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Variation in target attainment of β -lactam antibiotic dosing between international pediatric formularies

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50 ABSTRACT

51 As antimicrobial susceptibility of common bacterial pathogens decreases, ensuring optimal dosing may preserve the use of
52 older antibiotics in order to limit the spread of resistance to newer agents. β -lactams represent the most widely prescribed
53 antibiotic class, yet most were licensed prior to legislation changes mandating their study in children. As a result,
54 significant heterogeneity persists in the pediatric doses used globally, along with quality of evidence used to inform
55 dosing. This review summarizes dose recommendations from the major paediatric reference sources and tries to answer
56 the question: does β -lactam dose heterogeneity matter? Does it impact on pharmacodynamic (PD) target attainment? For
57 three important severe clinical infections - pneumonia, sepsis and meningitis - pharmacokinetic (PK) models were
58 identified for common β -lactam antibiotics. Real-world demographics were derived from three multi-center point
59 prevalence surveys. Simulation results were compared with minimum inhibitory concentration (MIC) distributions, to
60 inform appropriateness of recommended doses in targeted and empiric treatment. Whilst cephalosporin dose regimens are
61 largely adequate for target attainment, they also pose most risk of neurotoxicity. Our review highlights aminopenicillin,
62 piperacillin and meropenem doses as potentially requiring review/optimisation in order to preserve the use of these agents
63 in future.

64

65 INTRODUCTION

66 In a 2020 report on child mortality led by UNICEF and WHO¹, infectious diseases were found to be the leading cause of
67 death in children under the age of 5 years, and are estimated to cause over half of deaths in this age group². Bacterial
68 infections, increasingly involving multi-drug resistant (MDR) organisms, are responsible for a significant proportion of
69 these deaths, with pneumonia accounting for 15%, sepsis 7% and meningitis 2%, respectively¹. In many cases these
70 infectious diseases are preventable and need to be targeted both by policies aimed at prevention, but also optimal
71 treatment.

72

73 One barrier to optimal treatment is the rise of antimicrobial resistance (AMR), particularly amongst Gram-negative
74 organisms. Over the last 20 years in Malawi, blood stream isolates have changed from mainly sensitive to mainly resistant
75 to first-line antibiotics (gentamicin, ampicillin and cefotaxime), with resistance in *Klebsiella spp.* now over 90%³. This
76 concerning trend is seen throughout other low- and middle-income countries², and may mean that previous gains in
77 reductions in mortality may be impacted by infections caused by MDR organisms⁴. In an effort to reduce the spread of
78 AMR the WHO has categorised the Essential Medicines List (EML) agents into Access, Watch and Reserve antibiotics⁵,
79 to manage global antibiotic usage. This seeks to limit the use of “Watch” and “Reserve” agents where possible. *In vitro*
80 there is evidence to suggest that low antibiotic exposure can select for or induce resistance, whereas when concentrations
81 are higher resistance is less likely to appear⁶. Whilst clinical dosing guidelines should primarily recommend “Access” and
82 “Watch” agents, a key aspect of preserving their efficacy is therefore to ensure dosing is optimised.

83

84 Historically, there were limited antimicrobial studies in children but in 2003 the USA introduced the Best Pharmaceuticals
85 for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) to ensure all new agents had to be studied⁷;
86 regulators in other territories followed suit shortly thereafter. This meant that new antimicrobial agents were formally
87 studied - although those studies often lag significantly behind adult development⁷. Since most antimicrobials in the WHO
88 EML “Access” and “Watch” groups were licensed before 2003, inconsistent dosing guidelines are common. By far the
89 largest proportion of “Access” and “Watch” agents are the β -lactams, which were licensed prior to these legislative
90 changes and therefore variably studied in children.

91

92 Recent large global antimicrobial point prevalence surveys have confirmed that wide variability in antimicrobial dosing in
93 children persists in clinical practice⁸. Differences include the prescribed doses, frequencies and in some cases the route of
94 administration. Information on optimal dosing across different pediatric age groups is still lacking for many antibiotics and
95 has often been omitted from drug labelling information. Formularies established by national and international expert
96 groups are one of the main resources for pediatric drug dosing guidelines used in clinical care. Many of these have
97 recently switched to digital platforms in order to increase their instant availability and contemporary information⁹.

98 Nevertheless, most formularies do not include references that informed the stated dosing recommendations. It is currently
99 unclear whether the heterogeneity in international dosing guidelines is affecting antibiotic efficacy and safety in children,
100 and if so whether certain dose guidelines should be preferred over others.

101

102 For treatment to be successful, it is commonly recognized that attaining concentrations above a certain critical target is
103 required¹⁰. The usual pharmacodynamic marker that guides antibiotic efficacy is the minimal inhibitory concentration
104 (MIC). Based on *in vitro* studies, the optimal pharmacokinetic target in relation to an organism's MIC has been defined for
105 each antibiotic: fC_{max}/MIC, ratio of maximal free drug concentration to MIC, fAUC/MIC, ratio of the area under the free
106 drug concentration time curve to MIC, fT>MIC, fraction of time of the free drug concentration being above the MIC, with
107 the latter usually used for β -lactam antibiotics¹¹. However, to define a drug's therapeutic window, an assessment of likely
108 efficacy needs to be accompanied by an assessment of the proposed dose's potential to cause adverse drug reactions. For
109 some antibiotics with narrow therapeutic windows such as nephrotoxicity associated with aminoglycosides or
110 glycopeptides, these toxicity cut-offs are well defined. For the β -lactams, toxicity thresholds are less well defined, but
111 increasing evidence points towards neurotoxicity possibly becoming dose-limiting, especially when new dosing regimens
112 such as continuous infusion dosing are gaining in popularity¹².

113

114 Focussing on three clinically important severe syndromes - pneumonia, sepsis and meningitis - this review aimed to assess
115 variability and appropriateness in pediatric β -lactam dose recommendations for selected WHO AWaRe antibiotics based
116 on the assumption that these were severe infections in hospitalised neonates and children. We collated dosing guidance
117 from national and international pediatric formularies, searched for the most appropriate model for suggested drugs and
118 simulated target attainment in a real-world setting by sampling underlying syndrome-specific populations from point
119 prevalence surveys.

120

121 METHODS

122 **Choice of β -lactam antibiotics and pharmacokinetic (PK) model selection**

123 For pneumonia, sepsis and meningitis common β -lactam antibiotic / organism (drug / bug) combinations were extracted
124 from the most recent ESPAUR Report in 2018-2019¹³. For pneumonia, the antibiotics selected were: amoxicillin-
125 clavulanate (co-amoxiclav), ampicillin/sulbactam and benzylpenicillin (penicillin G). Oral co-amoxiclav was also
126 evaluated for step-down treatment. For sepsis the following antibiotics were chosen: cefotaxime, ceftazidime, ceftriaxone,
127 co-amoxiclav, piperacillin-tazobactam and meropenem. For meningitis, cefotaxime, ceftriaxone and meropenem were
128 selected.

129

130 For each drug a pediatric PK model was identified from our recently published systematic review¹⁴. This review suggested
131 an evidence grading based on the data and modelling presented. Briefly, a scoring system was developed to rate the
132 conducted PK assessment through the PKPD dosing evidence score. On top of the score, extracted publications were then
133 assessed regarding the underlying studies' quality to derive the overall quality of evidence rating, which was summarized
134 to strong, intermediate or weak strength of recommendation. The literature search was limited to articles published on
135 pediatric PK studies for AWaRe antibiotics and the search was conducted in PubMed. A graphical overview of the scoring
136 system can be found in Supplemental Figure 1. The search was repeated for the subsequent time frame May 2018 to
137 October 2020 to include more recently published literature.

