WHO REPORT ON CONSENSUS GUIDANCE ON PEDIATRIC DOSING REGIMENS FOR ACCESS ANTIBIOTICS ON THE ESSENTIAL MEDICINE LIST FOR CHILDREN

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Introduction

Global antibiotic consumption increased markedly between 2000 and 2010, with the emerging economies of Brazil, Russia, India, China, and South Africa accounting for 76% of the increase (1). The need to optimize prescribing of antibiotics has been highlighted as Objective 4 in the World Health Organization's (WHO) Global Action Plan on Antimicrobial Resistance (AMR) (2). Recently, classification of antibiotics within the WHO Essential Medicines List (EML) has undergone a substantial revision (3, 4). The new AWaRe (Access, Watch, Reserve) categorization aims to encourage rational use of antibiotics and optimal prescribing (3).
For children, antimicrobials are among the most commonly prescribed classes of drugs (5-9). Paediatric dosing regimens for many antimicrobial drugs have been historically derived from pharmacokinetic data in adults and have been based on assumed linearity between exposure and total body weight (10, 11). This approach, although clinically widespread, lacks empiric evidence and may result in inappropriate systemic drug exposures of many drugs in neonates and children (12, 13).

Formularies are one of the tools available to clinicians to inform prescribing practice. Researchers and policymakers can use expert and evidence-based formularies to recommend optimized antibiotic doses to best balance efficacy, toxicity and drivers of antimicrobial resistance. However, in many instances, recommendations are historical practise-based and not strongly evidence-based (14). In an analysis published by the BMJ the authors wrote: "*Drug dosing in children is more complex than in adults. As the organs and immune system develop throughout childhood, the way in which drugs are absorbed, transported, and eliminated by the body (pharmacokinetics) changes, which in turn affects the drug's action on the body (pharmacodynamics). During the first two years of life, the evolution of renal function and hepatic metabolism have an important effect on the optimal antibiotic dose. Inaccurate dosing can lead to problems because higher antibiotic doses potentiate undesirable side effects, especially diarrhoea, and may promote the selection of resistant bacteria* (14)*."* Limited evidence is available from studies of efficacy, safety and pharmacokinetics for children (15-17). Historically, national preferences for weight-based (US) and age-banded (UK) dosing strategies have resulted in quite widely varying recommendations. WHO used a weight banded approach derived from WHO standardized growth charts (18). This lack of uniform rationale has led to heterogeneous guidance, which creates ambiguity, especially for health professionals with limited experience (19, 20). Confusion about age- and weight-appropriate doses and safe use can lead to inappropriate or delayed treatment.
The Essential Medicines List for children – EMLc – antibiotic listing has not previously included dosing regimens. To improve the overall quality of prescribing a sub-group of the EML Antibiotic Working Group was developed to hold a dedicated meeting with the goal of producing summary dosing guidance of the key EML-c antibiotics. The Working Group has produced interim suggestions for the EML Committee.

A full systematic review of all neonatal and paediatric pharmacokinetic studies has been commissioned by the WHO EML Secretariat, and it is ongoing. Preliminary results were presented and discussed during the Working Group meeting and will be published as soon as they are available.

The methodology chosen for this work was to therefore first identify and summarise the dosing guidance of key antibiotics in the major national guidelines, complemented by key literature, and then to produce a short summary table based on an expert consensus meeting.

This interim WHO EML-c guidance is not condition but antibiotic specific. However, the international guideline review aimed to determine whether dosing guidance varied by clinical indication. The clinical indications used to guide the review of national clinical practice guidelines were taken from

the 2017 EML-c. In general, for most antibiotics dosing guidance was sufficiently consistent across guidance documents and did not markedly vary between conditions, apart from meningitis. This dosing guidance for the WHO EML-c therefore does not include central nervous system infections, where it should be noted that doses are significantly higher.

