



**QUEEN'S  
UNIVERSITY  
BELFAST**

## **Pediatric pharmacokinetics of the antibiotics in the access and watch groups of the 2019 WHO model list of essential medicines for children: a systematic review**

Rashed, A. N., Jackson, C., Gastine, S., Hsia, Y., Bielicki, J., Standing, J. F., Tomlin, S., & Sharland, M. (2019). Pediatric pharmacokinetics of the antibiotics in the access and watch groups of the 2019 WHO model list of essential medicines for children: a systematic review. *Expert Review of Clinical Pharmacology*, 12(12), 1099-1106. Advance online publication. <https://doi.org/10.1080/17512433.2019.1693257>

**Published in:**  
Expert Review of Clinical Pharmacology

**Document Version:**  
Peer reviewed version

**Queen's University Belfast - Research Portal:**  
[Link to publication record in Queen's University Belfast Research Portal](#)

**Publisher rights**  
Copyright 2019 Taylor & Francis. This work is made available online in accordance with the publisher's policies. Please refer to any applicable terms of use of the publisher.

**General rights**  
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**  
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact [openaccess@qub.ac.uk](mailto:openaccess@qub.ac.uk).

**Open Access**  
This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. – Share your feedback with us: <http://go.qub.ac.uk/oa-feedback>

1 **Title Page**

2 **Paediatric pharmacokinetics of the antibiotics in the Access and Watch groups of the**  
3 **2019 WHO Model List of Essential Medicines for Children: A systematic review**

4

5 Asia N Rashed<sup>1,2\*</sup>(<https://orcid.org/0000-0003-1313-0915>), Charlotte Jackson<sup>3</sup>, Silke  
6 Gastine<sup>3,4</sup>, Yingfen Hsia<sup>3,7</sup>, Julia Bielicki<sup>3,4</sup>, Joseph F Standing<sup>3,5,6</sup>, Stephen Tomlin<sup>6</sup>, Mike  
7 Sharland<sup>3</sup>

8

- 9 1. Institute of Pharmaceutical Science, King's College London, London, UK  
10 2. Pharmacy Department, Evelina London Children's Hospital, Guy's & St Thomas NHS  
11 Foundation Trust, London, UK  
12 3. Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity,  
13 St George's, University of London, London, UK  
14 4. Paediatric Pharmacology Group, University of Basel Children's Hospital, Basel,  
15 Switzerland  
16 5. Great Ormond Street Institute of Child Health, University College London, London, UK  
17 6. Pharmacy Department, Great Ormond Street Hospital for Children NHS Foundation  
18 Trust, London, UK  
19 7. School of Pharmacy, Queen's University Belfast, Belfast, UK

17

18

19

20

21 **\*Corresponding Author**

22 \*Dr Asia Rashed

23 Research and Teaching Fellow

24 King's College London

25 London SE1 9NH

26 Email: [asia.rashed@kcl.ac.uk](mailto:asia.rashed@kcl.ac.uk)

27 Tel: +44 207 848 4844

28

29

30

31

32

33

34

35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71

**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

72 **Article highlights:**

- 73
- 74 ~~— The proposed dosing recommendations guidance for antibiotics listed in the Access~~  
75 ~~and Watch groups of the 2019 WHO EMLc can help to provide guidance for paediatric~~  
76 ~~prescribers and policymakers.~~
- 77 • The PK-PD Eevidence base for the optimal dose for most commonly used antibiotics  
78 infections, is remarkably limited.
  - 79 • We propose dosing guidance for antibiotics listed in the Access and Watch groups of  
80 the 2019 WHO EMLc to help to advise paediatric prescribers and policymakers.
  - 81 • Given the limited PK-PD evidence identified, any guidance for antibiotic dosing needs  
82 to be regarded as interim until further higher quality evidence is available.
  - 83 • These findings provide the basis for a future research prioritisation exercise to  
84 strengthen the evidence base for dosing of commonly used antibiotics in children.
  - 85 • A more pioneering andFuture work should seek to develop effective and efficient  
86 methodology to assess PK-PD in children need to be undertaken as part of the  
87 strategic investigator-initiatedwithin clinical trials.
- 88
- 89
- 90
- 91
- 92
- 93
- 94
- 95
- 96
- 97
- 98
- 99
- 100
- 101
- 102
- 103
- 104
- 105
- 106