138

139 For the current assessment, PK models were chosen based on their quality of evidence rating. Where pediatric models
140 were not available, adult models were scaled down to pediatric populations by including allometric scaling and maturation
141 functions.^{15, 16, 17, 18} If multiple models of the same evidence score were found eligible, a decision was made taking size of
142 the modelled cohort, published goodness-of-fit criteria, as well as the included significant covariates available in the point
143 prevalence data set into account. For the models designated for our simulations model code was retrieved from the
144 publication's supplementary information. If model code was not published, the authors were contacted to share the
145 original code.

146

147 **Neonatal and pediatric demographic population development**

148 Demographics for a population of hypothetical neonates, infants and children with pneumonia, sepsis and meningitis was
149 then generated. Real demographics were sampled using R from three different data sets: a one-day point prevalence
150 survey (PPS) on antibiotic prescription, which was collected from the Global Antimicrobial Resistance, Prescribing and
151 Efficacy in Neonates and Children (GARPEC) Network⁸, the Global Point Prevalence Survey on Antimicrobial
152 Consumption and Resistance (Global PPS) network⁸ and the Antibiotic Resistance and Prescribing in European Children

153 (ARPEC) project¹⁹. Patients aged <19 years receiving at least one antibiotic on the day of the respective survey were
154 included.

155

156 In total, 116 hospitals from 26 countries participated in the GARPEC PPS between 2015 and 2017. The Global PPS
157 survey, conducted between October 2014 and November 2015, included 335 hospitals from 53 countries. ARPEC was
158 carried out in 18 centers across 11 countries. Patients were assigned to pneumonia, sepsis or meningitis based on the
159 documented reason for starting antibiotics in the respective survey databases. From each data set the demographic
160 covariates age, weight and sex were extracted: for neonates post-natal age and gestational age (GA) were extracted and
161 post-menstrual age (PMA) calculated.

162

163 The individual patient's age-dependent typical creatinine concentration was derived from the equation by Ceriotti et al.²⁰
164 This method has previously been used to model age-adjusted creatinine in PK studies^{21, 22, 23}. Typical albumin
165 concentration was calculated based on the patients post-menstrual age in-line with previous publications^{24, 25}. The
166 demographics derived from the PPS data sets can be seen as real-world cases, and the formed subpopulations represent the
167 actual target population for each treatment indication.

168

169 **Systematic search for dosing guidelines**

170 Pediatric formularies were searched to identify the dose regimens for each antibiotic to treat each clinical infection. The
171 following national and international formularies were chosen, in order to cover the range of regimen per drug, that are
172 used globally: British National Formulary for Children (BNFc)²⁶, Dutch/German Database for Pediatric Dosing
173 (Kinderformularium)²⁷, German Pediatric Infectious Diseases Society Handbook (DGPI Handbook)²⁸, Swiss Database for
174 Dosing Medicinal Products in Pediatrics (SwissPedDose)²⁹, Indian National Centre for Disease Control guidance
175 (NCDC)³⁰, Nelson's Pediatric Antimicrobial Therapy (Bradley et al.)³¹, Manual of Childhood Infections (Blue Book)³²,
176 Report of the Committee on Infectious Diseases (Red Book)³³, and the WHO Pocket Book³⁴.

177

178 For the three infectious diseases, pneumonia, sepsis and meningitis, dose guidance was extracted from each formulary.
179 Additionally, the minimum and maximum regimen were listed alongside WHO expert consensus regimen⁵ aiming to
180 display a median regimen across all formularies. Dosing info was collected for the following pediatric age groups:
181 neonates (≤ 28 days); infants/children (>28 days – 12 years) and adolescents (>12 years).

182

183 **Pharmacokinetic-Pharmacodynamic Analysis**

184 Simulations for the chosen drugs' PKPD relationships were conducted from the chosen models using NONMEM 7.4. Post
185 simulation processing and graphical evaluations were performed in R. For pneumonia the EUCAST non-species related
186 drug-specific sensitivity and resistance breakpoints were compared with target attainment, whereas for sepsis and
187 meningitis the breakpoints for Enterobacterales were used. Histograms of some the following example organisms drawn
188 from EUCAST MIC distribution database were displayed for comparison: *Streptococcus pneumoniae* and *Staphylococcus*
189 *aureus* for pneumonia and *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* for sepsis and
190 meningitis. The chosen organism/ antibiotic (bug/drug) combinations and extracted common, minimum and maximum
191 dose recommendations were used to generate probability of target attainment (PTA) simulations within the targeted
192 subpopulation by using the PKPD model with the highest level of evidence in this setting. The evaluated targets were
193 dependent on the respective simulated drugs. Susceptibilities were displayed as MIC distributions, breakpoints reflecting
194 sensitive and resistant isolates were derived from the EUCAST database for the respective microorganisms. For
195 simulations in each clinical condition 10000 demographic sets were sampled with replacement from the GARPEC/Global
196 PPS/ARPEC subpopulation datasets. For clinical markers creatinine, creatinine clearance and albumin, that were derived
197 from age-dependent functions, a variance of 10% around the calculated typical values was introduced.

198

199 **Target attainment analysis**

200 Pharmacodynamic (PD) analysis was carried out through PTA assessment from the simulations. Targets were chosen
201 depending on the pharmacodynamics of the investigated drug/ drug class. As suggested by Mouton et al.³⁵ the fraction of
202 time above MIC is seen as the appropriate target for β -lactam antibiotics. Free, unbound concentrations were used to
203 evaluate the PKPD target. For ceftriaxone, free concentration accounting for nonlinear concentration-dependent protein
204 binding was assumed³⁶. For the other agents the following fraction unbound was assumed: amoxicillin 83%³⁷, ampicillin
205 80%³⁸, benzylpenicillin 45%³⁹, cefotaxime 70%³⁹, ceftazidime 83%⁴⁰, meropenem 98%³⁷ and piperacillin 70%³⁷. In-line
206 with current guidance for severe hospitalized patients, an overall β -lactam PKPD target of 100% $fT > MIC$ within a 24h
207 time frame at steady state was chosen⁴¹. Further investigation was performed looking at 50% $fT > MIC$ for less severe
208 infections that can be found in the community setting and 100% $fT > 4xMIC$ when a critically ill population is targeted⁴².

209

210 Results from the target attainment analysis were compared graphically and numerically with isolate specific MIC
211 distributions from EUCAST clinical break-point reports. For sepsis and meningitis sensitive and resistant breakpoints
212 reflecting Enterobacterales were added. In pneumonia non-species related breakpoints were chosen.

213

214 **Toxicity analysis**

215 For the simulated drug toxicity, cut-offs were extracted from the literature. A general neurotoxicity threshold of 316 mg/L
216 was used for β -lactams in line with findings by Imani et al.¹² For cephalosporins a threshold of 35 mg/L as reported by

217 Huwylar et al.⁴³ for cefepime was chosen, which is seen as the cephalosporin with the highest risk for causing
218 neurotoxicity. Other drug specific targets reported in literature for trough concentrations correlated with a pro-convulsive
219 risk, that were tested are 64mg/L for meropenem and 157 mg/L for piperacillin when combined with tazobactam¹².

220

Accepted Article

221 RESULTS

222 **Demographic datasets**

223 After cleaning and combining the three point-prevalence data sets GARPEC/Global PPS and ARPEC, subpopulations that
224 were treated for pneumonia, sepsis and meningitis consisted of 2932, 2269 and 1358 individuals, respectively, with age
225 ranging from 23 weeks PMA to 18 years PNA, and weight ranging from 0.31 kg to 95.5kg.

226

227 Figure 1 shows the age-related weight distribution for each subpopulation with an additional panel showing the included
228 neonates. Each graph also shows the typical weight for age distribution published for preterm and term neonates by Fenton
229 et al.^{44, 45}, for up to 5 year olds by the WHO⁴⁶ and for 5 to 18 year olds by the CDC⁴⁷.

