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Title Page

Paediatric pharmacokinetics of the antibiotics in the Access and Watch groups of the 2019 WHO Model List of Essential Medicines for Children: A systematic review

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Abstract

Introduction:

Pharmacokinetic-pharmacodynamic (PK-PD) studies of antibiotics in paediatrics are limited. Paediatric dosing regimens for many antimicrobial drugs have been historically derived from adult pharmacokinetic data. Most paediatric formularies and dosing guidelines globally are expert based and provide no rationale for the recommended doses, leading to heterogeneous guidance.

Areas covered:

We systematically reviewed the current dosing for 28 antibiotics listed in the Access and Watch groups of the 2019 World Health Organisation (WHO) Essential Medicines List for children (EMLc). PubMed and EMBASE were searched for all PK-PD and pharmacological studies in paediatrics up to May 2018. In total, 262 paediatric related articles were deemed eligible. The most studied drugs were those where therapeutic drug monitoring is routine (aminoglycosides, glycopeptides) and study reporting detail was variable, with only 60.0% using the PK-PD results to make dosing recommendations. Based on this evidence, dose recommendations for each antibiotic were made.

Expert opinion:

We provide an up-to-date review of the limited available evidence on paediatric dosing for the 28 commonly prescribed antibiotics in the 2019 WHO EMLc. We propose synthesised dosing recommendations for those antibiotics administered systemically for the treatment of serious infections. Further PK-PD studies in children, particularly with underlying conditions, are needed.

Keywords:

Antibiotics; WHO; Access group; Watch group; EMLc; children; pharmacokinetics; pharmacodynamic; clinical pharmacology, systematic review

Article highlights:

- ~~The proposed dosing recommendations guidance for antibiotics listed in the Access and Watch groups of the 2019 WHO EMLc can help to provide guidance for paediatric prescribers and policymakers.~~
- The PK-PD ~~E~~evidence base for the optimal dose for most commonly used antibiotics ~~infections,~~ is remarkably limited.
- We propose dosing guidance for antibiotics listed in the Access and Watch groups of the 2019 WHO EMLc to help to advise paediatric prescribers and policymakers.
- Given the limited PK-PD evidence identified, any guidance for antibiotic dosing needs to be regarded as interim until further higher quality evidence is available.
- These findings provide the basis for a future research prioritisation exercise to strengthen the evidence base for dosing of commonly used antibiotics in children.
- ~~A more pioneering and~~Future work should seek to develop effective and efficient method~~sology~~ to assess PK-PD in children ~~need to be undertaken as part of the strategic investigator-initiated~~within clinical trials.

1. Introduction

Antimicrobials are among the most commonly prescribed classes of drugs in children [1-6]. However, paediatric dosing regimens for many antimicrobials have been historically derived from pharmacokinetic (PK) data in adults and have been based on assumed linearity between exposure and total body weight [1, 2]. This approach, although widely used in clinical practice, lacks empiric evidence and may result in inappropriate systemic drug exposures of many drugs in neonates and children [3, 4]. By providing rational dosing guidelines for a number of agents, the Essential Medicines List for children (EMLc) was developed in part to address these concerns [5].

To tackle emerging antimicrobial resistance and assist antibiotic stewardship, in 2017 the WHO EML Antibiotic Working Group proposed to classify antibiotics into three groups: Access, Watch, and Reserve, collectively known as the AWaRe classification and based on the drugs' importance in treating common conditions, probability of resistance emerging, and affordability [5-6]. The Access group contains generally narrower spectrum antibiotics recommended as first and second choice for most common clinical infection syndromes. The Watch group contains generally broader spectrum antibiotic classes. The Reserve group consists of last resort antibiotics for targeted use in multidrug resistant infections. In 2019, the AWaRe list was revised to include more antibiotics which were not classified on the 2017 list [5].

Several initiatives over the last two decades have led to the development of paediatric formularies [7-8]. However, at present, there are a limited number of paediatric formularies globally, including the USA "Red Book" [9], the European "Blue Book" [2], the British National Formulary for children (BNFc) [10] and the WHO Pocket Book of Hospital Care in Children [11]. The Red Book from the American Academy of Pediatrics, for example, provides guidance for 63 antibiotics, but does not provide any rationale behind the dosing recommendations. It is difficult for clinicians to determine whether the dose recommendations were derived from pharmaceutical summary of product characteristics, academic publications, historical practice, expert opinion or any combination of these sources. For example, the dosing guidance published in the Blue Book comes from a guidance committee considering and simplifying the recommendations from the BNFc, rather than from systematic evidence review.

Recently the Dutch Children's formulary has been developed [12] which aims to address some of the limitations in established formularies. The Dutch Children's formulary~~,~~ provides evidence-based dosing recommendations with references, offering transparency on the evidence used. However, since it is written in Dutch, this may make it difficult to be adopted

by other countries. The overall lack of standardized rationale in paediatric formularies has led to heterogeneous guidance which has the potential to cause confusion [13-14].

