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SUPPLEMENT ARTICLE

Optimal Clinical Doses of Faropenem, Linezolid, and Moxifloxacin in Children With Disseminated Tuberculosis: Goldilocks

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Background. When treated with the same antibiotic dose, children achieve different 0- to 24-hour area under the concentration-time curves (AUC_{0-24}) because of maturation and between-child physiological variability on drug clearance. Children are also infected by *Mycobacterium tuberculosis* isolates with different antibiotic minimum inhibitory concentrations (MICs). Thus, each child will achieve different AUC_{0-24}/MIC ratios when treated with the same dose.

Methods. We used 10 000-subject Monte Carlo experiments to identify the oral doses of linezolid, moxifloxacin, and faropenem that would achieve optimal target exposures associated with optimal efficacy in children with disseminated tuberculosis. The linezolid and moxifloxacin exposure targets were AUC_{0-24}/MIC ratios of 62 and 122, and a faropenem percentage of time above MIC >60%, in combination therapy. A linezolid AUC_{0-24} of 93.4 mg × hour/L was target for toxicity. Population pharmacokinetic parameters of each drug and between-child variability, as well as MIC distribution, were used, and the cumulative fraction of response (CFR) was calculated. We also considered drug penetration indices into meninges, bone, and peritoneum.

Results. The linezolid dose of 15 mg/kg in full-term neonates and infants aged up to 3 months and 10 mg/kg in toddlers, administered once daily, achieved CFR ≥ 90%, with <10% achieving linezolid AUC_{0-24} associated with toxicity. The moxifloxacin dose of 25 mg/kg/day achieved a CFR > 90% in infants, but the optimal dose was 20 mg/kg/day in older children. The faropenem medoxomil optimal dosage was 30 mg/kg 3–4 times daily.

Conclusions. The regimen and doses of linezolid, moxifloxacin, and faropenem identified are proposed to be adequate for all disseminated tuberculosis syndromes, whether drug-resistant or -susceptible.

Keywords. Monte Carlo experiments; pharmacokinetic variability; dosage design; combination regimen; target setting.

Tuberculosis in infants and toddlers often manifests as disseminated or intrathoracic disease. *Mycobacterium tuberculosis* (*Mtb*) is predominantly intracellular in such children, in contrast to the predominantly extracellular disease in cavitary pneumonia. Diagnosis and treatment of tuberculosis in this age group has been identified as a priority of the world tuberculosis community and the World Health Organization (WHO), for which one strategic goal is the development of novel regimens for "shorter, safer, and simplified treatment" of both drug-susceptible and drug-resistant tuberculosis for these children [1]. In addition, available treatments for pediatric drug-susceptible and drug-resistant tuberculosis "are hampered by high pill burden, long duration of treatment, coexistent toxic effects, and an overall scarcity of suitable child-friendly formulations" [2].

The most devastating form of the disseminated form of disease in children is arguably tuberculous meningitis (TBM). In high-burden tuberculosis places such as South Africa, the incidence of TBM is 31.5 per 100 000 of all children <1 year of age, and 17.1 per 100 000 children 1–4 years of age, making this a common problem [3]. With treatment, 20% of children with drug-susceptible TBM die, and of those who survive, only 16% will regain normality whereas 71% develop persistent neurological deficits [4]. In adult TBM, about 60% of patients were dead by the end of a 4-year period after completion of standard therapy [5]. Thus, current treatment regimens for TBM are inadequate. This may be due to the poor penetration of several first-line drugs into the subarachnoid space, bone, peritoneum, and pericardium, common sites for disseminated tuberculosis [6–10].

Multidrug-resistant (MDR) tuberculosis is relatively common in children. In a recent study of approximately 1300 children in India with extrapulmonary disease, 20% had positive *Mtb* cultures, of which approximately 20% was MDR and extensively drug-resistant (XDR) tuberculosis from specimens such

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as gastric aspirates, lymph nodes, and cerebrospinal fluid (CSF); resistance to isoniazid was 31% and to ethionamide 38% [11]. The same rates are likely encountered in the >80% of children with tuberculosis who are culture negative, for whom we have no current way of diagnosing the presence of resistance. According to the WHO, MDR and XDR tuberculosis drive 25% of global tuberculosis deaths [12]. When properly diagnosed, and with appropriate regimens chosen, the response rates are about 80% [13]. This was accomplished, as one newspaper headline put it, with "14 600 pills over 2 years" [14], a staggering amount of pills and shots for infants and toddlers. The success rate also comes at the cost of high levels of toxicity. Seddon et al identified hearing loss in 1 in every 4 children treated for MDR tuberculosis in South Africa, who continued to develop to deafness after the end of drug injections, potentially devastating given that children are at the stage of language, learning, and social skill acquisition [15]. Thus, one of the goals is to develop a regimen for treatment of MDR tuberculosis for which doses are high enough to achieve optimal efficacy but not too high as to be associated with high rates of toxicity: "not too high or too low, but just right," or a Goldilocks paradigm.

