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# **GAPPS (Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies) A Critical Appraisal System for antimicrobial PKPD studies – Development and Application in Paediatric Antibiotic studies**

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## **Abstract**

### Introduction

There are limited data on optimal dosing of antibiotics in different age groups for neonates and children. Clinicians usually consult paediatric formularies or online databases for dose selection, but these have variable recommendations, are usually based on expert opinion and are not graded based on the existing pharmacokinetic-pharmacodynamic (PKPD) studies. We describe here a potential new tool that could be used to grade the strength of evidence emanating from PKPD studies.

### Areas covered

A scoring system was developed ( GAPPS tool) to quantify the strength of each PK assessment and rate the studies quality in already published articles. GAPPS was evaluated by applying it to paediatric PKPD studies of antibiotics from the 2019 Essential Medicines List for children (EML<sub>c</sub>), identified through a search of PubMed.

### Expert opinion

Evidence for most antibiotic dose selection decisions was generally weak, coming from individual PK studies and lacked PKPD modelling and simulations. However, the quality of evidence appears to have improved over the last two decades.

Incorporating a formal grading system, such as GAPPS, into formulary development will provide a transparent tool to support decision making in clinical practice and guideline development, and guide PKPD authors on study designs most likely to influence guidelines.

Keywords: Antibiotic dosing, Grading Evidence, Paediatric Dosing, PKPD, WHO EML<sub>c</sub>

## 1 INTRODUCTION

2

3 Recently the WHO essential medicines list for children (EMLc) has classified antibiotics  
4 into the following groups: Access, Watch, Reserve (AWaRe). This provides a new  
5 metric for antimicrobial stewardship to monitor appropriate use of antibiotics in children,  
6 as antibiotics are the most commonly prescribed drug class in this population [1-11].  
7 However, data on optimal dosing in different paediatric age groups are sparse for most  
8 of these drugs. Information on paediatric dosing has often been omitted from drug  
9 labelling information, although regulatory authorities now demand this information in  
10 paediatric investigational plans for newly registered drugs [12]. Further compounding  
11 the lack of information on antibiotic dosing for older drugs is that unlicensed and off-  
12 label use of medicines in paediatric clinical practice is globally widespread [13].  
13 Formularies are one of the tools available to clinicians to inform dosing but vary between  
14 countries and usually lack referencing or grading of their stated recommendations [14].  
15 Part of the problem has been the lack of a widely accepted method to grade  
16 pharmacokinetic-pharmacodynamic (PKPD) studies. We therefore have developed a  
17 simple tool to grade dose recommendations for antibiotics regarding their PKPD  
18 evidence, which can provide a transparent rationale for evidence-based clinical  
19 recommendations.

20

### 21 *Evidence-based dosing in children*

22

23 Dose recommendations for children have mostly been derived from adult PK studies  
24 [15,16]. Assuming linearity between drug exposure and body weight, as in some early  
25 recommendations, does not correctly account for growth and maturation processes  
26 [17,18], lacks empiric evidence, and may result in inappropriate systemic drug  
27 exposures of many drugs in neonates, infants and children [19,20]. Extrapolation of

28 dosing from adults is better accomplished by acknowledging the standard principle, that  
29 PK processes scale with allometric size in children, and include terms for expected  
30 maturation in neonates and infants [21,22].

31 Globally, the most widely referred to paediatric formularies on antibiotic dosing are the  
32 WHO Pocket Book on Hospital Care in Children, the USA Red Book, the UK British  
33 National Formulary for Children (BNFc), and the European Blue Book [23-25]. In  
34 addition, several national formularies have been developed and published in the  
35 country's official language. Although formularies have been well established in clinical  
36 practice and their content is reviewed by a board of experts in the field, the quality of  
37 the evidence included from PKPD studies is generally not formally assessed. The Dutch  
38 Paediatric Formulary provides a comprehensive reference list associated with each  
39 recommendation [26], based on advice from an editorial board, but again the strength  
40 of the evidence is not given.