Selecting the Guidelines to review

We aimed to identify leading guidelines which are either widely used internationally or originate from countries in which antibiotic use has increased markedly in recent years (Brazil, Russia, India, China and South Africa) (1). We identified guidance endorsed by national and international bodies by contacting national co-ordinators of the Global Antibiotic Prescribing, Efficacy and Resistance (GARPEC) network for the countries of interest (https://penta-id.org/antimicrobials/garpec/). We did not aim to comprehensively review all existing antibiotic guidance from every individual country globally or identify all patient management pathways. The following major formularies were identified:

- *The Manual of Childhood Infections: The Blue Book (4th Edition)* is endorsed by the Royal College of Paediatrics and Child Health (RCPCH) and European Society of Paediatric Infectious Diseases (ESPID) and is a leading handbook used in Europe (21).
- The *British National Formulary for Children (BNFC),* last published in 2017, is a commonly used paediatric reference for prescribing in the United Kingdom (22).
- *Red Book (2018): Report of the Committee on Infectious Diseases (31st Edition)* is endorsed by the American Academy of Pediatrics Committee on Infectious Disease (23).
- The WHO Pocket book of hospital care for children (2013) is part of a series of documents and tools that support the Integrated Management of Childhood Illness (IMCI) (24).
- South Africa's *Paediatric Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicines List (EML)* (2013) were developed by an Expert Review Committee, National Essential Medicine List Committee and external stakeholders involved in paediatric care (25).
- The Indian *National Treatment Guidelines for Antimicrobial Use in Infectious Diseases* were developed by the National Centre for Disease Control (NCDC) and were published in 2016 (26).

We consulted national experts extensively but were unable to find clearly nationally endorsed paediatric antibiotic guidelines from Brazil, China and Russia. However, we did identify Chinese guidelines specifically on paediatric community-acquired pneumonia - *Guidelines for the management of community-acquired pneumonia in children (revised in 2013)* (in Mandarin) - developed by the Chinese Paediatric Society and translated into English (27).

Comparing the Guidelines: Dosing by Antibiotic

Method

Guidelines selected for comparison were those with specific paediatric dosing formularies or summaries. These were available for the BNFC, Blue Book, Red Book, Pocket Book and NCDC. The dosing recommendations for each antibiotic were compared descriptively. Dosing for all antibiotics listed in Section 6.2 Antibacterials of the 2017 EMLc (with the exception of benzathine benzylpenicillin, procaine benzyl penicillin, cefixime, tigecycline, fosfomycin, daptomycin, polymyxins e.g., colistin, fourth generation cephalosporins [with or without beta-lactamase inhibitor] e.g., cefepime, fifth generation cephalosporins [with or without beta-lactamase inhibitor] e.g, ceftaroline) was included in the initial assessment. Ceftazidime, while not listed in the 2017 EMLc was included in

our analysis. Dosing for commonly used first and second choice antibiotics listed in the current 2017 EMLc were then extracted and taken forward to the expert panel review.

The BNFC, in general, arranges guidance by route and then by age-band. The Red Book presents separate tables for neonates and children, with neonatal doses stratified by gestational age and then by postnatal age (where applicable), and presented as dosage per kg by frequency. Paediatric doses are presented as a total daily dose with dosing frequency. The Pocket Book presents separate summary tables for neonates and children. Neonatal dosing guidance is sorted by route and stratified by age into first week of life and weeks 2-4. The NCDC presents two dosing summary tables. The paediatric doses presented in the 'Dosing Guide for Commonly Used Antimicrobial Agents' were primarily consulted. The second table 'Drug Doses in Pediatric Age Group' was less complete and was consulted with the text to resolve inconsistencies. NCDC guidance did not present a separate table for neonates.

Across the guidelines, when dosing guidance was specified by syndromes or suspected causative organisms, those for priority syndromes and severe infections identified by the EML were included. Doses for prophylaxis, loading doses, non-priority syndromes and doses for very low-birth weight and low-birth weight (VLBW/LBW) new-borns were excluded. In cases where guidance in the summary tables was unclear, the primary text was consulted.

Priority has been placed on comparing total daily dose for each antibiotic. As such, dosing guidance has been calculated and presented as mg/kg/day where possible. For consistency, frequency is presented as the total daily dose divided by frequency (e.g. q12h representing every 12 hours or twice per day).

Expert Meeting

An expert consensus meeting then reviewed the final dosing recommendations and endorsed the enclosed Table to be presented to the next WHO Expert Committee. The doses were separated into neonatal and pediatric and are for treatment, not prophylaxis. A single total daily dose is presented for both the intravenous and oral route; it could be divided by frequency. Weight/age banded doses are nor provided and would need to be derived from the total daily dose given. Ranges have been given that includes the most commonly used clinical practice guidelines.