107 **1. Introduction**

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

116  
117 To tackle emerging antimicrobial resistance and assist antibiotic stewardship, in 2017 the  
118 WHO EML Antibiotic Working Group proposed to classify antibiotics into three groups: Access,  
119 Watch, and Reserve, collectively known as the AWaRe classification and based on the drugs'  
120 importance in treating common conditions, probability of resistance emerging, and affordability  
121 [5-6]. The Access group contains generally narrower spectrum antibiotics recommended as  
122 first and second choice for most common clinical infection syndromes. The Watch group  
123 contains generally broader spectrum antibiotic classes. The Reserve group consists of last  
124 resort antibiotics for targeted use in multidrug resistant infections. In 2019, the AWaRe list was  
125 revised to include more antibiotics which were not classified on the 2017 list [5].

126  
127 Several initiatives over the last two decades have led to the development of paediatric  
128 formularies [7-8]. However, at present, there are a limited number of paediatric formularies  
129 globally, including the USA "Red Book" [9], the European "Blue Book" [2], the British National  
130 Formulary for children (BNFc) [10] and the WHO Pocket Book of Hospital Care in Children  
131 [11]. The Red Book from the American Academy of Pediatrics, for example, provides guidance  
132 for 63 antibiotics, but does not provide any rationale behind the dosing recommendations. It  
133 is difficult for clinicians to determine whether the dose recommendations were derived from  
134 pharmaceutical summary of product characteristics, academic publications, historical practice,  
135 expert opinion or any combination of these sources. For example, the dosing guidance  
136 published in the Blue Book comes from a guidance committee considering and simplifying the  
137 recommendations from the BNFc, rather than from systematic evidence review.

138  
139 Recently the Dutch Children's formulary has been developed [12] which aims to address some  
140 of the limitations in established formularies. The Dutch Children's formulary<sub>7</sub> provides  
141 evidence-based dosing recommendations with references, offering transparency on the  
142 evidence used. However, since it is written in Dutch, this may make it difficult to be adopted

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

145  
146 Pharmacokinetic-Pharmacodynamic (PK-PD) studies measure the drug concentrations  
147 reached in relevant tissues under specified dosing strategies. Together with data on clinical  
148 effectiveness and / or surrogates of effectiveness such as the relationship between PK-[PD](#)  
149 parameters (C<sub>max</sub>, AUC or time above [MIC](#)) and the minimum inhibitory concentration (MIC)  
150 of expected pathogens [15] , such studies can contribute to the evidence base for dosing  
151 recommendations and monitoring these concentrations over time (therapeutic drug  
152 monitoring, TDM).

153  
154 This review aims to summarise the evidence base for the dosing regimens in neonates and  
155 children of commonly prescribed antibiotics in the Access and Watch groups of the 2019 WHO  
156 EMLc [list](#)-based on the published PK-PD literature. This review has the potential to inform  
157 specific recommendations for the dosing guidance for antibiotics listed on EMLc.

158

## 159 **2. Methods**

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

163

### 164 *2.1 Literature search strategy*

165 A literature search using PubMed and EMBASE (from inception up to 31 May 2018) was  
166 conducted by one investigator ([ANR](#)) to identify studies describing the PK-PD of systemically  
167 administered antibiotics listed in the Access and Watch groups of the WHO ~~model~~-EMLc 2019  
168 [5]. This comprised all 19 antibiotics listed in the Access group and nine ~~most~~ commonly used  
169 antibiotics appearing in the Watch group (Supplementary Table 1) [16]. Separate searches  
170 were undertaken for each of the 28 antibiotics, with search terms relating to the international  
171 non-proprietary drug name, pharmacokinetics, neonatal and paediatric age groups and routes  
172 of administration (Supplementary Figure 1).

173

### 174 *2.2 Inclusion and exclusion criteria*

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

179

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

188

### 189 *2.3 Data extraction*

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

194

### 195 *2.4 Quality of evidence assessment*

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

205

### 206 *2.5 Recommendations for new dosing guidance*

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

213

### 214 *2.6 Data analysis*

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

217

218

### 219 **3. Results**

#### 220 *3.1 Search results*

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

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

227 The most studied antibiotic was gentamicin (24%, 62/262), followed by vancomycin (18.3%,  
228 48/262) and amikacin (8.4%, 22/262). There were only three antibiotics for which no eligible  
229 studies were retrieved: nitrofurantoin, doxycycline, and spectinomycin.

