure 1: Ten most commonly prescribed antibiotic regimens amongst hospitalised neonates and children with sepsis, by country income status. (The graphs for children in both HICs and LMICs includes 12 regimens as there were equal numbers of prescriptions for some regimens). Numbers show the percentage of patients.



Pip. and inhibitor = piperacillin and beta lactamase inhibitor

## APPENDIX

*Appendix Table 1: Number of centres contributing data and number of neonates and children with sepsis receiving one or more antibiotics at the time of the PPS in each country.*

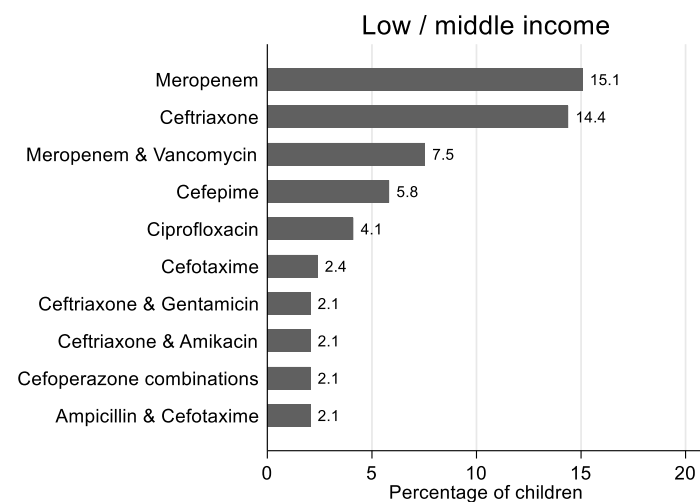
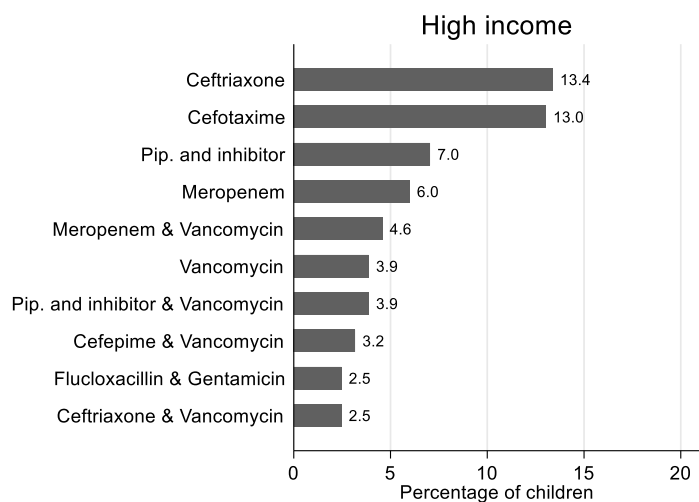
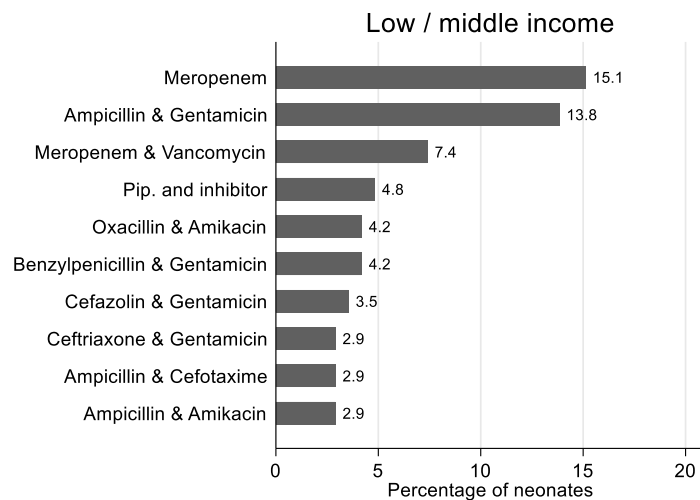
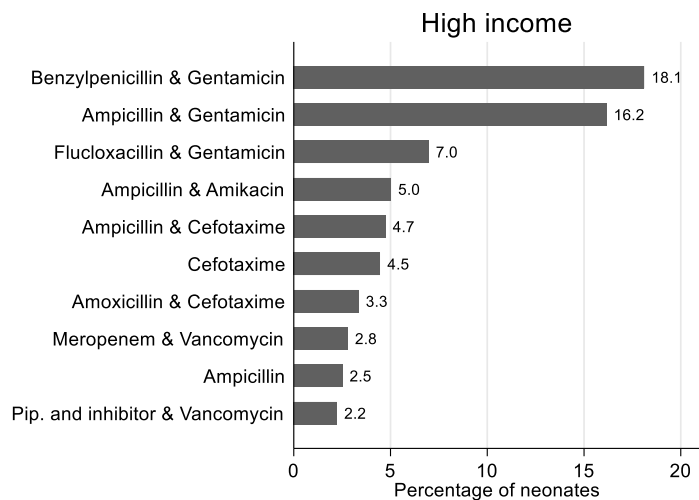
Country	Neonates		Children	
	Number of centres	Number of patients	Number of centres	Number of patients
<b>GARPEC</b>				
Argentina	1	4	1	2
Australia	3	52	3	21
Brazil	5	55	6	39
Finland	1	1	1	4
The Gambia			1	1
Germany	4	14	5	29
Greece	5	53	5	19
India	10	111	7	67
Israel	1	1	1	2
Italy	3	10	3	29
Japan			1	14
Mexico	1	11	1	89
Nigeria	1	17	2	8
Pakistan	1	2	1	4
Singapore			1	13
Slovenia	1	9	1	5
South Africa	2	60	2	28
Spain	2	27	2	7
Taiwan			1	1
Thailand	2	34	2	41
Turkey	2	11		
United Kingdom	11	112	12	115
United States	1	20	1	44
<b>GLOBAL-PPS (2015)</b>				
Albania			2	5
Argentina			2	2
Australia	2	11		
Bahrain	1	6	1	4
Belgium	4	7	8	9
Brazil			1	3
Canada	5	9	2	6
Chile	3	6	4	6
China			1	1
Costa Rica	2	5		
Finland	1	3		
Former Yugoslav Republic of Macedonia	1	1	1	1
Georgia	1	3	3	5
Germany	1	2	1	1
Ghana	1	7	1	12
Greece	1	11	1	4
Iran	3	8	3	14
Iraq	3	9	3	8
Ireland	2	5		
Italy	1	2	1	2
Japan	4	7	6	12
South Korea	1	2	1	1
Kosovo	2	4	2	4
Kyrgyzstan			1	1
Latvia	1	9	1	1

Country	Neonates		Children	
	Number of centres	Number of patients	Number of centres	Number of patients
Lithuania			1	3
Malta			1	1
Montenegro	1	3		
The Netherlands	3	6	1	4
Nigeria	2	7	3	16
Russian Federation	1	2	1	5
Saudi Arabia	1	7	1	15
Serbia	1	9	1	1
Singapore	2	3		
Slovenia	1	3	1	6
South Africa	1	20	1	13
Spain	1	1	1	3
Switzerland	1	4		
United Kingdom	7	18	6	27
United States	5	20	5	8

Empty cells: no cases reported



Appendix Figure 1: Ten most commonly prescribed empiric antibiotic regimens amongst hospitalised neonates and children with sepsis, by country income status. Numbers show the percentage of patients.



Pip. and inhibitor = piperacillin and beta lactamase inhibitor