Pharmacokinetic-Pharmacodynamic (PK-PD) studies measure the drug concentrations reached in relevant tissues under specified dosing strategies. Together with data on clinical effectiveness and / or surrogates of effectiveness such as the relationship between PK-PD parameters (Cmax, AUC or time above MIC) and the minimum inhibitory concentration (MIC) of expected pathogens [15] , such studies can contribute to the evidence base for dosing recommendations and monitoring these concentrations over time (therapeutic drug monitoring, TDM).

This review aims to summarise the evidence base for the dosing regimens in neonates and children of commonly prescribed antibiotics in the Access and Watch groups of the 2019 WHO EMLc ~~list~~ based on the published PK-PD literature. This review has the potential to inform specific recommendations for the dosing guidance for antibiotics listed on EMLc.

2. Methods

The review was conducted and reported in accordance with the PRISMA guideline for systematic reviews and was registered on PROSPERO with registration number CRD42018094396.

2.1 Literature search strategy

A literature search using PubMed and EMBASE (from inception up to 31 May 2018) was conducted by one investigator (ANR) to identify studies describing the PK-PD of systemically administered antibiotics listed in the Access and Watch groups of the WHO ~~model~~ EMLc 2019 [5]. This comprised all 19 antibiotics listed in the Access group and nine ~~most~~ commonly used antibiotics appearing in the Watch group (Supplementary Table 1) [16]. Separate searches were undertaken for each of the 28 antibiotics, with search terms relating to the international non-proprietary drug name, pharmacokinetics, neonatal and paediatric age groups and routes of administration (Supplementary Figure 1).

2.2 Inclusion and exclusion criteria

All studies reporting the PK-PD of one or more of the included drugs in children below the age of 18 years were included. Studies were limited to those reported in English using the language filter on the two databases, and no restrictions on year of publication were applied. Relevant studies were also identified from the reference lists of the included articles.

Studies reporting topical route of administration, describing administration of drug in participants >18 years old, from which paediatric data could not be separated or administration of a related or precursor compound, that does not include dosing of the search drug were excluded. Animal and *in-vitro* studies, conference abstracts, letters, editorials and descriptive review articles, and clinical studies in which no PK-PD parameters or TDM were measured were also excluded. All search results were screened for eligibility by two reviewers (ANR, CJ), with disagreements resolved by discussion; if necessary, a third reviewer (YH) was consulted.

2.3 Data extraction

Data were extracted from included articles by two reviewers (ANR, CJ) into a Microsoft Excel spreadsheet, with disagreements resolved as above. Data extracted from each study included information related to the reference, setting and participants, treated conditions (if reported), route of administration, dosing details, and authors' dose recommendations.

2.4 Quality of evidence assessment

There is currently no standard system for assessing the quality of PK-PD studies. Therefore, we adapted the grading system described in Barker et al. [17] to assess the quality of evidence. Each study was classified based on the quality of evidence as weak, intermediate or strong. This grading system is described in more detail in Gastine et al's study [~~I~~GAPPS (Grading and Assessment of Pharmacokinetic-Pharmacodynamic studies): ~~Developing~~ a ~~Critical~~ critical ~~Appraisal~~ appraisal ~~System~~ system for antimicrobial PK-PD studies - ~~Grading and Assessment of Pharmacokinetic-Pharmacodynamic~~ development and application in pediatric antibiotic Studies; Expert Review of Clinical Pharmacology Journal 2019 – ~~submitted~~accepted].

2.5 Recommendations for new dosing guidance

Considering the available literature, clinical experience, existing guidelines [2, 9-12], and the practical ease of administration, a panel of experts (consultant paediatrician, consultant paediatric pharmacist, paediatric pharmacokinetic expert, clinical paediatric research pharmacist) proposed new dosing guidance for antibiotics in the Access and Watch groups of WHO EMLc 2019. Our dosing recommendations were reviewed by the WHO EML Antibiotic Working Group and further amended based on their comments.

2.6 Data analysis

We carried out a narrative descriptive analysis due to the heterogeneity of the results between studies.

3. Results

3.1 Search results

Our search, after removing duplicates, identified 589 articles (Figure 1). Of these, 345 were potentially relevant and their full texts were assessed for eligibility, and 262 articles met the inclusion criteria and were included in the review, with four of the studies includinged more than one drug.

The included studies were published between 1967 and 2018 and the greatest number were from the USA (42%, 110/262, Tables 1).

The most studied antibiotic was gentamicin (24%, 62/262), followed by vancomycin (18.3%, 48/262) and amikacin (8.4%, 22/262). There were only three antibiotics for which no eligible studies where retrieved: nitrofurantoin, doxycycline, and spectinomycin.