230

#### 231 *3.2 Route of administration*

232 In 80.1% (210/262) of the studies antibiotic was given via intravenous (IV) route, in 10.3%  
233 (27/262) studies the drug was given orally, and in 5.3% (14/262) of the studies the drug was  
234 administered intramuscularly (IM) (Table 2). The route of administration was not standardised:  
235 in 2% (5/262) of the studies the drug was administered either IM or IV, and in 2.3% (6/262)  
236 either IV or orally.

237

#### 238 *3.3 Treated indications*

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

243

#### 244 *3.4 Quality of evidence assessment*

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



252 [application in pediatric S](#)studies; Expert Review of Clinical Pharmacology Journal 2019 –  
253 [submittedaccepted](#)].

254

### 255 *3.4 New dosing guidance recommendation*

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

260

## 261 **4. Discussion**

### 262 *4.1 Principal findings*

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

267

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

276

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

285

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

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

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

301

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

306

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

314

#### 315 *4.2 Strengths and limitations*

316 This is the most comprehensive review on paediatric dosing of 28 antibiotics included in the  
317 2019 WHO EMLc. Hence, we were able to devise evidence-guided dosing [recommendations](#)  
318 [guidance](#) which was also assessed by an expert panel.

319

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

326

## 327 **5. Conclusion**

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

332

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

341

## 342 **6. Expert opinion**

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

351

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

358

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

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

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

384  
385 There remains a serious challenge in defining the “optimal” dose of any antibiotic given to a  
386 child. Previously, PK-PD exposure to target the commonest pathogens causing a specific  
387 clinical infection syndrome could be defined and dosing regimens derived based on  
388 maximising efficacy usually extrapolated from adult data. [Also, despite although there are very  
389 few studies that are considered real PD studies, it is easier to extrapolate PD target for  
390 antibiotics compared to other drugs, because antimicrobials target-effect targets a micro-  
391 organisms and not a physiological mechanism.](#) More recently regulators have accepted that  
392 safety parameters can also be extrapolated from adult data for at least well-established  
393 classes of antibiotics [27]. The therapeutic index, which is used to compare the serum level of  
394 the therapeutically effective dose to the toxic dose of a drug, has been challenged recently  
395 with increasing rates of antimicrobial resistance in both high and LMICs. Standard dosing  
396 regimens for common antibiotics may no longer be adequate with steadily increasing minimum  
397 inhibitory concentrations (MICs) of common pathogens. Increasing exposure to try and

398 combat this problem, such as increasing the dose to achieve higher C<sub>max</sub>, may in turn lead  
399 to increased toxicity. The balance will be to optimise dosing regimens as needed to maintain  
400 clinical outcomes, while keeping the risks of toxicity minimal. This adds complexity to dosing  
401 guidance, where optimal exposures may vary geographically due to varying rates of resistance  
402 between countries or regions. Further complexity is added by the need to alter dosing  
403 guidance for either a child who has complex underlying disease or is critically ill. Standard  
404 European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for  
405 deriving optimal clinical outcomes from drug exposure are based virtually entirely on adult  
406 clinical outcome data [2728]. Higher antibiotic exposures may be required for children with  
407 developing or impaired immune systems, such as neonates or those with malnutrition, HIV or  
408 other complex underlying conditions. Neonates and children with severe infections, such as  
409 sepsis, may also have complex alterations in PK characteristics, including volume of  
410 distribution and excretion, such as augmented renal clearance. Historically the approach that  
411 has been taken is, for example in the UK, to double the dose in severe infection, but this may  
412 be inadequate in the context of severe and/or resistant infections.