230

231 **Dosing regimen**

232 Table S1 summarises the dose recommendations for the different age groups (from preterm neonates to adolescents)
233 extracted from SmPCs and formularies, together with the common, minimum and maximum regimen.

234 Within the three different infections, pneumonia, sepsis, and meningitis 6/120 (5%), 10/180 (6%), 40/90 (44%) of the
235 single dose recommendations, respectively, were specific recommendations for the evaluated disease. Overall, for 88/390
236 (23%) dosing recommendations were lacking for the respective age group, drug and formulary.

237

238 **Selected PK models for simulation**

239 The systematic literature search and evidence grading resulted in five models with a mean dose evidence score (DES) of 8
240 [7-10]. The overall quality of evidence (QoE) was rated strong (n=2) or intermediate (n=3). The β -lactams
241 benzylpenicillin, intravenous co-amoxiclav, piperacillin-tazobactam, cefotaxime and meropenem were well described by
242 Lonsdale et al.¹⁵ (DES = 7, strong QoE) across the entire age range. Oral co-amoxiclav was simulated according to the
243 model by deVelde et al.⁴⁸ (DES=10, intermediate QoE), ampicillin-sulbactam was modelled according to Soto et al.⁴⁹
244 (DES=9, intermediate QoE), ceftriaxone according to Standing et al.³⁶ (DES=10, intermediate QoE) and ceftazidime by
245 using the model from Li et al.⁵⁰ (DES=7, strong QoE). Selected models are summarised in Supplementary Table 3.

246

247 **Evaluating Probability of Target attainment**

248 Common, minimum and maximum dosing was simulated for each drug using the chosen highest evidence models. Figure
249 2 shows the target attainment results for pneumonia, Figure 3 for sepsis and Figure 4 for Meningitis. Dark shaded areas
250 show the 90% prediction interval across the simulated subpopulation for the common regimen, with the solid black line

251 showing the population mean. Light shaded areas show the prediction interval stretching from the 5th percentile of the
252 minimum dose to the 95th percentile of the maximum dose. The simulation results were explored graphically for each
253 disease against the chosen isolates EUCAST MIC distribution through the presentation of colored histograms representing
254 the respective isolates distribution. The EUCAST sensitive and resistant breakpoints for Enterobacterales are shown as
255 solid grey lines within the sepsis and meningitis assessments. For pneumonia the EUCAST non-specific sensitive and
256 resistant breakpoints are shown.

257

258 The predicted MIC at which the targets 100%fT>MIC and 100%fT>4xMIC are crossed is reported for each antibiotic
259 alongside the EUCAST ECOFF and empiric target MIC values for the considered isolates (Supplemental Table 2).

260 The percentage of patients reaching the 100%fT>MIC PKPD target, when sensitive and resistant breakpoints for
261 Enterobacterales (sepsis and meningitis) or non-species related (pneumonia) are considered is summarized in Figure 5.

262

263 **Toxicity**

264 The probability of trough concentrations crossing the literature reported toxicity thresholds, is depicted in Figure 6. The
265 trough concentration at steady state was evaluated for every individual and the proportion of individuals crossing the
266 threshold is displayed. Only the risk of toxicity for the different cephalosporin regimens to cross the reported cefepime
267 trough threshold of 35 mg/L are shown, as other drug classes did not notably exceed the toxicity threshold for any of the
268 simulated regimens.

269

270 DISCUSSION

271 In our analysis we focussed on commonly used β -lactam antibiotics featuring in the WHO Essential Medicines List for
272 children⁵. Point prevalence surveys have revealed heterogeneity in dosing across and within countries⁵¹ and we found this
273 to be reflected in varying dosing recommendations provided by national and international formularies.

274

275 Due to developmental differences in drug handling (mainly lower clearance)⁵² neonates are usually given lower per-kg
276 doses, hence we split assessment of target attainment between neonates and children. Figures 2 – 4 show each drug's
277 PKPD target attainment trajectory across MIC values for 100% $fT > MIC$ in neonates and children. The simulated common
278 dose regimen showed third generation cephalosporin dose guidelines are generally appropriate (Figure 5). Sufficient
279 coverage was achieved for ceftriaxone when used in empiric sepsis and meningitis treatment, with at least 90% of the
280 simulated patient population being covered for sensitive Enterobacterales. Cefotaxime also showed good coverage in both
281 severe syndromes, yielding at least 80% of patients reaching the PKPD target considering sensitive Enterobacter MICs
282 (Figure 5). When MIC targets reflecting resistant breakpoints are chosen, ceftriaxone still performs well.

283

284 Considering the resistant breakpoints for Enterobacterales, ceftazidime reached at least 70% coverage in sepsis treatment
285 and cefotaxime covered at least 70% of the population for sepsis and meningitis, whereas meropenem failed to
286 successfully reach adequate concentrations in both diseases. This is largely due to the high empiric MIC cut-off of 2mg/L
287 reflecting the fact that target attainment in settings with borderline carbapenem resistance would likely require higher
288 meningitis doses even when treating sepsis and the use of an overall beta-lactam PKPD target of 100% $fT > MIC$.
289 Carbapenems show a higher post-antibiotic effect compared to other beta-lactams. A target of 20% $fT > MIC$ has been
290 shown to be bacteriostatic in *in-vitro* models, with 40% $fT > MIC$ resulting in bactericidal effects.

291

292 Whilst piperacillin-tazobactam also achieved sufficient levels in more than 75% of the pediatric population regarding
293 sensitive breakpoints (Figure 5), isolate specific ECOFFs, representing the critical epidemiological MIC that covers all
294 MICs of wild-type isolates values, are however higher than this non-species-specific value. Coverage for the resistant
295 Enterobacterales breakpoint of 16mg/L only accounts for 70% [79 -46%]. A re-analysis of the microbiology data from the
296 MERINO trial showed that infection with extended-spectrum β -lactamase (ESBL) organisms that whilst “sensitive” (with
297 MICs below 16 mg/L) were still associated with increased mortality⁵³, with insufficient target attainment a possible cause.

298

299 In pneumonia, none of the studied scenarios led to adequate coverage when considering target attainment with sensitive
300 non-species related MIC values (Figure 5). However, taking commonly detected species into account, pneumonia is
301 dominated by Gram positive strains like *S. aureus* and *S. pneumoniae*, that generally show low MICs. When examining

302 the EUCAST MIC distributions in Figure 2 describing these two strains plus the Gram-negative non type-b *H.*
303 *influenzae*⁵⁴, co-amoxiclav sufficiently covers the Gram-positive strains, whereas penicillin G and ampicillin-sulbactam
304 cover the median of the simulated population at best. When looking at sepsis, EUCAST MIC distributions for *E. coli* and
305 *K. pneumoniae* are fairly well covered by cephalosporins and meropenem. Pseudomonas, on the other hand was less
306 sensitive to most of the studied drugs (Figure 3). Pseudomonas generally causes sepsis in hospitalised
307 immunocompromised children and hence in this setting drug choices and combination therapies with better Pseudomonas
308 cover would be more appropriate than increasing the doses of the agents discussed here.

309

310 Our findings are in-line with Hartman et al.⁵⁵, who recently reviewed the pharmacokinetics and target attainment of
311 antibiotics in critically ill children, reporting, that target attainment in this patient group is suboptimal. They found, that
312 for highly monitored substances like glycopeptides and aminoglycosides, there is a large number of publications available.
313 In fact, 41 vancomycin and 53 gentamicin studies have also been detected in our previous grading evidence review with a
314 median dose evidence score of 4 [2-11] and 3 [1-10], respectively. For most β -lactams, however, the available information
315 is sparse or completely lacking for children, especially when narrowing it down to the critical care setting. Throughout
316 literature, the PKPD adequacy for β -lactams in pediatric patient populations has most commonly been assessed using the
317 following targets: penicillins 40-50%fT>MIC, cephalosporins 50-70%fT>MIC and carbapenems, which display post-
318 antibiotic effects 40%fT>MIC^{56, 57, 58}.