3.2 Route of administration

In 80.1% (210/262) of the studies antibiotic was given via intravenous (IV) route, in 10.3% (27/262) studies the drug was given orally, and in 5.3% (14/262) of the studies the drug was administered intramuscularly (IM) (Table 2). The route of administration was not standardised: in 2% (5/262) of the studies the drug was administered either IM or IV, and in 2.3% (6/262) either IV or orally.

3.3 Treated indications

Overall, 55 indications were reported in 88.2% (231/262) studies, with “proven or suspected infections” being the most common reported indication (18.2%, 42/231), followed by “various infections” (13.0%, 30/231) and sepsis (13.0%, 30/231) (Supplementary table 2). Indications for treatment were not clearly stated in 12.0% (31/262) studies.

3.4 Quality of evidence assessment

The strength of evidence was assessed as intermediate in 82.4% (216/262) of the studies and weak in 10.3% (27/262) studies. Only in 7.2% (19/262) of the studies, the strength of the evidence was considered strong; these studies were published between 2006 and 2018. Further details on the quality of evidence are presented in the second study by Gastine et al [GAPPS (Grading and Assessment of Pharmacokinetic-Pharmacodynamic studies): Developing a Critical critical Appraisal appraisal System system for antimicrobial PK-PD studies - Grading and Assessment of Pharmacokinetic-Pharmacodynamic development and

application in pediatric Sstudies; Expert Review of Clinical Pharmacology Journal 2019 – submittedaccepted].

3.4 New dosing guidance recommendation

More than half of the studies (60.0%, 157/262) made dose recommendations (Supplementary table 2) based on their studies' findings, while in 40.1% (105/262) no dose recommendation was reported. Table 3 presents suggested new guidance for treatment (not prophylaxis) doses for common conditions via the oral or intravenous route.

4. Discussion

4.1 Principal findings

To our knowledge, this is the largest comprehensive systematic review on the PK-PD of antibiotics to date. In this review, we have been able to identify 262 PK-PD studies in children giving an up-to-date summary for the 25 out of the 28 antibiotics listed in the Access and Watch groups of the 2019 WHO EMLc.

The studies identified in this review suggested that the PK-PD for commonly prescribed antibiotics have not been well established in children. There is very little PK-PD data on the relatively new antibiotics compared to older and thus more investigated antibiotics like gentamicin, vancomycin and amikacin. The included studies made a wide range of dosing recommendations, often based on limited evidence. By combining these with existing guidelines and clinical experience, the panel made suggestions for future dosing guidelines; however, the evidence base was generally intermediate in strength, and recommendations may change if future, robust studies suggest that this is appropriate.

Although this review found that the strength of the dosing recommendations in the majority of the included studies was rated to be intermediate, it is noticeable that the studies providing strong evidence were published recently, perhaps because PK-PD studies are now being conducted using appropriate, sophisticated analytical techniques [18]. There are multiple possible explanations for the otherwise weak evidence base. Low parental consent rates and ethical issues impede the involvement of children in PK-PD studies [19]. The use of innovative clinical trial design can overcome these obstacles; e.g. sparse and scavenged PK samples, and population PK techniques [20].

It is worth noting that this review started before the release of the updated WHO EMLc 2019. We initially started researching antibiotics listed in the Access group of the WHO EMLc 2017. In the initial AWaRe classification, the Access group included a total of 28 antibiotics; "Core

access antibiotics" and selected antibiotics that are also listed in the Watch group. These selected Watch antibiotics are commonly used in clinical practice [16]. In the 2019 version, the EML Expert Committee made a clear separation between the AwaRe groups and the nine antibiotics that were listed in both Access and Watch groups are now only listed in the latter group [5]. Hence, two drugs (ceftazidime, cefuroxime) listed in the Watch group of the 2019 EMLc were not included in this review.

The heterogeneity in the reporting of PK-PD studies complicates synthesis of evidence from multiple studies, which may use very different analytical approaches and present different PK parameters. There is limited consensus on reporting paediatric PK-PD data [21-23]. Developing a consensus in paediatric population-PK reporting and meta-analytical methodsology for traditional and population studies would help to standardise reporting, aiding comparison and synthesis of study results.

It is acknowledged that there are widely varying dosing recommendations across countries. For example, dosing strategies may be weight-based (United States [9]), age-banded (United Kingdom [10]) or weight-banded (WHO [11]). These national preferences make it difficult for a single set of recommendations to be adopted worldwide.

Thus, considering the literature and the lack of harmony in the currently available international formularies, we have derived evidence-based dosing guidance (Table 3) for 28 antibiotics listed in the WHO EMLc 2019 and included in this review. These recommendations should be used as guidance for the treatment (not prophylaxis) of the most common conditions via oral or parenteral route of administration. Though these recommendations might help prescribers in devising treatment regimens, they are intended as guidance only and clinical evaluation of the patients should always be used to inform subsequent therapy.

4.2 Strengths and limitations

This is the most comprehensive review on paediatric dosing of 28 antibiotics included in the 2019 WHO EMLc. Hence, we were able to devise evidence-guided dosing ~~recommendations~~ guidance which was also assessed by an expert panel.