413

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

421

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

431

## 432 **Funding**

433 The review was funded by the World Health Organisation.

434

435 **Declaration of interest**

436 ANR was funded by the WHO during this study. Other authors declare no conflict of interest.

437

438 **References**

- 439 1. Ahmed U, Spyridis N, Wong IC, et al. Dosing of oral penicillins in children: is big  
440 child=half an adult, small child=half a big child, baby=half a small child still the best we  
441 can do? *Bmj* 2011; 343:d7803.
- 442 2. Sharland M, Butler K, Cant A, et al editors. *Manual of Childhood Infections: The Blue*  
443 *Book*, 4<sup>th</sup> ed. Oxford: OUP; 2016.
- 444 3. van den Anker JN. Getting the dose of vancomycin right in the neonate. *Int J Clin*  
445 *Pharmacol Ther.* 2011; 49(4):247-9.
- 446 4. Bartelink IH, Wolfs T, Jonker M, et al. Highly variable plasma concentrations of  
447 voriconazole in pediatric hematopoietic stem cell transplantation patients. *Antimicrob*  
448 *Agents Chemother.* 2013; 57(1):235-40.
- 449 5. WHO. Executive summary: the selection and use of essential medicines 2019. Report  
450 of the 22<sup>nd</sup> WHO Expert Committee on the selection and use of essential medicines.  
451 [cited 25 July 2019] Available from:  
452 [https://apps.who.int/iris/bitstream/handle/10665/325773/WHO-MVP-EMP-IAU-](https://apps.who.int/iris/bitstream/handle/10665/325773/WHO-MVP-EMP-IAU-2019.05-eng.pdf?sequence=1&isAllowed=y)  
453 [2019.05-eng.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/325773/WHO-MVP-EMP-IAU-2019.05-eng.pdf?sequence=1&isAllowed=y)
- 454 6. Sharland M, Pulcini C, Harbarth S, et al. Classifying antibiotics in the WHO Essential  
455 Medicines List for optimal use-be AwaRe. *Lancet Infect Dis.* 2018; 18(1):18-20.
- 456 7. Lenney W. The development of a national children's formulary. *Br J Clin Pharmacol.*  
457 2015; 79(3):441-5.
- 458 8. Hoppu K, Anabwani G, Garcia-Bournissen F, et al. The status of paediatric medicines  
459 initiatives around the world—What has happened and what has not? *Eur J Clin*  
460 *Pharmacol.* 2012; 68(1):1-10.
- 461 9. Kimberlin DW, Lond S, Brady MT, et al., editors. *Red Book 2015: Report of the*  
462 *Committee on Infectious Diseases*, 30<sup>th</sup> ed. American Academy of Pediatrics; 2015.
- 463 10. National Institute for Health and Care Excellence. *British National Formulary for*  
464 *Children.* 2019. [Accessed 25 July 2019]; Available from: <https://bnfc.nice.org.uk/>.
- 465 11. World Health Organization. *Pocket book of hospital care for children: Guidelines for*  
466 *the management of common illnesses with limited resources.* 2005 [Accessed 25 July  
467 2019]; Available from:  
468 [http://www.who.int/maternal\\_child\\_adolescent/documents/9241546700/en/](http://www.who.int/maternal_child_adolescent/documents/9241546700/en/).
- 469 12. Kinderformularium. [Accessed 16 Aug 2019]; available from:  
470 [www.kinderformularium.nl](http://www.kinderformularium.nl)