319

320 A current analysis by van Donge et al.⁵⁹ evaluated common amoxicillin dosing in neonates by simulating these more
321 conservative PKPD targets along with higher 100%fT>MIC or 100%fT>4xMIC and the probability of reaching
322 neurotoxic exposures. Here, low PKPD targets were well covered with common regimens. Higher targets, when a
323 PTA>90% was aspired, were failed by all regimens, with the highest simulated regimen expecting exposure above the
324 Cmax toxicity threshold of 140 mg/L.

325

326 We focused on EUCAST MIC reporting, but empiric treatment decisions are dependent on local resistance patterns and
327 may deviate from what is simulated with the non-species related MICs, globally. Figures 2 – 4 are depicted with common
328 MIC ranges and can be used for local dose regimen design based on local MIC distributions. The selection of a PKPD
329 target in antibiotic treatment depends on the severity of the targeted disease, focus of the infection, individual patient
330 factors and local resistance patterns⁶⁰. As β -lactams show time-dependent bactericidal effects, the fraction of time that the
331 free concentration is above a multiple of the MIC should be targeted. For our simulations we focussed on an overall β -
332 lactam PKPD target of 100%fT>MIC.

333

334 Bactericidal effect for β -lactam classes is detectable for $\%fT > MIC$ as low as 40% in carbapenems, and 50-70% in
335 cephalosporins and penicillins⁴¹. In critical care the 100% $fT > MIC$ target, however, resulted in favourable outcomes
336 according to the DALI trial⁴². The desired PD targets, however still remain to be elucidated across different routes of
337 administration and patient populations⁶¹. The use of continuous infusion regimen, as studied in BLING I-III for adult
338 critical care patients, is often not feasible in neonatal and pediatric settings, where IV accessibility, volumes and
339 compatibilities have to be taken into account when performing infusion management⁶².

340

341 Thus, across the heterogenous severity stages, that are seen in the simulated syndromes, a PKPD target of 100% $fT > MIC$
342 seems sensible for achieving overall clinical efficacy, with the option to accept lower coverage between 50-100% $fT > MIC$
343 (Supplemental Figures 2-4) in less severe infections and increasing the target to 100% $fT > 4xMIC$ (Supplemental Figures
344 5-7) in critically-ill patients cared for in PICU and NICU settings. These PKPD targets are used with simulations of
345 plasma concentrations as surrogates for the less accessible focusses in meningitis and pneumonia, cerebrospinal fluid
346 (CSF) and epithelial lining fluid (ELF). A drug's ability to cross into these deeper compartments correlates with its
347 physicochemical properties enabling the passage through membranes, transporter affinities and physiological conditions
348 that are also influenced by the pathology of infectious disease, such as pH-changes and membrane permeabilities⁶³. More
349 insight is needed to understand how maturation influences a drugs distribution to the site of infection and the ability of
350 plasma concentrations to serve as surrogates for this.

351 Similarly, our simulation population includes creatinine concentrations used as covariate in some of the selected models,
352 varying around the typical age-related value. Our simulations therefore represent target attainment overall.

353 To depict the influence acute kidney injury (AKI) and augmented clearance would have on the performed simulations, we
354 assessed models including the creatinine covariate. Simulated populations with at least 50% increase from baseline
355 creatinine, in line with the Kidney Disease: Improving Global Outcomes (KIDGO) criteria diagnosing AKI⁶⁴, and 50%
356 decrease in creatinine for augmented renal function are given in Supplementary Figure 8. This highlights the
357 corresponding improvement or worsening in target attainment with AKI or augmented renal function respectively.

358

359 The formularies used in this review were both national (four European, two US-American, one Indian) and international.
360 The SmPC recommendation for each drug was also studied. Despite consulting national experts, it was not possible to find
361 pediatric formularies from Brazil, China, the Russian Federation or South Africa, that were clearly endorsed nationally,
362 which is in line with a previous analysis by Mathur et al.⁹ We therefore acknowledge, that the presented dose collection is
363 strongly influenced by European and North American dose guidance. The consulted formularies each state dose
364 recommendations for almost every drug that was selected. However, there are gaps regarding age specific and disease
365 specific recommendations. The lack of information is most marked for neonates, whereas adult information is often used
366 for adolescents and is thus is available.

367

368 A trend in diversity of dose recommendations, age-banding and weight-based dosing can be found in older drugs like
369 penicillin G. For this particular drug, doses are historically stated in IU for some countries and mg in others. For co-
370 amoxiclav, some formularies state volume of a specified strength of suspension rather than a drug specific dose amount.
371 This was also found for the other fixed-combination β -lactam and β -lactamase inhibitor preparations, where it is not
372 always clearly stated whether the dose amounts in the formularies refer to the β -lactam component or the combination.

373

374 Through our previous study to grade evidence in pediatric antibiotic PK reporting^{14, 65}, supplemented by an updated
375 literature search, we identified the models used in the target attainment simulations. All models used in the simulations
376 were rated with a dose evidence score between 7 and 10, with 12 being the maximal achievable score. The overall quality
377 of evidence was rated strong or intermediate, with intermediate rating rather than strong due to most studies being
378 conducted in a single-centre setting, without additional data for validation. A key criteria for choosing appropriate models
379 was that covariate parameterisation allowed for extrapolation across the neonatal and pediatric age range, which is often
380 not possible for models developed in sub populations with empirical covariate structures⁶⁶.

381

382 Models, that are scalable across the entire pediatric age range are still lacking for many antibiotics. For β -lactams a recent
383 study by Lonsdale et al.¹⁵ developed a maturation function that is able to describe the maturation of the mostly renal
384 clearance mechanisms in β -lactams from neonates to elderly patients. For other drug classes similar investigations are still
385 missing. In adults, PK studies on antibiotics have recently focused increasingly on determining elimination and
386 distribution mechanisms in the disease and syndrome specific context. Many adult PK studies are investigating specific
387 patient subpopulations with, for example, pneumonia or intra-abdominal infections and exploring the effects of supportive
388 therapies, such as dialysis or extra corporeal membrane oxygenation (ECMO), on PK.

389 A limitation of our work is that we did not consider subpopulations of the pediatric group. In pediatrics, special
390 subpopulation PK is still not well characterised, as is the PK for most fragile pediatric subpopulation of preterms, neonates
391 and the influence of prematurity for low and very-low birthweight neonates^{67, 68}. The influence of nutritional status is also
392 lacking for most PK studies conducted in pediatrics, but is important to inform dose decisions, when treating infections in
393 underweight and malnourished children^{69, 70, 71}. Children treated on intensive care, and particularly those requiring renal
394 replacement therapy and ECMO may need altered dosing^{72, 73}.

395

396 The evaluated toxicity simulations show that for the cephalosporins, the increased meningitis dosing may be associated
397 with an increased risk of neurotoxicity (Figure 5). Apart from cephalosporins, other drug classes did not show the risk of
398 neurotoxicity in the studied scenarios and were therefore not reported in the graphic. β -lactam neurotoxicity is not well-
399 studied and difficult to distinguish from other neurological symptoms, that can occur when treating infectious disease

400 syndromes like bacterial meningitis. In the literature, mostly case reports are available. Imani et al.¹² retrospectively
401 evaluated β -lactam concentration-toxicity relationships through regression analysis concluding that penicillins like
402 piperacillin show neurotoxicity at trough concentrations as high as 361 mg/L. Animal studies report trough concentrations
403 at 157 mg/L for piperacillin and 64mg/L for meropenem toxicity⁷⁴. These targets were not or only barely (piperacillin)
404 reached with the simulated carbapenems and penicillins. For cephalosporins, cefepime is seen as the most neurotoxic drug
405 and therefore is studied more intensively compared to other drugs in this group. A threshold trough concentration of 35
406 mg/L is reported as threshold by Huwylar et al.⁴³ and served as reference concentration for this analysis. It is anticipated,
407 that other cephalosporins bare lower risks of neurotoxicity. So far case reports dominate neurotoxicity reporting for
408 cephalosporins other than cefepime and thus the cefepime neurotoxic threshold serves as a surrogate for a regimen's
409 neurotoxic potential in this review. When treating severe infections involving organisms with high MICs the potential risk
410 of neurotoxicity needs to be balanced with treatment success and resistance suppression. For example, treating
411 *Pseudomonas* infections using ceftazidime with a target of 100% $fT > 4 \times MIC$ will result in an optimal trough exposure of
412 32mg/L to cover resistant strain MICs of 8mg/L. This highlights the need of antibiotic stewardship to consider
413 personalised dosing based on patient and organism considerations.