However, the limitations of this review must be considered when interpreting our findings. The heterogeneity among included studies precluded meta-analysis. In addition, though our search strategy and inclusion criteria were designed to be highly sensitive, some studies, especially unpublished, may have been missed. Studies not indexed in Embase or PubMed will have been omitted. Finally, we did not include studies published in languages other than English.

5. Conclusion

We reviewed the available evidence base for 28 antibiotics listed in the Access and Watch groups of the WHO EMLc 2019. The variation in the reported parameters, the small sample sizes, and the outdated methods of analysis in a lot of the studies showed that paediatric PK-PD for commonly prescribed antibiotics have not been well established.

Given the insufficient evidence for dosing of the widely used antibiotics included in this review, there is therefore a need for collaboration between paediatric pharmacokinetic researchers and clinical trial networks internationally to tackle the evidence gaps in a complementary and strategic manner. Where there are critical gaps, innovative and efficient approaches towards assessing PK-PD e.g. as part of strategic investigator-initiated trials should be undertaken. Furthermore, paediatric-specific PK-PD and dosing studies should generally be included as part of the licensing process for newly developed antibiotics such as third generation cephalosporins (e.g. cefixime).

6. Expert opinion

Further work beyond the scope of this review is needed to fully inform dosing recommendations. Firstly, formal methods of assessing the strength of evidence provided by PK studies are needed. This could build upon a proposed checklist for the reporting of clinical PK studies [23] as well as a proposed hierarchy of PK evidence [16], such as the GAPPS presented by Gastine et al [Developing a Critical Appraisal System for antimicrobial PK-PD studies - Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies; Expert Review of Clinical Pharmacology Journal 2019 – submitted].

Secondly, clinical outcomes (including drug toxicity) should be considered. Full review of toxicity data would require inclusion of studies of clinical endpoints which were not eligible for this review of PK data, as well as a consensus on PD targets. A systematic review of adverse events in paediatric randomised controlled trials of antibiotics reported a median of 22.5% of children experienced an adverse event in 33 trials, but was not able to compare toxicity under different dosing regimens [24].

Thirdly, the duration of antibiotic treatment is an important factor to consider in guidelines. Together with the timing of switch from intravenous to oral treatment, duration of treatment has been reviewed for a range of paediatric infection syndromes, based on clinical

outcome data [25]. As with dosing data, the evidence in this area is limited, but recommended total (intravenous plus oral) durations were typically between 7 and 14 days, depending on the condition. Shorter durations were recommended for community-acquired pneumonia (3 days if mild, ≤7 days if moderate or severe uncomplicated), lower urinary tract infection (3-4 days) and meningococcal bacteraemia (4-5 days) [25]. Durations of several weeks were recommended for conditions including bacterial endocarditis, brain abscess and subdural empyema, lung abscess, and several musculoskeletal infections, where it takes time to build up the level in the target region.

There are an estimated 1.9 billion children in the world currently, around 27% of the total world population [26]. Children are frequently exposed to antibiotics in their early life. There is limited data on rates of prescribing for children in low-middle income country (LMIC) settings, but it is likely there are around 1-2 billion courses of antibiotics taken by children each year, by far the commonest medicine that children receive. The results of this review are therefore very disappointing in that for nearly all common infections, the optimal dose of antibiotic is still unknown. Indeed, the evidence base for the optimal choice of drug for most common infections, as well as for dose, duration and delivery/formulation is remarkably limited. Clearly much remains to be done. The WHO has made a good start by defining the most important "Access" and "Watch" antibiotics that are needed to treat the most common and serious infections. These two submitted papers [Rashed et al. 2019, Gastine et al. 2019] provide a framework that can be used to clarify where the gaps in evidence are and what studies need to be performed to improve the quality of prescribing through a more formal and reproducible process.

There remains a serious challenge in defining the "optimal" dose of any antibiotic given to a child. Previously, PK-PD exposure to target the commonest pathogens causing a specific clinical infection syndrome could be defined and dosing regimens derived based on maximising efficacy usually extrapolated from adult data. Also, ~~despite~~although there are very few studies that are considered real PD studies, it is easier to extrapolate PD target for antibiotics compared to other drugs, because antimicrobials target ~~effect targets a~~ micro-organisms and not a physiological mechanism. More recently regulators have accepted that safety parameters can also be extrapolated from adult data for at least well-established classes of antibiotics [27]. The therapeutic index, which is used to compare the serum level of the therapeutically effective dose to the toxic dose of a drug, has been challenged recently with increasing rates of antimicrobial resistance in both high and LMICs. Standard dosing regimens for common antibiotics may no longer be adequate with steadily increasing minimum inhibitory concentrations (MICs) of common pathogens. Increasing exposure to try and