The most important driver of suboptimal concentrations in patients is between-patient pharmacokinetic variability, which drives acquired drug resistance, therapy failure, and death [16–21]. There are specific concentration thresholds associated with optimal outcomes in children, which differ in some drugs from those identified in adults [16–21]. This means doses should be designed to achieve concentrations above these thresholds to maximize outcomes in children. Here, we identified optimal doses of faropenem, linezolid, and moxifloxacin (FLAME regimen) for the treatment of disseminated and intrathoracic tuberculosis in infants and toddlers, including TBM and peritoneal disease, whether MDR or drug-susceptible tuberculosis, in accordance with current goals for treatment of children <5 years of age.

At a minimum, the treatment of childhood tuberculosis should be with antibiotics that achieve high intracellular concentrations. A second important requirement is the ability to penetrate anatomically privileged sites such as the subarachnoid space, bone, and peritoneum. In this regard, first-line antibiotics such as rifampin perform poorly, while the new antituberculosis drugs such as bedaquiline are even worse [22]. On the other hand, moxifloxacin achieves high CSF 0- to 24-hour area under the concentration-time curves (AUC_{0-24}) [23]. Similarly, linezolid achieves inflammation-independent CSF/plasma AUC_{0-24} ratios of 1.0 in children [24]. In retrospective studies of TBM patients treated with the standard first-line drugs, addition of linezolid led to rapid and dramatic recovery in consciousness and CSF parameters and a 30% higher response rate [25, 26]. The CSF penetration of faropenem is unknown, but based on the Overton rule and penetration of the structurally related carbapenems and cephalosporins, penetration ratios of 30% are predicted [27]. A third important requirement is that given the difficulty of culturing *Mtb* in children, antibiotics should treat both MDR and drug-susceptible tuberculosis in children. Fourth, one important goal in global health is that of a regimen to treat infants, toddlers, and preschoolers that is oral and in child-friendly formulations such as oral suspensions and syrups, which are available for components of the FLAME regimen. In the hollow fiber system (HFS), we have identified target moxifloxacin, linezolid, and faropenem exposures that lead to the same microbial kill rate slopes as the current short-course chemotherapy regimen [28, 29]. We have also identified concentration thresholds associated with toxicity of linezolid [30]. Based on the between-child variability of these drugs, we were able to accurately aim for that "Goldilocks" zone of drug concentrations and exposures with doses to optimally treat disseminated tuberculosis, including all of the common syndromes such as TBM, in drug-susceptible and MDR tuberculosis.

METHODS

Scientific Philosophy

Drug exposures for the treatment of tuberculosis are expressed as either AUC_{0-24} to minimum inhibitory concentration (MIC) or peak/MIC or percentage of time concentration persists above MIC ($\%T_{MIC}$) [31]. The relationships between microbial kill and antibiotic exposures are invariant, and thus can be transformed from the HFS to children [31]. In contradistinction, the AUC_{0-24} and peak concentrations achieved after treatment with a specific milligram per kilogram (mg/kg) dose vary from child to child due to maturation, between-person evolutionary and physiological variation, and lifestyle differences, as an example of a nondeterministic system [32–35]. In contrast, the antibiotic MICs in clinical *Mtb* isolates differ from patient to patient due to evolution [36]. Therefore, when each child with tuberculosis is treated with a specific dose of an antibiotic, a wide distribution of AUC_{0-24}/MIC, peak/MIC, and $\%T_{MIC}$ exposures are achieved, which affects the extent of microbial kill and cure rates. These exposures, the result of stochastic biological processes, thus have a random distribution. The optimal dose and dosage of a drug is defined as that which achieves the exposure associated with optimal kill in >90% of patients [36–38]. However, such doses must also achieve concentrations below those associated with concentration-related toxicity in >90% of children. Not too high to cause toxicity, and not too low to cause therapy failure, is the Goldilocks zone to aim for with dosages.