414

415 Renal failure and drug accumulation due to impairment dominant elimination pathway is one of the main risk factors for
416 β -lactam neurotoxicity. Findings for meropenem and piperacillin/tazobactam, that relate free plasma trough concentration
417 to the high *Pseudomonas* break points suggest that fC_{min} above eight times the MIC will result in less favourable risk-
418 benefit ratio. This highlights the need to maintain a balance of sufficient exposure, while avoiding unnecessarily high
419 concentrations

420

421 Overall, our review focussed on β -lactam dosing on the EMLc Access and Watch antibiotic list. We aimed to find
422 recommendations across the entire age range and thus did not choose antibiotics such as tetracycline or quinolones, that
423 are not recommended in younger children and neonates due to their negative effects on joint, teeth and ligament
424 development. We also did not evaluate glycopeptides or aminoglycosides, as therapeutic drug monitoring is standard
425 practice, and these classes are already thoroughly studied.

426

427 CONCLUSION

428 The results of this review demonstrate that the high variability of dosing recommendations in national and international
429 formularies impacts on PKPD target attainment. Whilst to some this may seem unsurprising, since β -lactams are generally
430 thought to be drugs with a large therapeutic window, commonly used dosing schemes could routinely be set so high that
431 variability does not in fact impact target attainment. However, a combination of increasing resistance and therefore MICs,
432 and the often lack of regulatory licensing studies to set pediatric dosing, increasingly mean that choosing which guideline

433 to follow is important, and should be informed by local sensitivity patterns and disease severity in the individual or
434 population to be treated.

435

436 Pneumonia treatments show adequate target attainment in common Gram-positive infections. Here, co-amoxiclav showed
437 the best coverage across all extracted recommendations. Common regimens for cephalosporins in treatment of sepsis and
438 meningitis cover sensitive Enterobacterales infections reasonably well, although more than 75% of the pediatric
439 population adequately covered in some instances, this leaves a small but significant proportion who are not. For
440 intermediate to resistant MICs, Enterobacterales infections are covered in just over half of the population when using
441 cephalosporins, with even lower target attainment for the penicillins and meropenem. Given that piperacillin-tazobactam
442 and meropenem are less likely to cause neurotoxicity than the cephalosporins, this suggests the need for reviewing current
443 dose recommendations in settings where MICs are typically in the intermediate range. The data presented here suggest
444 that a “one size fits all” dosing recommendations may not be optimal in future and local dosing guidelines of AWaRe
445 antibiotics may indeed be warranted to reflect variation in AMR resistance patterns globally.

446

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Figure 1: Weight compared to age for the three simulated subpopulations - pneumonia, sepsis and meningitis. Black dots are single subjects filtered from GARPEC/ARPEC/Global PPS. Grey lines represent the Median, 3rd and 97th percentiles from demographic surveys by Fenton et al, CDC and WHO.

Figure 2: Probability of Target Attainment ($100\%fT > MIC$) for simulated dose regimen in the pneumonia subpopulation. Solid line – Median for common regimen; dark grey area – 90% prediction interval for common regimen; light grey area – 5th percentile of min regimen to 95th percentile of max regimen. Coloured histograms refer to the MIC distribution for common pathogens *Haemophilus influenzae* (red), *Streptococcus Pneumoniae* (blue) and *Staphylococcus aureus* (green) according to EUCAST. The grey solid vertical line represents the non-species-specific breakpoints values for each drug to guide empiric treatment.

Figure 3: Probability of Target Attainment ($100\%fT > MIC$) for simulated dose regimen in the sepsis subpopulation. Solid line – Median for common regimen; dark grey area – 90% prediction interval for common regimen; light grey area – 5th percentile of min regimen to 95th percentile of max regimen. Coloured histograms refer to the MIC distribution for common pathogens *E.coli* (red), *Klebsiella pneumoniae* (green) and *Pseudomonas aeruginosa* (blue) according to EUCAST. The grey solid vertical line represents Enterobacterales breakpoints for each drug to guide empiric treatment.

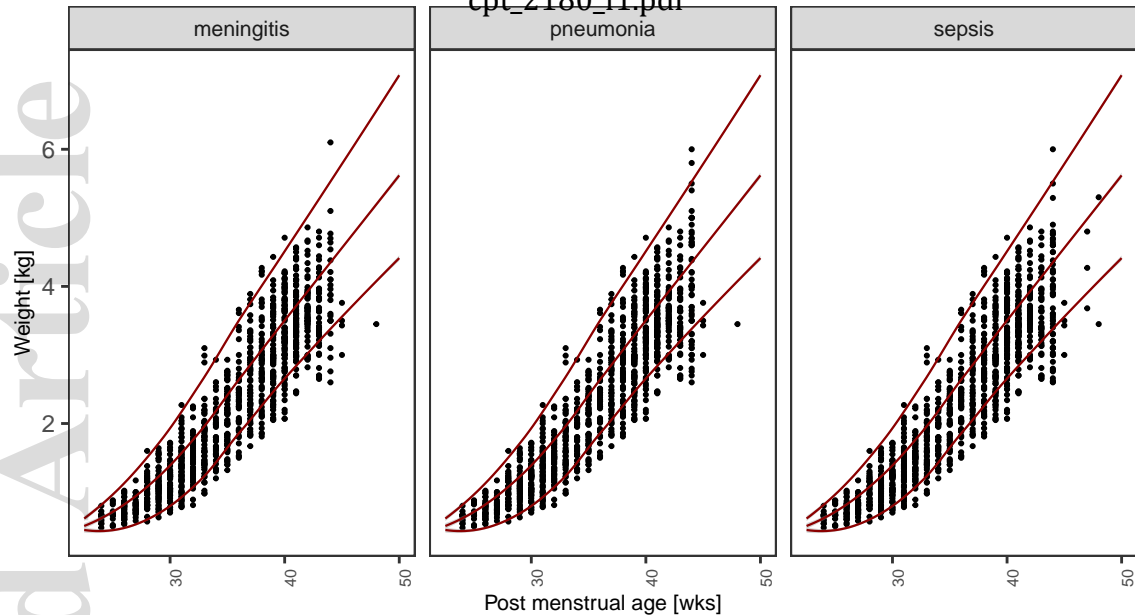
Figure 4: Probability of Target Attainment ($100\%fT > MIC$) for simulated dose regimen in the meningitis subpopulation. Solid line – Median for common regimen; dark grey area – 90% confidence interval for common regimen; light grey area – 5th percentile of min regimen to 95th percentile of max regimen. Colored histograms refer to the MIC distribution for common pathogens *Neisseria meningitidis* (green), *Streptococcus pneumoniae* (blue) and *E. coli* (red) according to EUCAST. The dark grey solid vertical line represents Enterobacterales breakpoints for each drug to guide empiric treatment.