41

42 To assess what is needed for adequate reporting on clinical pharmacokinetic studies  
43 Kanji et al. [27] performed a Delphi survey resulting in a checklist with 24 necessary  
44 items. The checklist can be seen as a good basis to establish standards for clinical  
45 pharmacokinetics, as it facilitates reporting clinical pharmacokinetic studies in a more  
46 standardized way and therefore also aids in grading their evidence by a standard  
47 conduct.

48 The lack of a standardized approach to assessing PKPD evidence likely contributes to  
49 variation in guidance, and therefore in clinical practice. Due to increasing rates of  
50 antimicrobial-resistant infections, robust evidence-based prescribing guidance to  
51 support optimal dosing strategies is important. Critical appraisal of the design conduct  
52 and analysis of PKPD studies is essential to optimal dosing, particularly with the  
53 increasing use of population analyses in paediatric dosing studies. Critical appraisal  
54 methods are now needed to assess PKPD evidence along with the evaluation of study  
55 quality in order to assess the quality of evidence for each drug.

56

57 We therefore aimed to describe the development and initial application of a new  
58 Grading and Assessment system for PKPD studies (GAPPS) to evaluate the strength  
59 of the evidence underlying dosing recommendations for antibiotics used widely in the  
60 treatment of paediatric infections.

61

62 **METHODS**

63

64 *Literature Search*

65

66 The data used were from a systematic review on PKPD studies on antibiotic use in  
67 neonates and children. In brief, the literature searches in Pubmed and EMBASE were  
68 from 1966 to 31 May 2018. Only PK related studies were included. Studies on  
69 Therapeutic Drug Monitoring or reporting plasma concentration without any PK  
70 parameters calculated were excluded. Study eligibility was independently assessed by  
71 two authors (from AR, SG, YH, CJ) and disagreements resolved by a third reviewer  
72 (YH). Full details are given in Rashed et al. *Pharmacokinetics of the antibiotics in the*  
73 *Access and Watch groups of the 2019 WHO Model List of Essential Medicines for*  
74 *Children: A systematic review*, Expert Review of Clinical Pharmacolgy, submitted  
75 08/2019.

76

77 *Developing GAPPS (Grading and Assessment of Pharmacokinetic-*  
78 *Pharmacodynamic Studies)*

79 In accordance with the GRADE systems methodology [28], scoring systems were  
80 developed for GAPPS to account for the analytical strength of the methods used to  
81 derive reported PK Parameters for each PKPD evidence (Dosing Evidence Score,  
82 DES), as well as the quality of the underlying study (Quality of Evidence Level, QoE).  
83 The results of both assessments were then summarized to give one of three strength  
84 of recommendation levels (“weak”, “intermediate”, “strong”). There are several  
85 decisions made in selecting the best model when conducting a PK study. Any PK model  
86 is inherently a simplification of reality and each model makes some concessions. PKPD  
87 studies differ in their analytical approach, observational quality and model validation.

88 Each of these qualities was incorporated into the GAPPS analysis (Figure 1).  
89 Introductory descriptions of each of the metrics assessed by the GAPPS system and  
90 can be found in Supplement 1.

91

### 92 *Scoring evidence using PKPD Dosing Evidence Score*

93

94 Studies were scored using the PKPD Dosing Evidence Score (Figure 1). The scoring  
95 system accounts for the

- 96 i) Analytical Approach (target identification, simulation-based dosing  
97 recommendations); Observation Quality (meta-analysis with prospective or  
98 retrospective data pooling);
- 99 ii) Model Appraisal and Validation (Observation-based and simulation-based  
100 diagnostics),
- 101 iii) Consistency of the model structure with other available evidence.

102

103 It was developed by an expert group, that comprised of paediatricians, paediatric clinical  
104 pharmacologists and pharmacists based in Europe as part of the Global Research in  
105 Paediatrics (GRiP) work plan [29].

106

### 107 *Evaluation of Quality of Evidence using the GAPPS Grading System*

108

109 The QoE score was used to rate the underlying study design. The highest achievable  
110 quality level is given by a meta-analysis performed on the raw PK-data of previously  
111 published prospective studies, level 1a. If a study was performed on data from  
112 prospective data warehousing or pooling, level 1b was assigned.