combat this problem, such as increasing the dose to achieve higher Cmax, may in turn lead to increased toxicity. The balance will be to optimise dosing regimens as needed to maintain clinical outcomes, while keeping the risks of toxicity minimal. This adds complexity to dosing guidance, where optimal exposures may vary geographically due to varying rates of resistance between countries or regions. Further complexity is added by the need to alter dosing guidance for either a child who has complex underlying disease or is critically ill. Standard European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for deriving optimal clinical outcomes from drug exposure are based virtually entirely on adult clinical outcome data [~~27~~28]. Higher antibiotic exposures may be required for children with developing or impaired immune systems, such as neonates or those with malnutrition, HIV or other complex underlying conditions. Neonates and children with severe infections, such as sepsis, may also have complex alterations in PK characteristics, including volume of distribution and excretion, such as augmented renal clearance. Historically the approach that has been taken is, for example in the UK, to double the dose in severe infection, but this may be inadequate in the context of severe and/or resistant infections.

The dosing of antibiotics needs to consider not only the child in front of the clinician now, but also the child yet to come. Inadequate dosing that selects for future resistance by failing to inhibit the growth of resistant mutants is a major issue when there is such a limited pipeline of future antibiotics. Dosing regimens need to consider exposure above the resistance inhibitory concentration as well as the MIC. As further work rapidly explores the impact of antibiotics on the young child's microbiome, it is also likely that dosing regimens will need to be explored that minimise this important potential adverse effect on children's health.

These are complex issues with many potentially conflicting influences on optimal dosing, some of which are highly specific to paediatrics. Future dosing guidance will need to be based not only on improved modelling, but also clinical outcomes established in well planned studies collecting data on the most important real-world endpoints, toxicity, selection of resistance and impact on the microbiome. Dosing regimens also need to consider the simplest reasonable formulations that can be produced at low cost and high quality so access to appropriate antibiotics can be enhanced and maintained for the poorest children. These considerations will need teams of experts and multiple stakeholders to provide explicit evidence-based recommendations that will need to be reviewed regularly as data emerge.

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Declaration of interest

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543 **Table 1. Number of studies and country**

Drug	Total number of studies*	Country (no. of studies)
Amikacin	22	Belgium (6), Canada (1), China (1), France (3), Germany (1), Greece (1), Israel (1), Italy (1), New Zealand (1), South Africa (2), South Korea (1), USA (3), Netherlands (1)
Amoxicillin	8	Australia (1), Brazil (1), Germany (1), Netherlands (3), USA (2)
Ampicillin	10	Japan (1), USA (8), Uruguay (1)
Azithromycin	11	Costa Rica (1), Saudi Arabia (1), Sub-Saharan Africa (1), USA (8)
Benzathine benzylpenicillin	1	USA (1)
Benzylpenicillin	5	Estonia (2), Ethiopia (1), Netherlands (1), Uruguay (1)
Cefalexin	2	Canada (1), USA (1)
Cefazolin	5	Belgium (2), Japan (2), USA (1)
Cefixime	1	Greece (1)
Cefotaxime	12	Australia (1), France (3), Netherlands (1), UK (1), USA (6)
Ceftriaxone	6	Switzerland (2), USA (3), Kenya (1)
Chloramphenicol	10	Ethiopia (1), Kenya (1), Mexico (1), Philippines-The Gambia (1), UK (2), USA (4)
Ciprofloxacin	10	Finland (2), France (2), Germany (1), Kenya (1), South Africa (1), UK (2), USA (1)
Clarithromycin	1	USA (1)
Clindamycin	5	USA (5)
Cloxacillin	1	Canada (1)
Co-amoxiclav	7	Belgium (1), Switzerland (2), UK (2), USA (2)
Gentamicin	62	Australia (2), Bangladesh (1), Canada (6), Chile (2), Czech Republic (1), Denmark (1), Ireland (1), Israel (1), Japan (1), Kenya (2), Mexico (1), Netherlands (7), Portugal (1), South Asia: India & Bangladesh (1), Spain (5), Sweden (1), Switzerland (1), Thailand (1), UK (4), USA (22)
Meropenem	16	Estonia (1), Italy (1), Japan (2), Netherlands (2), Czech Republic (1), Thailand (1), USA (9)
Metronidazole	7	Australia (1), Canada (1), India (1), Mexico (1), UK (1), USA (1)
Phenoxymethylpenicillin	1	Ethiopia (1), Kenya (1)
Piperacillin-tazobactam	9	Belgium (1), China (1), France (1), USA (6)
Procaine penicillin	1	Ethiopia (1)
Trimethoprim-sulfamethoxazole	6	Chile (1), Israel (1), Mexico (1), USA (3)
Vancomycin	48	Belgium (1), Canada (4), Egypt (1), France (6), Iran (1), Israel (1), Japan (1), Jordan (1), Malaysia (1), Netherlands (3), Portugal (1), South Korea (1), Spain (1), Turkey (1), UK (1), USA (23)