- 471 13. Pulcini C, Wencker F, Frimodt-Møller N, et al. European survey on principles of  
472 prudent antibiotic prescribing teaching in undergraduate students. Clin Microbiol Infect.  
473 2015; 21(4):354-61.
- 474 14. Pulcini C, Williams F, Molinari N, et al. Junior doctors' knowledge and perceptions of  
475 antibiotic resistance and prescribing: a survey in France and Scotland. Clin Microbiol  
476 Infect. 2011; 17(1):80-7.
- 477 15. Mouton JW, Dudley MN, Cars O, et al. Standardization of  
478 pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an  
479 update. J Antimicrob Chemother. 2005; 55(5):601-7.
- 480 16. Hsia Y, Lee BR, Versporten A, et al. Use of the WHO Access, Watch, and Reserve  
481 classification to define patterns of hospital antibiotic use (AWaRe): an analysis of  
482 paediatric survey data from 56 countries. Lancet Glob Health. 2019 ;7(7):e861-e871.
- 483 [17.](#) Barker CI, Standing JF, Turner MA, et al. Antibiotic dosing in children in Europe: can  
484 we grade the evidence from pharmacokinetic/pharmacodynamic studies – and when  
485 is enough data enough? Curr Opin Infect Dis. 2012; 25(3):235-42.  
486 [\\* This review triggers a debate on how to improve antimicrobial prescribing  
487 considering methods to develop optimal dosage in children](#)
- 488 [18.](#) Standing JF. Understanding and applying pharmacometric modelling and simulation  
489 in clinical practice and research. Br J Clin Pharmacol, 2017; 83(2):247-254.  
490 [\\*This study provides an examaples of real-world PKPD use in clinical practice and  
491 applied clinical research.](#)
- 492 ~~17-19.~~ Institute of Medicine (US) Committee on Clinical Research Involving Children .  
493 In: Ethical Conduct of Clinical Research Involving Children. Field MJ, Behrman RE,  
494 editors. National Academies Press (US); Washington (DC); 2004. [Accessed 25 July  
495 2019]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK25557/>
- 496 [20.](#) Laughon MM, Benjamin DK Jr, Capparelli EV, et al. Innovative clinical trial design for  
497 pediatric therapeutics. Expert Rev Clin Pharmacol. 2011;4(5):643-52.  
498 [\\*This article discussess the historical challenges in clinical trials in paediatric  
499 population.](#)
- 500 ~~18-21.~~ Dykstra K, Mehrotra N, Tornøe CW, et al. Reporting guidelines for population  
501 pharmacokinetic analyses. J Pharmacokinet Pharmacodyn. 2015;42(3):301-14.
- 502 ~~19-22.~~ Byon W, Smith MK, Chan P, et al. Establishing best practices and guidance in  
503 population modeling: an experience with an internal population pharmacokinetic  
504 analysis guidance. CPT Pharmacometrics Syst Pharmacol. 2013;2:e51.
- 505 ~~20-23.~~ Kanji S, Hayes M, Ling A, et al. Reporting Guidelines for Clinical  
506 Pharmacokinetic Studies: The ClinPK Statement. Clin Pharmacokinet. 2015;  
507 54(7):783-95.

508 24-24. Pansa P, Hsia Y, Bielicki J, et al. Evaluating Safety Reporting in Paediatric  
509 Antibiotic Trials, 2000-2016: A Systematic Review and Meta-Analysis. Drugs 2018;  
510 78(2):231-244.

511 25. McMullan BJ, Andresen D, Blyth CC, et al. Antibiotic duration and timing of the  
512 switch from intravenous to oral route for bacterial infections in children: systematic  
513 review and guidelines. Lancet Infect Dis. 2016; 16(8):e139-52.

514 \*This review provides recommendations on antibiotic duration and timing of switching  
515 between formulations for children.

516 22-26. United Nations. Population Division: World Population Prospects 2019.

517 [Accessed 23 Aug 2019], available from: <https://population.un.org/wpp/>

518 27. European Medicines Agency. Guideline on the evaluation of medicinal products

519 indicated for treatment of bacterial infections. 2011. [Accessed 07 Nov 2019],

520 available from:

521 <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation->

522 [medicinal-products-indicated-treatment-bacterial-infections-revision-2\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-2_en.pdf)

523 23-28. EUCAST. European society of clinical microbiology and infectious diseases.