113 Data from retrospective pooling or analysis was given the level 2a. When external data  
114 was available for validation purposes only, the study was rated level 2b. Dose



115 recommendations based on simulation or bridging methods without extra data pooling  
116 were assigned QoE level 2c.

117 The QoE level 3 was assigned for individual PK studies with no simulations performed,  
118 level 4 was given if a case study was reported with PK or TDM described.

119

### 120 *Assigning Strength of Recommendation using the GAPPS Grading System*

121

122 Levels from the GAPPS assessment of QoE were grouped into three categories of  
123 strength of recommendation. The strength of recommendation was determined by  
124 assigning the corresponding category for QoE Scores: Strong with QoE levels 1a, 1b,  
125 2a or 2b; Intermediate with QoE levels 2c or 3 or Weak with the QoE level 4.

126

127 **RESULTS**

128

129 *Antibiotic studies*

130

131 A total of 237 studies were identified that reported on the 28 selected antibiotics from  
132 the EMLc 2019 (13 beta lactams, 10 non-beta lactams). The most commonly studied  
133 antibiotics were gentamicin 53/237 (22.4%), vancomycin 41/237 (17.3%) and amikacin  
134 19/237 (8.0%). Non-beta lactams 159/237 (67.1 %) were more studied than beta  
135 lactams 78/237 (32.9%). There were 5 antibiotics (phenoxymethylpenicillin, procaine  
136 benzylpenicillin, doxycycline, nitrofurantoin and spectinomycin) for which no suitable  
137 study was retrieved, leaving 23 Antibiotics for analysis.

138

139 *Dosing Evidence*

140

141 Across all papers analysed, a median DES of 3 was scored, ranging from 1,  
142 individual descriptive PK study without any additional information available, to  
143 12, where a full PKPD study with target identification was performed, including  
144 information on model performance and validation. A DES of 3 was also the most  
145 frequently reported score, followed by a score of 2. The next most frequent  
146 scores were 7 and 5. The least frequent reported scores were 11 and 12. The  
147 frequencies of the reports' scores are shown in Figure 2, along with the Grading  
148 of the DES, that is subsequently used as a measure of quality of evidence.  
149 The median and ranges of the DES for each of the studied antibiotics is  
150 summarized in Table 1. The median DES varied somewhat, but low-quality

151 studies were identified for all antibiotics. Studies rated as providing strong quality  
152 evidence based on the DES were identified for 12 of the 28 reviewed antibiotics.  
153

#### 154 *Quality of Evidence*

155

156 The most frequent QoE grade based on study design and methods was level 3,  
157 as 153/237 (64.6%) were performed as an individual PK study with no simulation  
158 identified (Table 2, Figure 3). The next most frequent study grade was level 2c  
159 with 64/237 (27.0%), where studies included recommendations based on  
160 simulation or bridging methods. 7/237 (3.0%) studies were performed as  
161 prospective data warehousing/pooling (1b), whereas 7/237 (3.0%) were non-  
162 systematic/ retrospective data pooling/analysis (level 2a) and 4/237 (1.7%)  
163 studies contained external data collection /validation (level 2b). Only one study  
164 1/237 (0.4%) was rated Level 4, a case study with PK or TDM described, as well  
165 as just one study met the highest QoE 1a (meta-analysis of raw PK data).

166

## 167 **DISCUSSION**

168 Acknowledging GRADE philosophy [30], that evidence in the medical literature should  
169 be rated by finding categories of reliability for individual studies, we developed and  
170 employed an explicit, potentially reproducible methodology (the GAPPS system) for the  
171 assessment of PKPD studies. We then used GAPPS to assess 237 PKPD studies  
172 giving evidence for 23 paediatric antibiotics recommended by the WHO, which is to our  
173 knowledge the largest such review to date. This assessment of PK studies using the  
174 GAPPS system has demonstrated that there remains a strikingly poor evidence base  
175 for paediatric antibiotic dosing.