Target Drug Exposures in Combination Therapy for Infants and Toddlers

We identified the specific exposures and dosing schedules of faropenem, linezolid, and moxifloxacin associated with optimal effect, termed exposure targets, in the FLAME combination regimen [28–30]. The faropenem exposure target was a $T_{MIC} > 60\%$,

moxifloxacin AUC_{0-24}/MIC ratio of 122, and linezolid AUC_{0-24}/MIC ratio of 62, associated with additivity in the combination therapy regimen in the HFS [28–30]. On the other hand, the minimum linezolid AUC_{0-24} associated with mitochondrial toxicity was 93.4 mg × hour/L [30]. In adult tuberculosis, such HFS-derived targets in tandem with Monte Carlo experiments had a forecasting accuracy of within 94% of the value later identified in the clinic [38–40].

Monte Carlo Experiments

One of the techniques used for random sampling and to estimate uncertainties are Monte Carlo simulations. Monte Carlo methods were introduced by Ulam and Metropolis in the 1940s, and tested on the first electronic general-purpose computer made, the ENIAC, to solve the problem of fissile material during the Manhattan project [41, 42]. It is therefore not a surprise that some of the earlier uses of Monte Carlo simulations for clinical dosing involved radiation dosimetry by radiotherapists [43, 44]. In 1985 Katz and D'Argenio use this technique in antibiotic dose regimen selection, taking into account the population pharmacokinetic parameter estimates and variability derived in 42 patients [45]. In the late 1990s, the technique was used by Drusano et al to identify antibiotic doses and susceptibility breakpoints based on pharmacokinetic/pharmacodynamic exposure targets and pharmacokinetic variability [46]. These techniques were then applied to dose regimen design for tuberculosis in the early 2000s [47]. These methods use a random generator to give an output of a distribution of pharmacokinetic parameters, given the population variability for that antibiotic, to generate a distribution of concentrations from which exposures are calculated.

Monte Carlo Experiment Steps

Our aim was to use the HFS-derived exposures to identify doses and dosing frequencies for use in combination therapy using Monte Carlo experiments [36, 48]. Steps and quality control standards in performing Monte Carlo simulations were as outlined elsewhere in this supplement [31] and in past reports [36, 48]. The pharmacokinetic parameters and variances shown in Table 1 were input subroutine PRIOR of the ADAPT 5 program. For moxifloxacin, the age-dependent pharmacokinetic parameters and variances were based on results of a study by Bayer HealthCare (registered at https://clinicaltrials.gov/ct2/show/NCT01049022, with results available at http://trialfinder.bayerscheringpharma.de/html/pdf/11826_Study_Synopsis_CTP.pdf). For linezolid, age-dependent pharmacokinetic parameters were based on Jungbluth et al [33]. We found no published compartmental pharmacokinetic analysis for faropenem in children. However, pharmacokinetic studies with spreadsheets of dose, concentrations at various time points, and children's demographics have been published [49, 50]. We developed ADAPT .dat files from these, and identified population pharmacokinetic parameter estimates and covariance for the children in ADAPT 5 software. The resultant parameters used are shown in Table 1. For TBM, CSF/plasma AUC_{0-24} ratios of 1.0 were used for linezolid and 0.8 for moxifloxacin, while 0.3 was assumed for faropenem as described earlier [5, 23, 24, 51]. For peritoneal fluid, the concentrations were all assumed to be similar to plasma concentrations (in reality, the concentrations are higher in peritoneal fluid than in plasma) [52, 53].

Table 1. Pharmacokinetic Parameter Estimates and Variability

	PRIOR (Observed in Patients)		10 000 Simulated Children	
Drug and Age Group	Mean SCL, L/h/kg (%CV)	Mean Volume, L/kg (%CV)	Mean SCL, L/h/kg (%CV)	Mean Volume, L/kg (%CV)
Linezolid				
Full-term neonates	0.31 (22.0)	0.66 (29.0)	0.31 (22.24)	0.66 (29.26)
Infants	0.32 (32.0)	0.79 (27.0)	0.32 (32.15)	0.79 (26.61)
3 mo to 11 y	0.23 (53.0)	0.69 (28.0)	0.23 (53.23)	0.69 (27.83)
Moxifloxacin				
Infants	0.35 (27.0)	2.23 (31.35)	0.35 (26.86)	2.23 (31.62)
Toddlers	0.26 (24.34)	1.61 (22.93)	0.26 (23.98)	1.61 (23.06)
School age	0.25 (36.87)	2.08 (33.37)	0.25 (37.28)	2.08 (33.09)
Faropenem	1.99 (40)	2.93 (40)	2.01 (40.05)	2.94 (39.76)

Abbreviations: %CV, percentage coefficient of variation; SCL, total clearance.