**The total number of the studies does not add up to 262 as some studies covered more than one drug*

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Figure 1. Study selection flow chart

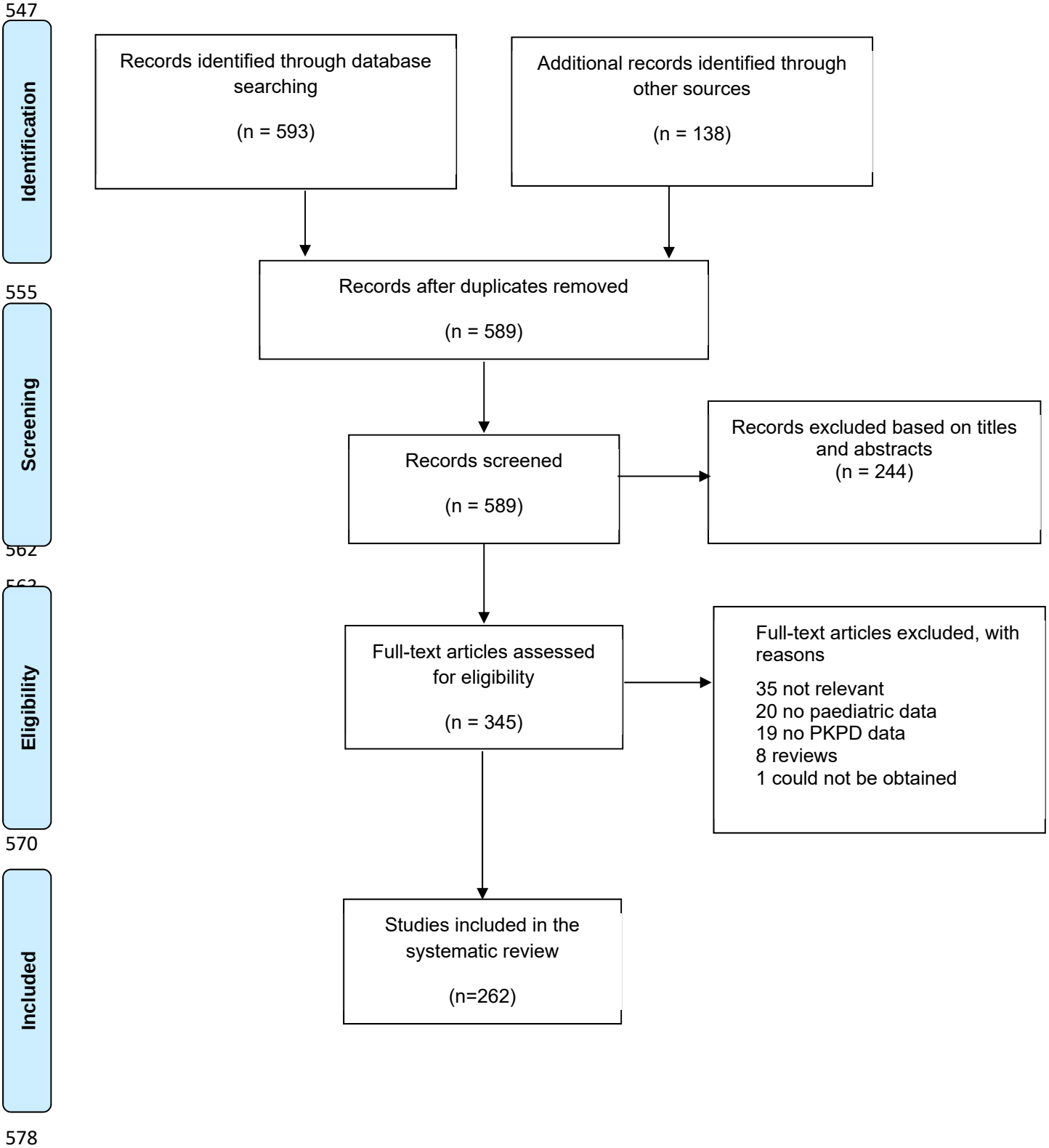


Table 2. General description of included studies per drug

Drug	No. of studies*	Publication years	Sample size	Population age	Route of administration
Amikacin	22	1975-2014	9-205	0 d – 17 y	IV, IM
Amoxicillin	8	1980-2007	17-150	24 w – 16 y	IV, PO
Ampicillin	10	1967-2018	3-131723	0 d – 14 y	IV, IM, PO
Azithromycin	11	1993-2015	10-179	<72 h – 16 y	IV, PO
Benzathine benzylpenicillin	1	1982	26	1.8 - 10.7y	IM
Benzylpenicillin	5	1995-2018	13-37	1 d – 14 y	IV
Cefalexin	2	1982-2013	12-20	2 m – 16 y	PO
Cefazolin	5	1988-20174	5-56	1d – 10 y	IV
Cefixime	1	1996	6	6-13y	PO
Cefotaxime	12	1981-2018	12-100	1 d – 18.7 y	IV, IM
Ceftriaxone	6	1982-2017	10-80	1 d – 70 m	IV
Chloramphenicol	10	1980-2005	14-81	<7 d – 13 y	IM, IV
Ciprofloxacin	10	1992-2014	10-150	1 d – 24 y	IV, PO
Clarithromycin	1	1992	24	6m - 10 y	PO
Clindamycin	5	1984-2017	40-220	1 d – 20 y	IV, PO
Cloxacillin	1	1990	14	0.5-15 y	IV
Co-amoxiclav	7	1983-2015	11-50*	<2 y – 18 y	IV, PO
Gentamicin	62	1971-2017	7-1854	0 d – 18 y	IM, IV
Meropenem	16	1995-2017	1-188	23 w to 17.3 y	IV
Metronidazole	7	1982-2017	11-68	1 d – 45 m	IV
Phenoxymethylpenicillin	1	1995	49	7m - 6.5y	PO
Piperacillin-tazobactam	9	1994-2017	12-746**	1 d – 15 y	IV
Procaine penicillin	1	1995	18	7m - 6.5y	IM
Trimethoprim-sulfamethoxazole	6	1975-2018	4-153	<3 d - 16 y	IV
Vancomycin	48	1986-2017	5-702	0 d -18 y	IV

d: day; m: month; y: year; w: week; h: hour; PO: by mouth; IV: intravenous; IM: intramuscular
*The total number of the studies does not add up to 262 as some studies covered more than one drug

Table 3. Suggested doses for the WHO Access and Watch antibiotics groups for the treatment of most common conditions in children

	Neonates		Children	
Antibiotic	Total daily dose (mg/kg/day)	Dosing frequency (divided every x hours)	Total daily dose (mg/kg/day)	Dosing frequency (divided every x hours)
Amikacin	15 - 20	Every 24 hours	15 - 20	Every 24 hours