176 The GAPPS system can categorize PKPD studies starting with the highest level of most  
177 reliable studies, a meta-analysis of raw PK data, to the low level and least reliable case  
178 studies and expert opinions based on in-vitro studies. Standardized appraisal of PKPD  
179 evidence has an important role in facilitating the prioritization of research and  
180 development resources by identifying areas where the least information about  
181 optimized dosing exists. Systematic assessment of dosing evidence is a useful tool  
182 which can be used for other vulnerable and less studied populations, where significant  
183 PK changes are expected, including pregnant women, the elderly or patients suffering  
184 from organ failure, needing renal replacement therapy or extracorporeal membrane  
185 oxygenation [31-33]. PK parameters, needed for dose finding, cannot be extrapolated  
186 in a simple linear way from adults to children. Underlying growth and maturation  
187 processes need to be considered by including allometric size scaling and when it comes  
188 to neonates and infants, maturation functions of the predominant eliminating organ[34-  
189 36]. If the population of interest has additional underlying conditions, such as paediatric  
190 haemato-oncology patients, HIV, malnutrition, NICU or PICU patients, additional  
191 physiological changes need to be included.

192 Proper investigation of PK in these settings is feasible but since they involve the use of  
193 assumed biological prior knowledge ideally PK data in the population of interest is  
194 required, in order to confirm extrapolation results. Our study has now developed a  
195 systematic way to grade the evidence arising from extrapolation and clinical PKPD  
196 study results.

197 With a median DES of 3 and median Quality of Evidence level 3, the investigated  
198 resources for dose recommendations were dominated by individual PK studies, mostly  
199 performed in the 1980s and 1990s, with relevant covariates available but lacking PKPD  
200 modelling and simulations to derive appropriate dose recommendations. Nevertheless,  
201 it is encouraging that the DES trajectory with time indicates that the quality of paediatric  
202 antibiotic PKPD research has probably improved over the last two decades (Figure 4).

203 An increase in DES over the last two decades, independent of the number of studies

204 published in the respective years, possibly reflects the increasing availability of more  
205 formal regulatory guidance documents and software, as well as improving  
206 computational power.

207 In 1999 the US Food and Drug Administration released the first version of their  
208 “Guidance for Industry: Population Pharmacokinetics”, providing details on how to  
209 conduct a population PK analysis [37]. This document has undergone continuous  
210 updating in draft status since and serves as one of the major guidance documents for  
211 conducting PKPD studies.

212 With not only industry, but also academic institutions and research organizations,  
213 adapting their PK studies’ standard conduct modelling and simulation has improved, as  
214 well as PK study planning and led to the emergence of PK simulation tools into clinical  
215 routine[38,39]. More sophisticated PKPD models are now feasible, including more  
216 computationally intensive estimation algorithms and quantitative systems  
217 pharmacology approaches, resulting in higher quality of PKPD research[40-42].

218

### 219 *Strengths and Limitations*

220 The pediatric population is very heterogenous, consisting of large age and weight  
221 ranges and, when it comes to antibiotic use, various potential underlying conditions that  
222 need to be taken into consideration.

223 To our knowledge, this is the first PKPD grading system to be applied to paediatric  
224 antibiotic studies. We believe that our proposed grading system could form the basis  
225 of a generic way to grade all PKPD studies and could be extended to cover analyses  
226 performed in adults, as well as various special populations. However, we acknowledge  
227 that GAPPS in itself is not evidence based, emerging from a consensus of a small  
228 number of experts. It certainly needs to be developed further (e.g. using a Delphi  
229 approach amongst a broader range of contributors) and validated before being adopted  
230 into practice. For example, the relative superiority of varying modelling approaches is

231 actively debated amongst PKPD researchers and further discussion of the hierarchy  
232 adopted in GAPPS might slightly affect studies' scores. Additionally, variability in study  
233 size or even the use of sample size and power estimation methods is not reflected by  
234 the current scoring system and will be a valuable addition in future adaptations of the  
235 GAPPS system. Furthermore, application of the GAPPS system to studies found  
236 through the literature review manually is subject to the reviewer's assessment of the  
237 data. Our systematic review may not have identified the entirety of clinical research in  
238 this field, but it is unlikely that any missed studies would change the overall result of  
239 poor but improving evidence. Recognizing that only one of the 237 assessed resources  
240 was graded with a QoE grade of 1a may require reassessment of what is realistically  
241 achievable in the context of paediatric PK research.