For linezolid, doses of 2.5, 5, 7.5, 10, 15, and 20 mg/kg per day were examined, and a distribution of pharmacokinetic parameters, variance, and AUC_{0-24} was generated in 10 000 children at each of 3 age groups of (1) full-term newborns up to 28 days, (2) infants (>28 days to 3 months, and (3) all other young children (>3 months to 11 years), based on the differences in clearance rates in these age groups [33]. Internal validation was performed by determining if simulated values correctly recapitulated pharmacokinetic parameters and variances identified in the clinic in children treated with the standard dose. As the CSF/plasma ratio of 1.0 is encountered, and high peritoneal concentrations achieved, we made no further adjustment to the linezolid for treatment of tuberculosis in any of these sites. Next, AUC_{0-24}/MIC ratios were generated at each MIC, based on the MIC range identified in the distribution from 234 *Mtb* isolates by Rodriguez et al [35]. For each dose, the probability of target attainment (PTA) was calculated at each MIC. Given the MIC distribution of Rodriguez et al, an expectation was taken over the MIC range and cumulative fraction of response (CFR) calculated as:

$$\mathrm{CFR} = \sum_{i=1}^{n} \mathrm{PTA}_i \times F_i,$$

where PTA is probability of target attainment at each MIC, and F is the proportion of isolates at each MIC.

The same process was repeated for moxifloxacin, for exactly the same doses as for linezolid. The 3 age groups examined for moxifloxacin were infants (0–1 years), toddlers (>1 to 4 years),

and school-aged children (up to 9 years), based on groupings from Bayer HealthCare results. The CSF AUC_{0-24}/MIC ratios were calculated as 0.80 of those in plasma. The moxifloxacin MIC distribution was from the same 234 isolates from Rodriguez et al [35]. Doses calculated were for TBM, and would thus be more than adequate for *Mtb* in other sites.

For faropenem medoxomil, we used the population pharmacokinetic parameters we identified, for children aged 1–11 years. We assumed that $\%T_{MIC}$ was the linked parameter for *Mtb*; targets were identified in HFS studies [29]. We generated concentration-time profiles over the entire 24 hours for dosing of 2 times daily, 3 times daily, and 4 times daily, to identify the $\%T_{MIC}$ for doses of 5, 7.5, 10, 15, 20, and 30 mg/kg. Summary concentrations such as the median peak and AUC_{0-4} were compared those achieved in 179 children 0.5–7 years of age who were treated with the dose of 7.5 mg/kg for otitis media, and published in abstract form for a meeting [54]. The faropenem MIC distribution is unknown for *Mtb*; based on laboratory strains we examined, and publications with a few other strains of *Mtb*, the $\%T_{MIC}$ over an MIC range of 0.125 mg/L–32 mg/L was chosen, with a mean of around 2.0 mg/L [29, 55–57].

Software and Hardware

Hardware used for pharmacokinetic modeling and simulations included a Macintosh desktop with a 2.7 GHz Intel Core i5 processor. The compartmental pharmacokinetic profile of faropenem was identified using ADAPT 5 software (Biomedical Simulations Resources, University of Southern California, California). Monte Carlo experiments were implemented by adding pharmacokinetic parameter estimates and covariance matrices of each drug, for the specified age groups, to subroutine PRIOR of ADAPT 5. Output of ADAPT is via .cvs files, which were converted to Excel files (Microsoft Office, Microsoft Corporation, Redmond, Washington) and then exported to GraphPad Prism 6 (GraphPad Software, La Jolla, California) for graphing.

RESULTS

Target Attainment for Linezolid in 3 Age Groups

The pharmacokinetic parameter estimates of 10 000 children in each group given linezolid are shown in Table 1. The table shows that the simulation faithfully recapitulated the pharmacokinetic parameters of the drug in children, and the variances thereof, identified by Jungbluth et al [33]. The mean and percentage coefficient of variation (%CV) AUC_{0-24} (in mg × hour/L) for the 10 mg/kg dose was 34.16 (21.86%) vs 34.00 (21.0%) in full-term neonates, 33.96 (31.97%) vs 33.00 (26.0%) in infants aged >28 days to 3 months, and 55.67 (52.50%) vs 58.0 (54%) in 3-month-olds to 11-year-olds in 10 000 simulated children vs those observed in the original clinical published pharmacokinetic study, respectively.

Probability of target attainment (PTA) in full-term neonates by the different linezolid doses at each MIC are shown in Figure 1*A*. At doses <10 mg/kg a day, virtually no child achieved the optimal linezolid exposures at all MICs above the median. Similarly, Figure 1*B* shows the target attainment at each MIC distribution for infants aged >28 days to 3 months; target attainment for the dose of 10 mg/kg/day falls to about 50% at median MIC. However, in older children, Figure 1*C* shows that the dose of 10 mg/kg does considerably better, reflecting reduced clearance of the drug in this age group.