Amoxicillin	80 - 100	Every 12 hours	80 - 100	Every 12 hours
Amoxicillin + clavulanic acid	65 - 100 (of amoxicillin component)	Every 12 hours	65 - 100 (of amoxicillin component)	Every 12 hours
Ampicillin	100 - 150	Every 8 -12 hours	80 - 100	Every 6 -12 hours
Azithromycin	10	Every 24 hours	10 - 20	Every 24 hours
Benzathine benzylpenicillin	See syphilis guidelines*		See syphilis guidelines*	
Benzylpenicillin	80 – 100	Every 8 -12 hours	80 – 100	Every 6 - 12 hours
Cefalexin	50 - 100	Every ~~12~~ 8 hours	50 - 100	Every ~~12~~ 8 hours
Cefazolin	50 - 100	Every 8 - 12 hours	50 - 100	Every 8 - 12 hours
Cefixime	No suggestion	-	8	Every 12 - 24 hours
Cefotaxime	50 (up to 200 in severe infection)	Every 6 -12 hours	100-150 (up to 200 in severe infection)	Every 6 -12 hours
Ceftriaxone	50	Every 24 hours	50-100	Every 24 hours
Ceftazidime	90 – 150	Every 8 hours	90 – 150	Every 8 hours
Chloramphenicol	No suggestion	-	50-100	Every 6 - 8 hours
Ciprofloxacin	20 - 30	Every 12 hours	20 - 30	Every 12 hours
Clarithromycin	15	Every 12 hours	15	Every 12 hours
Clindamycin	10 – 20	Every 6 - 8 hours	20 - 40	Every 6 - 8 hours
Cloxacillin	50 – 100	Every 12 hours	100 - 200	Every 6 hours

	Neonates		Children	
Antibiotic	Total daily dose (mg/kg/day)	Dosing frequency (divided every x hours)	Total daily dose (mg/kg/day)	Dosing frequency (divided every x hours)
Doxycycline	No suggestion		2 - 4	Every 12 - 24 hours
Gentamicin	5	Every 24 hours	7	Every 24 hours
Meropenem	60	Every 8 hours	60	Every 8 hours
Metronidazole	20 – 40	Every 8 - 12 hours	20 - 40	Every 8 - 12 hours
Nitrofurantoin	No suggestion	-	4	Every 6 -12 hours
Phenoxymethylpenicillin	No suggestion	-	100 - 200	Every 6 -12 hours
Piperacillin-tazobactam	300 - 400 (of piperacillin component)	Every 6 - 12 hours	300 - 400 (of piperacillin component)	Every 6 - 12 hours
Procaine benzylpenicillin	See syphilis guidelines*		See syphilis guidelines*	
Spectinomycin	No suggestion	-	No suggestion	
Trimethoprim + sulfamethoxazole	No suggestion	-	8-12 (of trimethoprim component)	Every 12 hours
Vancomycin	40 – 60	Every 12 hours	40 - 60	Every 6 -12 hours