Figure 5: Coverage calculated as percentage of individuals above the PKPD target of $100\%fT > MIC$ for each simulated drug for the three different syndromes. Each bar represents the coverage of the common regimen, with the error bar showing results of the min to max simulated regimen. Bars are split up by sensitive and resistant MIC breakpoints for Enterobacterales (sepsis and meningitis) or non-specific (pneumonia).

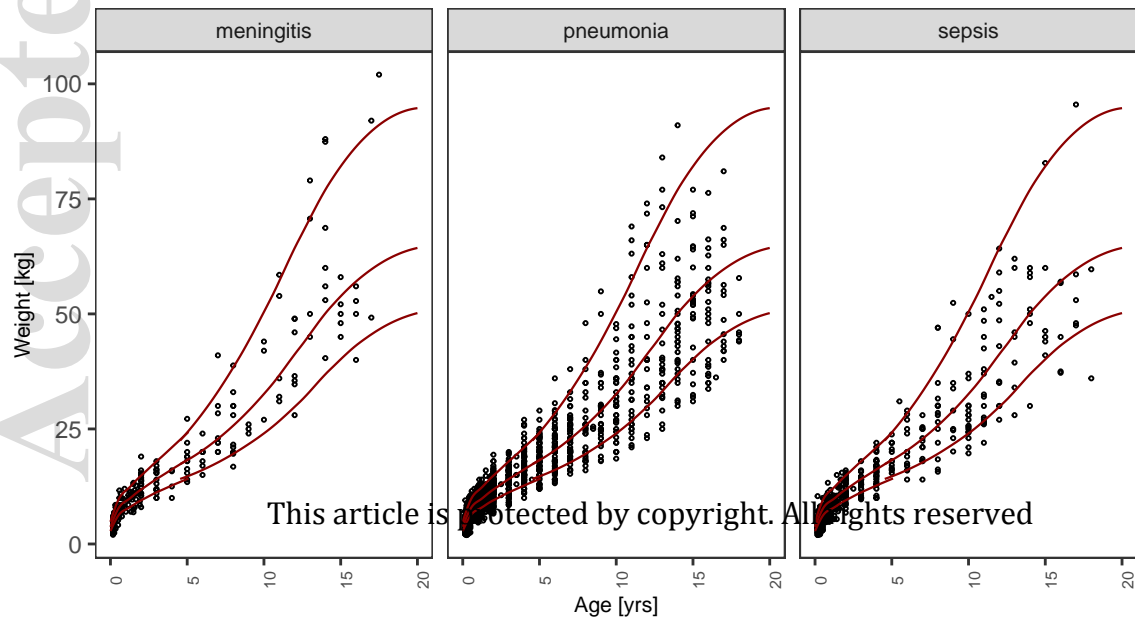
Figure 6: Percentage of Subjects above toxicity threshold (>35 mg/L) for cephalosporins and the respective syndrome. Plots are grouped by age. Each bar represents the fraction of simulated individual with a trough concentration at steady state above the toxicity threshold.

Supplementary Files:

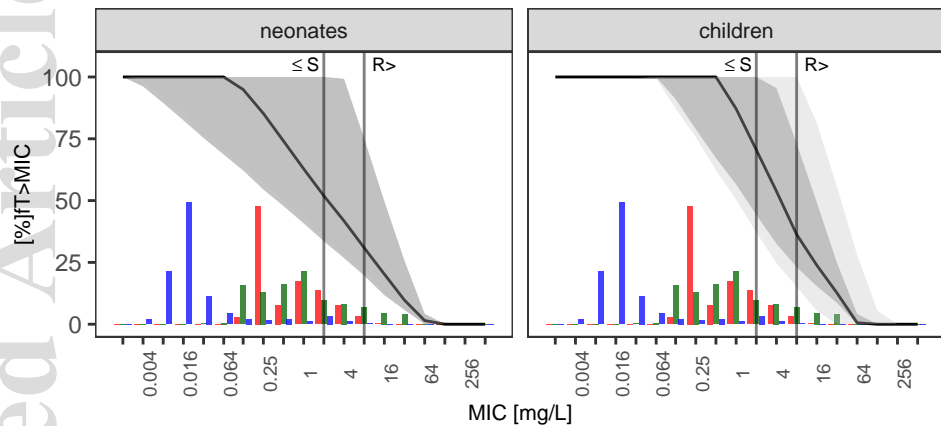
1. Table S1
2. Table S2
3. Supplemental Figures
4. Table S3



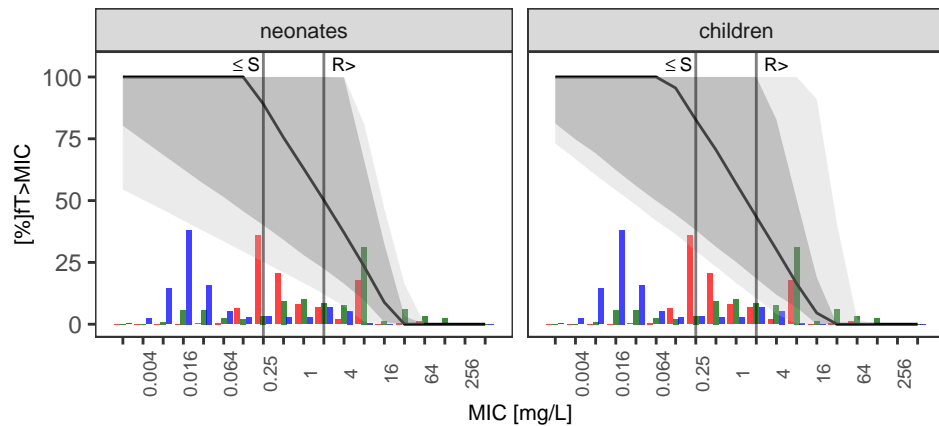
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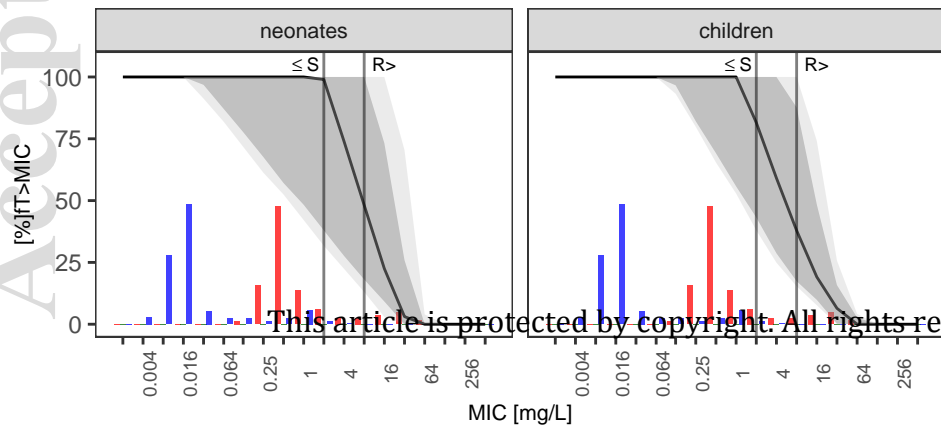
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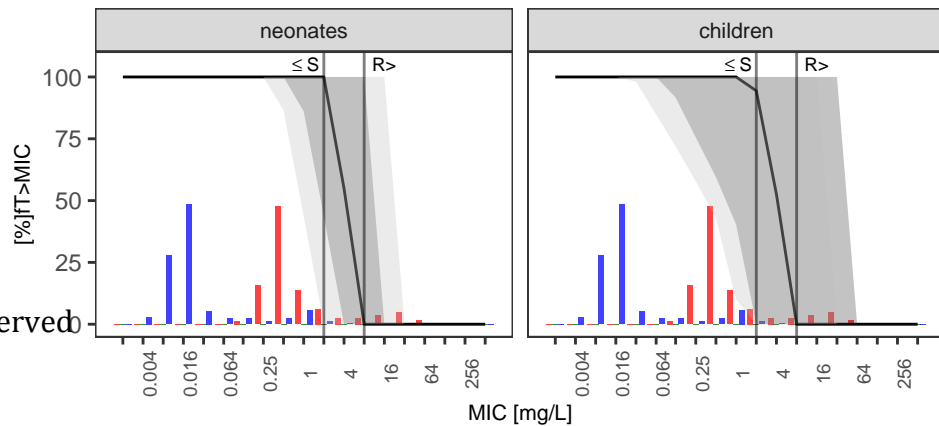
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Co-Amoxiclav – Amoxicillin IV