242

243 *Possible explanations for the poor evidence-base*

244

245 There are several possible explanations for the weak evidence base provided by  
246 paediatric PKPD studies of antibiotics. Low parental consent rates, heterogenous  
247 populations and ethical concerns can lead to small sample sizes [43], which in turn limit  
248 the complexity of analytical approaches which can be used. This hurdle can be  
249 addressed with innovative clinical trial designs, facilitated by pharmacometrics with the  
250 availability of power calculation methods and optimal design methods [44-46]. Broad  
251 inclusion criteria and utilization of drugs administered per standard of care,  
252 opportunistic drug sampling and scavenged PK samples have been effective tools in  
253 the past [33].

254

255 Another explanation is the heterogeneity in reporting of PKPD studies which hampers  
256 individual patient data meta-analysis of studies. Key guidelines for reporting population  
257 pharmacokinetic modelling are the US FDA Guidance for Industry: Population  
258 Pharmacokinetics [37] and European Medicines Agency (EMA) Guideline on Reporting

259 the Results of Population Pharmacokinetic Analyses [47]. In February 2017 a new EMA  
260 Guideline on the use of pharmacokinetics and pharmacodynamics in the development  
261 of antimicrobial medicinal products came into effect. However, there is limited  
262 consensus on reporting, and it remains a developing field [27,48,49]. The International  
263 Society of Pharmacometrics (ISoP) [50] has now formed working groups for data  
264 standards and model evaluation as part of a standards and best practice committee,  
265 but further consensus is needed especially for paediatric pharmacokinetic reporting and  
266 meta-analytical methodology for traditional and population studies.

267

## 268 **Expert Opinion**

269

270 Information on paediatric dosing, especially across the different age groups is sparse  
271 for most antibiotics. As guidance for dose finding is mainly provided by formularies and  
272 online data bases, there is a need to grade their evidence base to make  
273 recommendations more transparent regarding the underlying analytical approaches  
274 and study design.

275 A grading system such as the GAPPS system can categorize PKPD Studies starting  
276 with the highest level of most reliable studies, a meta-analysis of raw PK data, to the  
277 low level and least reliable case studies and expert opinions based on in-vitro studies.

278 Most evidence on paediatric dosing in the reviewed paediatric studies on  
279 antibiotics comes from individual PK studies. This is reflected in the median dose  
280 evidence score of 3, showing that most publications are lacking PKPD modelling  
281 and simulations. Nevertheless, with more guidance becoming available and  
282 software applications as well as computational power improving, the quality of  
283 evidence increased over the last two decades, with more sophisticated

284 modelling and simulation techniques being use ins study planning and dose  
285 finding of more recently approved antibiotics.

286

287 Standardized appraisal of PKPD evidence has an important role also in facilitating the  
288 prioritization of research and development resources by identifying areas where the  
289 least information about optimized dosing exists. Given the poor evidence-base for  
290 widely used older antibiotics, there is a need for collaboration between paediatric  
291 pharmacokinetic researchers and clinical trial networks internationally to tackle the  
292 evidence gaps in a complementary and strategic manner.

293

294 As formularies are increasingly becoming available electronically – either as e-books or  
295 desktop and mobile applications – direct in-line links to evidence and references for  
296 different dosing schedules should be encouraged. Reporting the GAPPs level of  
297 evidence and thus making the primary evidence along with its expert grading available  
298 to prescribers would allow them to gauge the quality of data underlying the dosing used  
299 in practice.