Suggested doses for antibiotics listed on the 2017 WHO Model List of Essential Medicines for Children (EMLc) as first or second choice treatment for specified infectious syndromes

The following dosing suggestions for the antibiotics † listed on the 2017 WHO Model List of Essential Medicines for Children (EMLc) have been made considering available literature and existing guidelines, clinical experience, and practical ease of administration. These doses are for treatment (not prophylaxis) of common and rare conditions via oral or intravenous route.

Table 1 Suggested doses for antibiotics listed on the 2017 WHO EMLc

Antibiotic	Neonates		Children	
	Total daily dose (mg/kg/day)	Dosing frequency (divided every x hrs)	Total daily dose (mg/kg/day)	Dosing frequency (divided every x hrs)
Amikacin	15 - 20	Every 24 hrs	15 - 20	Every 24 hrs
Amoxicillin	80 - 100	Every 12 hrs	80 - 100	Every 12 hrs
Amoxicillin + clavulanic acid	65 - 100 (of amoxicillin component)	Every 12 hrs	65 - 100 (of amoxicillin component)	Every 12 hrs
Ampicillin	100 - 150	Every 8 -12 hrs	80 - 100	Every 6 -12 hrs
Azithromycin	10	Every 24 hrs	10 - 20	Every 24 hrs
Benzathine benzylpenicillin	See syphilis guidelines*		See syphilis guidelines*	
Benzylpenicillin	80 - 100	Every 8 -12 hrs	80 -100	Every 6 - 12 hrs
Cefalexin	50 - 100	Every 12 hrs	50 - 100	Every 12 hrs
Cefazolin	50 - 100	Every 8 - 12 hrs	50 - 100	Every 8 - 12 hrs

Antibiotic	Neonates		Children	
	Total daily dose (mg/kg/day)	Dosing frequency (divided every x hrs)	Total daily dose (mg/kg/day)	Dosing frequency (divided every x hrs)
Cefixime	No suggestion		8	Every 12 - 24 hrs
Cefotaxime	50 (up to 200 in severe infection)	Every 6 -12 hrs	100-150 (up to 200 in severe infection)	Every 6 -12 hrs
Ceftriaxone	50	Every 24 hrs	50-100	Every 24 hrs
Ceftazidime	90 – 150	Every 8 hrs	90 – 150	Every 8 hrs
Chloramphenicol	No suggestion		50-100	Every 6 - 8 hrs
Ciprofloxacin	20 - 30	Every 12 hrs	20 - 30	Every 12 hrs
Clarithromycin	15	Every 12 hrs	15	Every 12 hrs
Clindamycin	10 - 20	Every 6 - 8 hrs	20 - 40	Every 6 - 8 hrs
Cloxacillin	50 - 100	Every 12 hrs	100 - 200	Every 6 hrs
Doxycycline	No suggestion		2 - 4	Every 12 - 24 hrs
Gentamicin	5	Every 24 hrs	7	Every 24 hrs
Meropenem	60	Every 8 hrs	60	Every 8 hrs
Metronidazole	20 - 40	Every 8 - 12 hrs	20 - 40	Every 8 - 12 hrs
Nitrofurantoin			4	Every 6 -12 hrs
Phenoxymethylpenicillin			100 - 200	Every 6 -12 hrs
Piperacillin-tazobactam	300 - 400 (of piperacillin component)	Every 6 - 12 hrs	300 - 400 (of piperacillin component)	Every 6 - 12 hrs

Antibiotic	Neonates		Children	
	Total daily dose (mg/kg/day)	Dosing frequency (divided every x hrs)	Total daily dose (mg/kg/day)	Dosing frequency (divided every x hrs)
Procaine benzylpenicillin	See syphilis guidelines*		See syphilis guidelines*	
Spectinomycin	No suggestion		No suggestion	
Trimethoprim + sulfamethoxazole	No suggestion		8-12 (of trimethoprim component)	Every 12 hrs
Vancomycin	40 - 60	Every 12 hrs	40 - 60	Every 6 -12 hrs

†Doses of beta-lactams may be doubled in treatment of meningitis.

*Syphilis guidelines (2016) available at https://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

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