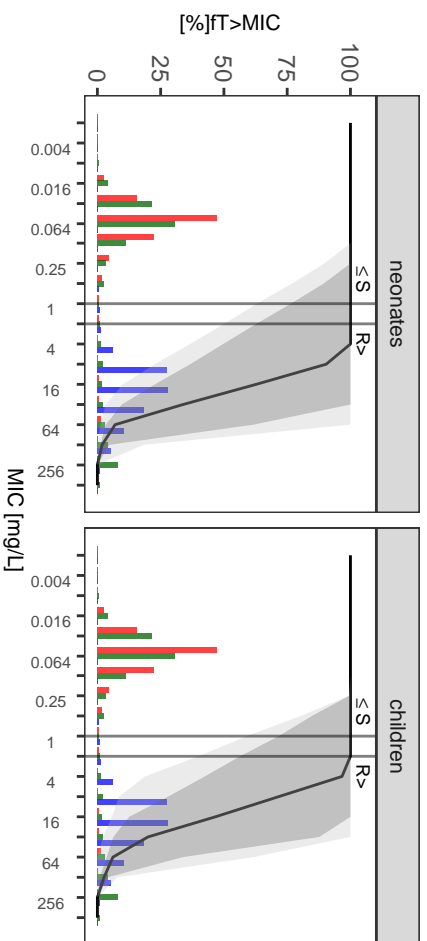


Co-Amoxiclav – Amoxicillin oral

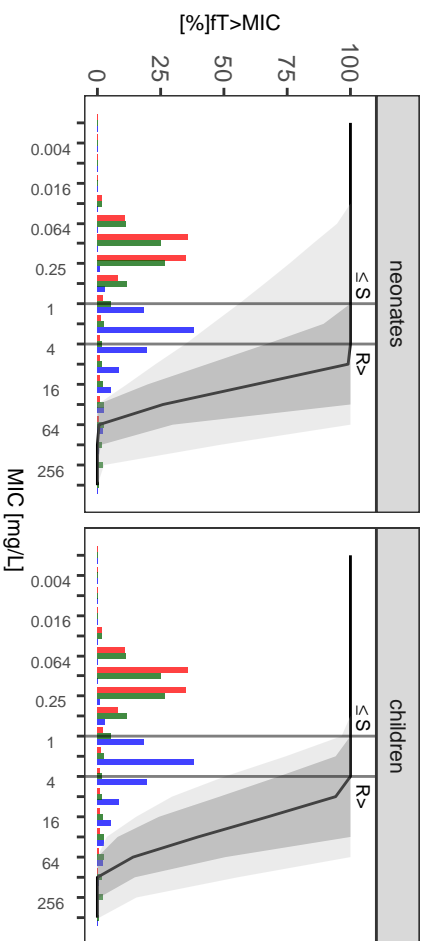


Sepsis Target Attainment

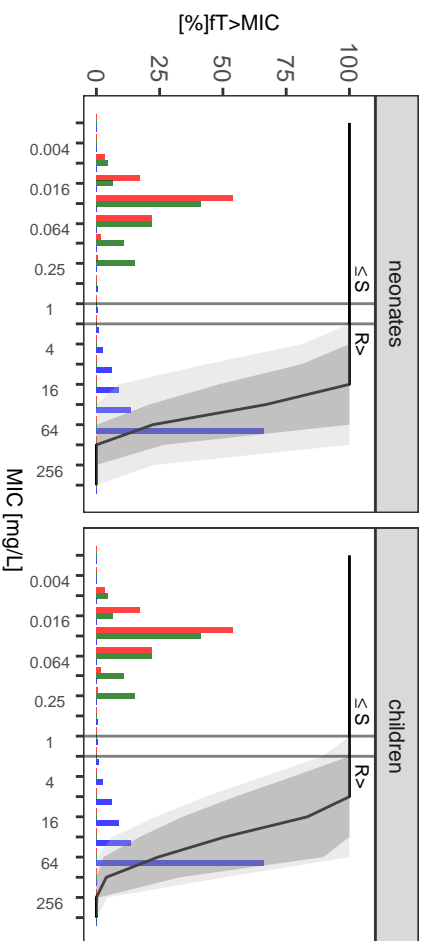
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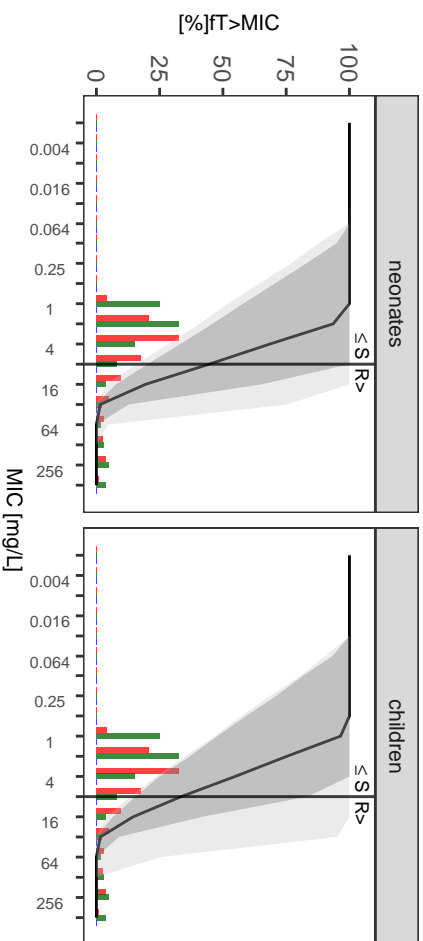
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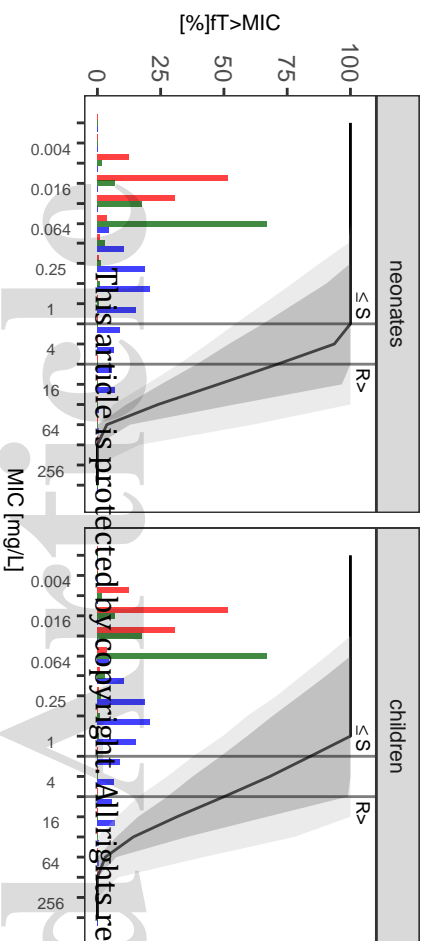
Ceftriaxone