524 [Accessed 16 Aug 2019]; available from: <http://www.eucast.org/>

525

526

527

528

529

530

531

532

533

534

535

536

537

538

539

540



541

542

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

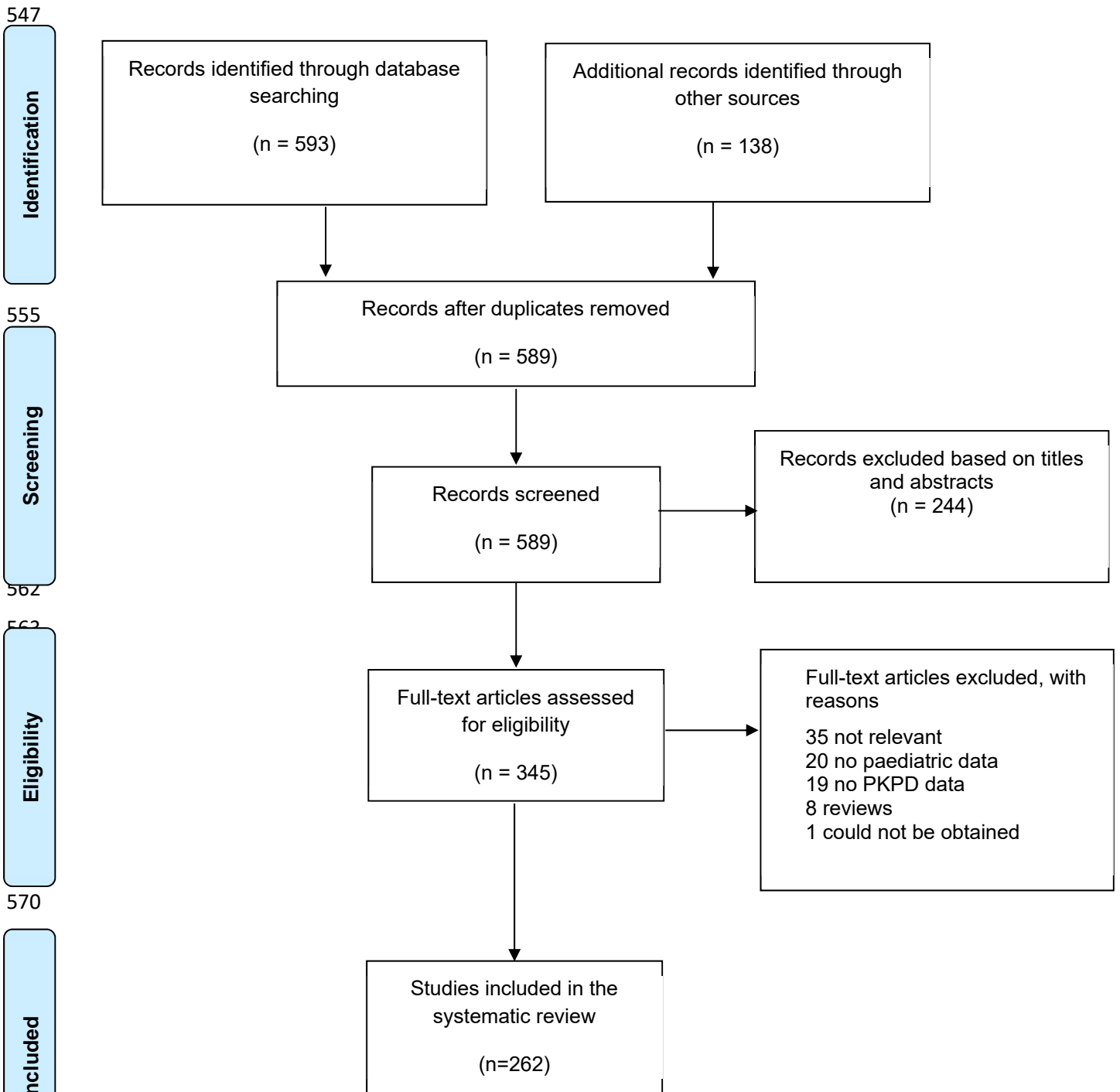
Drug	Total number of studies*	Country (no. of studies)
Amikacin	22	Belgium (6), Canada (1), China (1), France (3), Germany (1), Greece (1), Israel (1), Italy (1), New Zealand (1), South Africa (2), South Korea (1), USA (3), Netherlands (1)
Amoxicillin	8	Australia (1), Brazil (1), Germany (1), Netherlands (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

544



546 **Figure 1. Study selection flow chart**



**Table 2. General description of included studies per drug**

<b>Drug</b>	<b>No. of studies*</b>	<b>Publication years</b>	<b>Sample size</b>	<b>Population age</b>	<b>Route of administration</b>
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**

Antibiotic	Neonates		Children	
	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 <del>12</del> <u>8</u> hours	50 - 100	Every <del>12</del> <u>8</u> 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

Antibiotic	Neonates		Children	
	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](#)

<b>Key Access group</b>	<b>Watch group</b>
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

*Appropriate international non-proprietary drug name*

**AND**

(pharmacology OR pharmacokinetic\* OR pharmacodynamics\*).tw.

**AND**

Exp administration, oral/  
(Oral\$ OR per os or po).tw.

Infusion, intravenous/  
injections, intravenous/

injections, intramuscular/

(intravenous\$ OR intra-venous\$ OR iv OR intramuscular\$  
OR intra-muscular\$ or im OR parenteral\$).tw.

OR

**AND**

exp newborn/ OR infant/ OR exp child/ OR adolescent/

(infant\* OR child\* OR newborn\* OR babies or neonate\* or preterm\*  
or premature\* or full-term\* or boys or girls or adolescen\* or paediatric\*  
or pediatric\*, teen\*, young child preschool child\*).tw.

OR

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