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

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ABSTRACT

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

INTRODUCTION

In a 2020 report on child mortality led by UNICEF and WHO[1], infectious diseases were found to be the leading cause of death in children under the age of 5 years, and are estimated to cause over half of deaths in this age group[2]. Bacterial infections, increasingly involving multi-drug resistant (MDR) organisms, are responsible for a significant proportion of these deaths, with pneumonia accounting for 15%, sepsis 7% and meningitis 2%, respectively[1]. In many cases these infectious diseases are preventable and need to be targeted both by policies aimed at prevention, but also optimal treatment.

One barrier to optimal treatment is the rise of antimicrobial resistance (AMR), particularly amongst Gram-negative organisms. Over the last 20 years in Malawi, blood stream isolates have changed from mainly sensitive to mainly resistant to first-line antibiotics (gentamicin, ampicillin and cefotaxime), with resistance in *Klebsiella spp*. now over 90%[3]. This concerning trend is seen throughout other low- and middle-income countries[2], and may mean that previous gains in reductions in mortality may be impacted by infections caused by MDR organisms[4]. In an effort to reduce the spread of AMR the WHO has categorised the Essential Medicines List (EML) agents into Access, Watch and Reserve antibiotics[5], to manage global antibiotic usage. This seeks to limit the use of "Watch" and "Reserve" agents where possible. *In vitro* there is evidence to suggest that low antibiotic exposure can select for or induce resistance, whereas when concentrations are higher resistance is less likely to appear[6]. Whilst clinical dosing guidelines should primarily recommend "Access" and "Watch" agents, a key aspect of preserving their efficacy is therefore to ensure dosing is optimised.

Historically, there were limited antimicrobial studies in children but in 2003 the USA introduced the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) to ensure all new agents had to be studied[7]; regulators in other territories followed suit shortly thereafter. This meant that newantimicrobial agents were formally studied - although those studies often lag significantly behind adult development[7]. Since most antimicrobials in the WHO EML "Access" and "Watch" groups were licensed before 2003, inconsistent dosing guidelines are common. By far the largest proportion of "Access" and "Watch" agents are the β-lactams, which were licensed prior to these legislative changes and therefore variably studied in children.

Recent large global antimicrobial point prevalence surveys have confirmed that wide variability in antimicrobial dosing in children persists in clinical practice[8]. Differences include the prescribed doses, frequencies and in some cases the route of administration. Information on optimal dosing across different pediatric age groups is still lacking for many antibiotics and has often been omitted from drug labelling information. Formularies established by national and international expert groups are one of the main resources for pediatric drug dosing guidelines used in clinical care. Many of these have recently switched to digital platforms in order to increase their instant availability and contemporary information[9].

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

For treatment to be successful, it is commonly recognized that attaining concentrations above a certain critical target is required[10]. The usual pharmacodynamic marker that guides antibiotic efficacy is the minimal inhibitory concentration (MIC). Based on *in vitro* studies, the optimal pharmacokinetic target in relation to an organism's MIC has been defined for each antibiotic: fCmax/MIC, ratio of maximal free drug concentration to MIC, fAUC/MIC, ratio of the area under the free drug concentration time curve to MIC, fT>MIC, fraction of time of the free drug concentration being above the MIC, with the latter usually used for β-lactam antibiotics[11]. However, to define a drug's therapeutic window, an assessment of likely efficacy needs to be accompanied by an assessment of the proposed dose's potential to cause adverse drug reactions. For some antibiotics with narrow therapeutic windows such as nephrotoxicity associated with aminoglycosides or glycopeptides, these toxicity cut-offs are well defined. For the β-lactams, toxicity thresholds are less well defined, but increasing evidence points towards neurotoxicity possibly becoming dose-limiting, especially when new dosing regimens such as continuous infusion dosing are gaining in popularity [12].

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

METHODS

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

For pneumonia, sepsis and meningitis common β-lactam antibiotic / organism (drug / bug) combinations were extracted from the most recent ESPAUR Report in 2018-2019[13]. For pneumonia, the antibiotics selected were: amoxicillin-clavulanate (co-amoxiclav), ampicillin/sulbactam and benzylpenicillin (penicillin G). Oral co-amoxiclav was also evaluated for step-down treatment. For sepsis the following antibiotics were chosen: cefotaxime, ceftazidime, ceftriaxone, co-amoxiclav, piperacillin-tazobactam and meropenem. For meningitis, cefotaxime, ceftriaxone and meropenem were selected.

For each drug a pediatric PK model was identified from our recently published systematic review[14]. This review suggested an evidence grading based on the data and modelling presented. Briefly, a scoring system was developed to rate the conducted PK assessment through the PKPD dosing evidence score. On top of the score, extracted publications were then assessed regarding the underlying studies' quality to derive the overall quality of evidence rating, which was summarized to strong, intermediate or weak strength of recommendation. The literature search was limited to articles published on pediatric PK studies for AWaRe antibiotics and the search was conducted in PubMed. A graphical overview of the scoring system can be found in Supplemental Figure 1. The search was repeated for the subsequent time frame May 2018 to October 2020 to include more recently published literature.