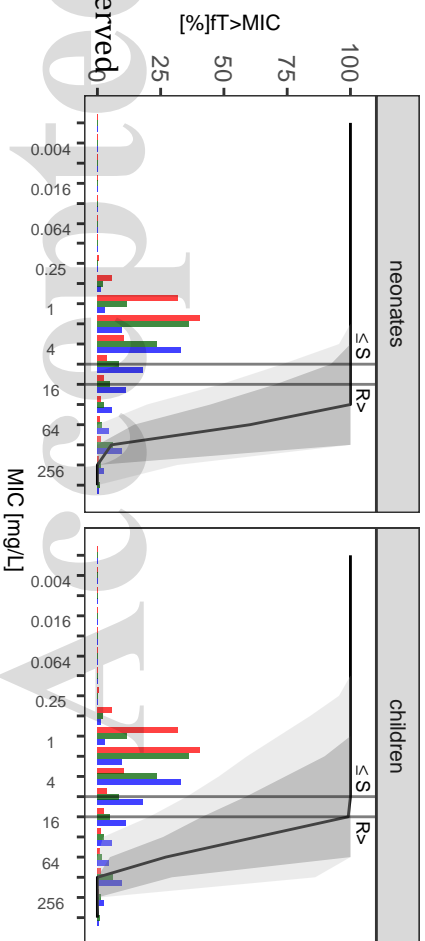
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Meropenem



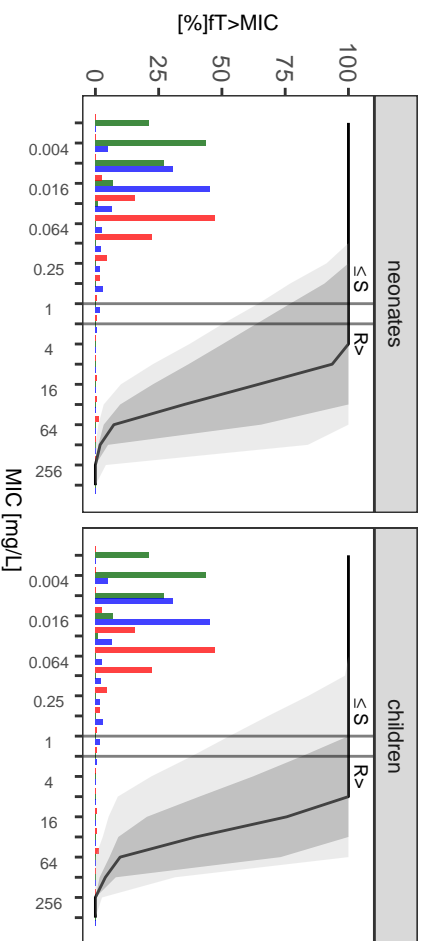
Piperacillin–tazobactam



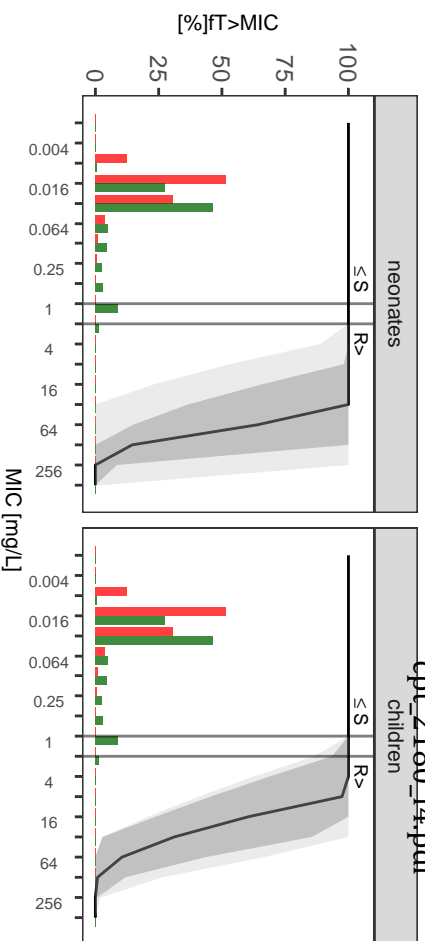
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Meningitis Target Attainment

Cefotaxime

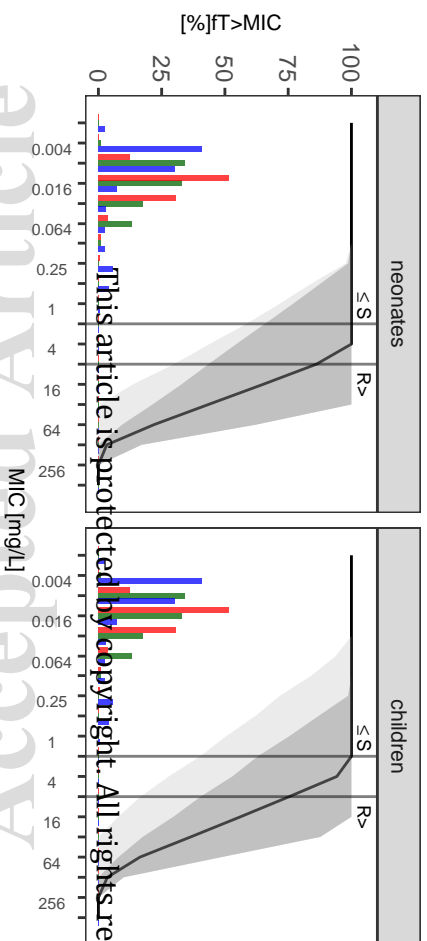


Ceftriaxone



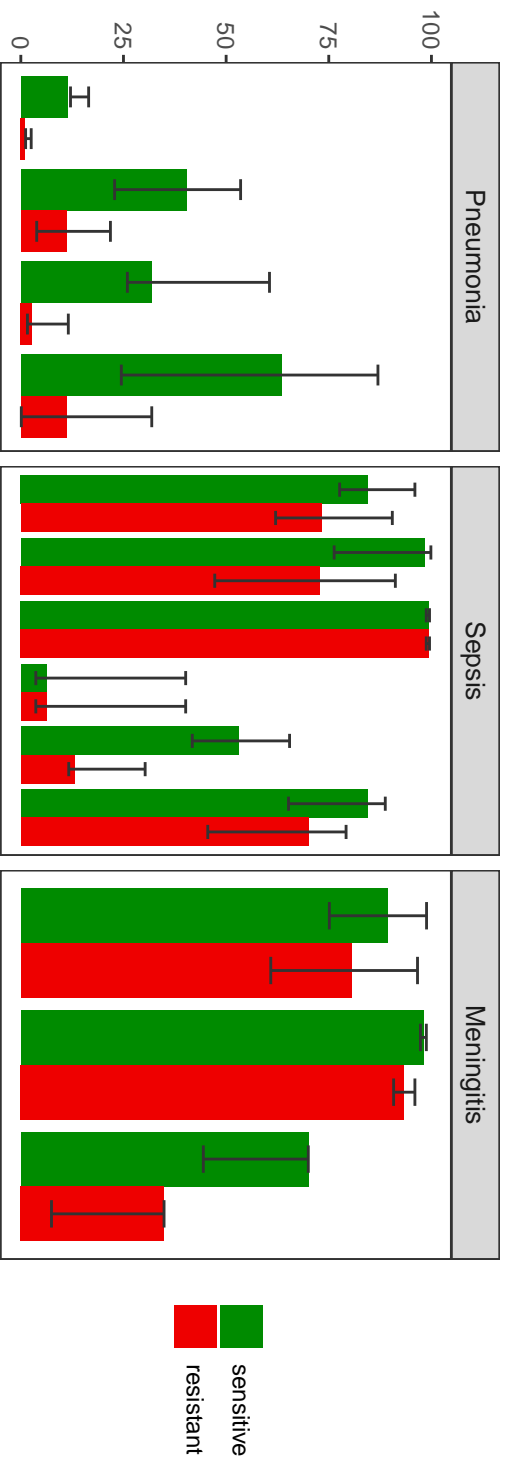
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