300

301 In 2017, the WHO published a list of antibiotic-resistant "priority pathogens" which pose  
302 the greatest threat to human health [51]. The list was drawn up to guide and promote  
303 research and development of new antibiotics and more research on the repurposing of  
304 older, less well studied drugs. The designation of a list of Access antibiotics by the WHO  
305 should provide a focus on the optimal dosing of this important group of medicines for  
306 children. A systematic appraisal of PKPD evidence of Access and Watch antibiotics  
307 focusses attention on the weakness of the evidence for current dosing guidance. The  
308 Blue Book formulary was the first paediatric formulary to alert prescribers to the  
309 potential strengths and weakness of the dosing guidance using smiley/sad faces.  
310 Prescribers need to be aware that potential treatment failure or unexpected toxicities



311 could be related to inadequate or over dosing following guidance correctly based on  
312 inadequate primary data.

313 The potential next step is to extend this analysis to other classes of medicines for  
314 children. International collaboration is then required between the leading paediatric  
315 formularies internationally, potentially convened by the WHO. Following a more  
316 thorough analysis of the data, a more harmonized consensus on current guidance can  
317 be achieved between formularies. In parallel a more formal process of research  
318 prioritization needs to be undertaken and international collaboration between the  
319 relevant stakeholders to undertake the relevant clinical studies required. This has been  
320 successfully achieved in other clinical areas, such as paediatric HIV and TB, so the  
321 principles are well established. Although there is a more considerable challenge when  
322 extending to antibiotics, the prioritization of Access antibiotics and these studies have  
323 demonstrated a clear path forward.

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## Tables and Figures

Table 1

<b>Antibiotics (studies included)</b>	<b>DES median [min - max]</b>
Gentamicin (n=53)	3[1-10]
Vancomycin (n=41)	4[2-11]
Amikacin (n=19)	3[2-11]
Meropenem (n=16)	7[1-9]
Cefotaxime (n=11)	3[2-12]
Ciprofloxacin (n=10)	5.5[2-10]
Ampicillin (n=10)	2.5[1-12]
Azithromycin (n=10)	3[2-9]
Piperacillin-tazobactam (n=9)	7[2-12]
Amoxicillin (n=7)	3[1-12]
Co-amoxiclav (n=7)	2[2-10]
Chloramphenicol (n=7)	3[2-5]
Metronidazole (n=6)	5[1-12]
Cotrimoxazol (n=6)	2.5[2-11]
Ceftriaxone (n=6)	2.5[1-8]
Clindamycin (n=5)	7[2-10]
Cefazolin (n=5)	3[2-10]
Benzylpenicillin (n=3)	6[3-8]
Cefalexin (n=2)	2.5[2-3]
Clarithromycin (n=1)	2
Cefixime (n=1)	3
Benzathine benzylpenicillin (n=1)	2
Cloxacillin (n=1)	2

Table 2

<b>Quality of Evidence</b>	<b>Number of studies (%)</b>	<b>Strength of Recommendation</b>	<b>Number of studies (%)</b>
1a	1/237 (0.4%)	Strong	19/237 (8.0%)
1b	7/237 (3.0%)		
2a	7/237 (3.0%)		
2b	4/237 (1.7%)		
2c	64/237 (27.0%)	Intermediate	217/237 (91.6%)
3	153/237 (64.6%)		
4	1/237 (0.4%)	Weak	1/237 (0.4%)

## Table legends

*Table 1 Dose Evidence Score (DES), listed as the median, minimal and maximal achieved DES score. The score metrics are listed by analysed Antibiotic*

*Table 2 Number of studies by GAPPS Quality of Evidence and Strength of Recommendation – summarized for each category*

## Figure legends

*Figure 1 The GAPPS system uses a three part sequential assessment: PKPD Dosing Evidence Score (DES, numeric scoring 1 -12), Quality of Evidence (QoE, Levels of Quality 1a -4) in summary the Strength of Recommendation in categories weak, intermediate, strong.*

*Figure 2 Percentages of observed Dosing Evidence Score – Score is summarized over all evaluated antibiotics.*

*Figure 3 Frequencies of reviewed studies at each Quality of Evidence Level 1a – 4, displayed per Antibiotic.*

*Figure 4 Evolution of the median Dose Evidence Score over time – black dots represent the median score across all studies reviewed per year, dashed dark grey line represents the general trend via a loeass fit of the median DES, dashed light grey line shows the number of studies reviewed per year*