‡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/

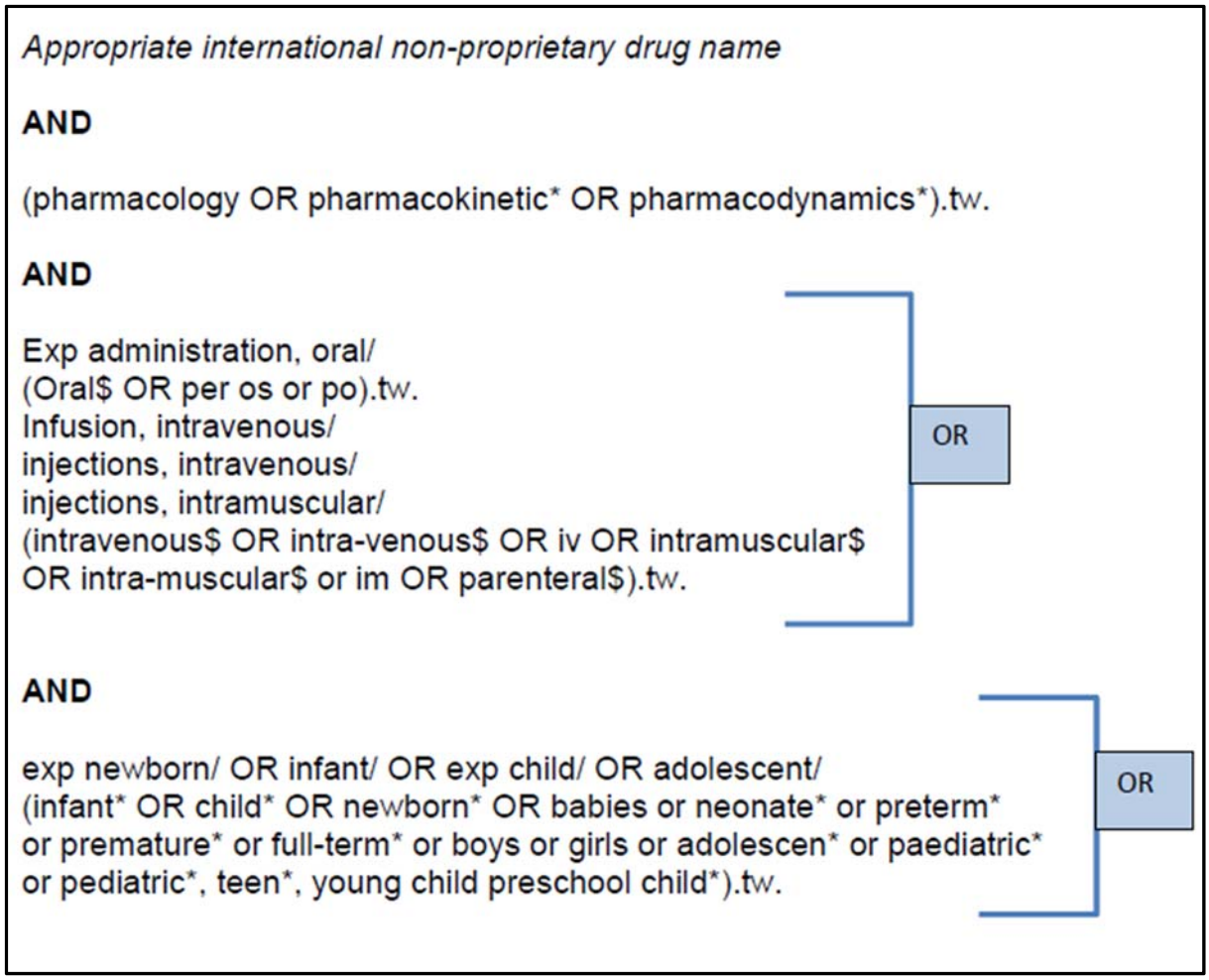
No suggestion: it is not used for the included age group.

Supplementary Table 1. Antibiotics included in the Access and Watch groups of the 2019 WHO EMLc ~~list~~

~~Key~~ Access group	Watch group
Amikacin	Azithromycin
Amoxicillin	Cefixime
Amoxicillin + clavulanic acid	Cefotaxime
Ampicillin	Ceftriaxone
Benzathine benzylpenicillin	Ciprofloxacin
Benzylpenicillin	Ceftazidime*
Cefalexin	Cefuroxime*
Cefazolin	Clarithromycin
Chloramphenicol	Piperacillin + tazobactam
Clindamycin	Meropenem
Cloxacillin	Vancomycin
Doxycycline	
Gentamicin	
Metronidazole	
Nitrofurantoin	
Phenoxymethylpenicillin	
Procaine benzylpenicillin	
Spectinomycin	
Sulfamethoxazole + trimethoprim	

*Not included in this review

Supplementary Figure 1. Search terms used in each literature search



Supplementary table 2. List of reported indications and dosing recommendation from the 262 included studies.