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

Neonatal and pediatric demographic population development

Demographics for a population of hypothetical neonates, infants and children with pneumonia, sepsis and meningitis was then generated. Real demographics were sampled using R from three different data sets: a one-day point prevalence survey (PPS) on antibiotic prescription, which was collected from the Global Antimicrobial Resistance, Prescribing and Efficacy in Neonates and Children (GARPEC) Network[8], the Global Point Prevalence Survey on Antimicrobial Consumption and Resistance (Global PPS) network[8] and the Antibiotic Resistance and Prescribing in European Children

(ARPEC) project[19]. Patients aged <19 years receiving at least one antibiotic on the day of the respective survey were included.

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

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

Systematic search for dosing guidelines

Pediatric formularies were searched to identify the dose regimens for each antibiotic to treat each clinical infection. The following national and international formularies were chosen, in order to cover the range of regimen per drug, that are used globally: British National Formulary for Children (BNFc)[26], Dutch/German Database for Pediatric Dosing (Kinderformularium)[27], German Pediatric Infectious Diseases Society Handbook (DGPI Handbook)[28], Swiss Database for Dosing Medicinal Products in Pediatrics (SwissPedDose)[29], Indian National Centre for Disease Control guidance (NCDC)[30], Nelson's Pediatric Antimicrobial Therapy (Bradley et al.)[31], Manual of Childhood Infections (Blue Book)[32], Report of the Committee on Infectious Diseases (Red Book)[33], and the WHO Pocket Book[34].

For the three infectious diseases, pneumonia, sepsis and meningitis, dose guidance was extracted from each formulary. Additionally, the minimum and maximum regimen were listed alongside WHO expert consensus regimen[5] aiming to display a median regimen across all formularies. Dosing info was collected for the following pediatric age groups: neonates (≤ 28 days); infants/children (>28 days – 12 years) and adolescents (>12 years).

Pharmacokinetic-Pharmacodynamic Analysis

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

Target attainment analysis

Pharmacodynamic (PD) analysis was carried out through PTA assessment from the simulations. Targets were chosen depending on the pharmacodynamics of the investigated drug/ drug class. As suggested by Mouton et al.[35] the fraction of time above MIC is seen as the appropriate target for β-lactam antibiotics. Free, unbound concentrations were used to evaluate the PKPD target. For ceftriaxone, free concentration accounting for nonlinear concentration-dependent protein binding was assumed[36]. For the other agents the following fraction unbound was assumed: amoxicillin 83%[37], ampicillin 80%[38], benzylpenicillin 45%[39], cefotaxime 70%[39], ceftazidime 83%[40], meropenem 98%[37] and piperacillin 70%[37]. In-line with current guidance for severe hospitalized patients, an overall β-lactam PKPD target of 100%fT>MIC within a 24h time frame at steady state was chosen[41]. Further investigation was performed looking at 50%fT>MIC for less severe infections that can be found in the community setting and 100%fT>4xMIC when a critically ill population is targeted[42].

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

Toxicity analysis

For the simulated drug toxicity, cut-offs were extracted from the literature. A general neurotoxicity threshold of 316 mg/L 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 Huwyler 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 tazobactam[12].

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RESULTS

Demographic datasets

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

Figure 1 shows the age-related weight distribution for each subpopulation with an additional panel showing the included neonates. Each graph also shows the typical weight for age distribution published for preterm and term neonates by Fenton et al.[44, 45], for up to 5 year olds by the WHO[46] and for 5 to 18 year olds by the CDC[47].

Dosing regimen

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

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

Selected PK models for simulation

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

Evaluating Probability of Target attainment

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

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

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

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

Toxicity

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

DISCUSSION

In our analysis we focussed on commonly used β-lactam antibiotics featuring in the WHO Essential Medicines List for children[5]. Point prevalence surveys have revealed heterogeneity in dosing across and within countries[51] and we found this to be reflected in varying dosing recommendations provided by national and international formularies.

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

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

Whilst piperacillin-tazobactam also achieved sufficient levels in more than 75% of the pediatric population regarding sensitive breakpoints (Figure 5), isolate specific ECOFFs, representing the critical epidemiological MIC that covers all MICs of wild-type isolates values, are however higher then this non-species-specific value. Coverage for the resistant Enterobacterales breakpoint of 16mg/L only accounts for 70% [79 -46%]. A re-analysis of the microbiology data from the MERINO trial showed that infection with extended-spectrum β-lactamase (ESBL) organisms that whilst "sensitive" (with MICs below 16 mg/L) were still associated with increased mortality[53], with insufficient target attainment a possible cause.

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

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

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

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

We focused on EUCAST MIC reporting, but empiric treatment decisions are dependent on local resistance patterns and may deviate from what is simulated with the non-species related MICs, globally. Figures 2 – 4 are depicted with common MIC ranges and can be used for local dose regimen design based on local MIC distributions. The selection of a PKPD target in antibiotic treatment depends on the severity of the targeted disease, focus of the infection, individual patient factors and local resistance patterns[60]. As β-lactams show time-dependent bactericidal effects, the fraction of time that the free concentration is above a multiple of the MIC should be targeted. For our simulations we focussed on an overall β-lactam PKPD target of 100%fT>MIC.

Bactericidal effect for β-lactam classes is detectable for %ft>MIC as low as 40% in carbapenems, and 50-70% in cephalosporins and penicillins[41]. In critical care the 100%fT>MIC target, however, resulted in favourable outcomes according to the DALI trial[42]. The desired PD targets, however still remain to be elucidated across different routes of administration and patient populations[61]. The use of continuous infusion regimen, as studied in BLING I-III for adult critical care patients, is often not feasible in neonatal and pediatric settings, where IV accessibility, volumes and compatibilities have to be taken into account when performing infusion management[62].

Thus, across the heterogenous severity stages, that are seen in the simulated syndromes, a PKPD target of 100%fT>MIC seems sensible for achieving overall clinical efficacy, with the option to accept lower coverage between 50-100%fT>MIC (Supplemental Figures 2-4) in less severe infections and increasing the target to 100%fT>4xMIC (Supplemental Figures 5-7) in critically-ill patients cared for in PICU and NICU settings. These PKPD targets are used with simulations of plasma concentrations as surrogates for the less accessible focusses in meningitis and pneumonia, cerebrospinal fluid (CSF) and epithelial lining fluid (ELF). A drug's ability to cross into these deeper compartments correlates with its physicochemical properties enabling the passage through membranes, transporter affinities and physiological conditions that are also influenced by the pathology of infectious disease, such as pH-changes and membrane permeabilities[63]. More insight is needed to understand how maturation influences a drugs distribution to the site of infection and the ability of plasma concentrations to serve as surrogates for this.

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

To depict the influence acute kidney injury (AKI) and augmented clearance would have on the performed simulations, we assessed models including the creatinine covariate. Simulated populations with at least 50% increase from baseline creatinine, in line with the Kidney Disease: Improving Global Outcomes (KIDGO) criteria diagnosing AKI[64], and 50% decrease in creatinine for augmented renal function are given in Supplementary Figure 8. This highlights the corresponding improvement or worsening in target attainment with AKI or augmented renal function respectively.

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

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

Through our previous study to grade evidence in pediatric antibiotic PK reporting[14, 65], supplemented by an updated literature search, we identified the models used in the target attainment simulations. All models used in the simulations were rated with a dose evidence score between 7 and 10, with 12 being the maximal achievable score. The overall quality of evidence was rated strong or intermediate, with intermediate rating rather than strong due to most studies being conducted in a single-centre setting, without additional data for validation. A key criteria for choosing appropriate models was that covariate parameterisation allowed for extrapolation across the neonatal and pediatric age range, which is often not possible for models developed in sub populations with empirical covariate structures[66] .

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

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

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

syndromes like bacterial meningitis. In the literature, mostly case reports are available. Imani et al.[12] retrospectively evaluated β-lactam concentration-toxicity relationships through regression analysis concluding that penicillins like piperacillin show neurotoxicity at trough concentrations as high as 361 mg/L. Animal studies report trough concentrations at 157 mg/L for piperacillin and 64mg/L for meropenem toxicity[74]. These targets were not or only barely (piperacillin) reached with the simulated carbapenems and penicillins. For cephalosporins, cefepime is seen as the most neurotoxic drug and therefore is studied more intensively compared to other drugs in this group. A threshold trough concentration of 35 mg/L is reported as threshold by Huwyler et al.[43] and served as reference concentration for this analysis. It is anticipated, that other cephalosporins bare lower risks of neurotoxicity. So far case reports dominate neurotoxicity reporting for cephalosporins other than cefepime and thus the cefepime neurotoxic threshold serves as a surrogate for a regimen's neurotoxic potential in this review. When treating severe infections involving organisms with high MICs the potential risk of neurotoxicity needs to be balanced with treatment success and resistance suppression. For example, treating Pseudomonas infections using ceftazidime with a target of 100%fT>4xMIC will result in an optimal trough exposure of 32mg/L to cover resistant strain MICs of 8mg/L. This highlights the need of antibiotic stewardship to consider personalised dosing based on patient and organism considerations.

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

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

CONCLUSION

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

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

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

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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 Enterobacteraes (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