Summation of the target attainment probabilities revealed the CFRs shown in Figure 2, which can be viewed as a dosing

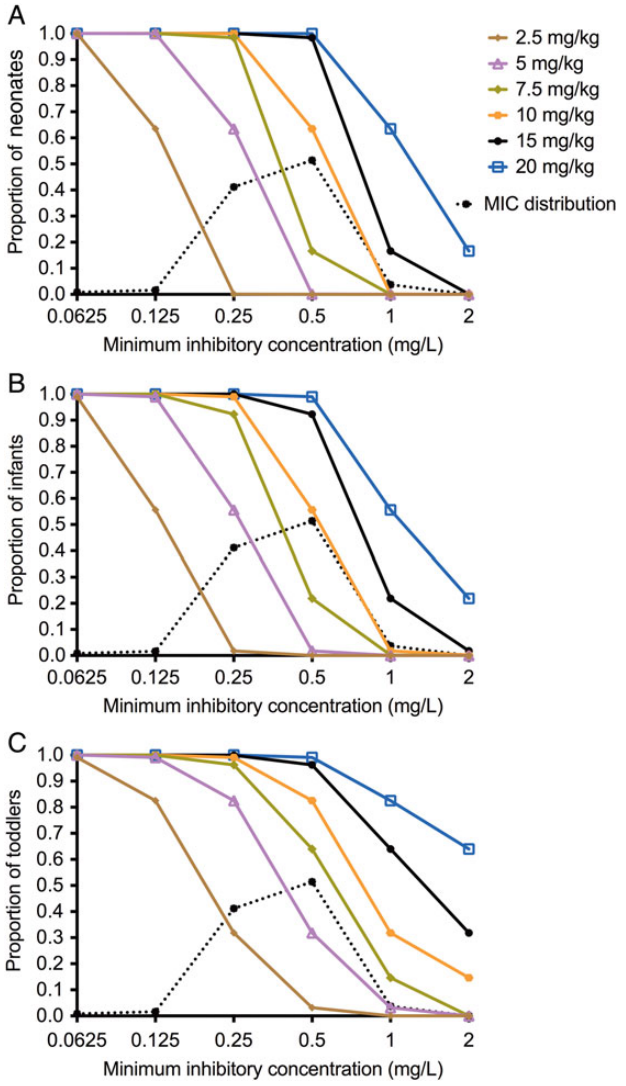

Figure 1. Linezolid probability of target attainment (PTA) in children with tuberculosis. Children have different linezolid elimination rates based on age group, as well as within-age-group between-child pharmacokinetic variability. The *Mycobacterium tuberculosis* minimum inhibitory concentration (MIC) also varies, with distribution shown in the figure. *A*, PTA in full-term neonates. The PTA of the standard dose of 10 mg/kg once daily falls below 90% at the modal MIC of 0.5 mg/L, while 15 mg/kg overcomes this. *B*, PTA in infants aged >28 days to 3 months. The dose of 10 mg/kg/day does even worse because of the drug clearance in children in this age group. *C*, Fortunately, the clearance is much lower in all other children >3 months, and the standard dose of 10 mg/kg performs better at the higher MICs.

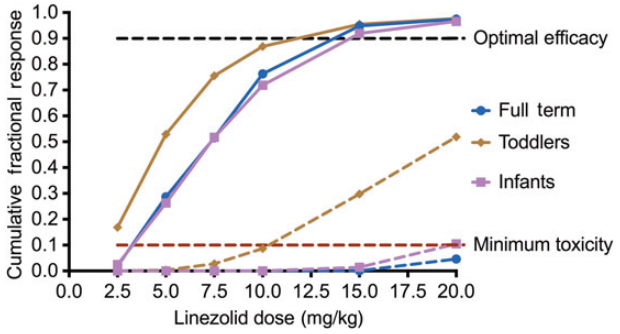

Figure 2. Cumulative fraction of response (CFR) for linezolid efficacy and toxicity. As doses increase from 2.5 mg/kg each day to 15 mg/kg, the CFR improves beyond 90% for all. We set a minimum standard of acceptable target attainment rates for the area under the concentration-time curve (AUC) associated with mitochondrial toxicity at 10% attainment, and this sets up a large "Goldilocks" zone for full-term neonates and infants, for whom a single dose of 15 mg/kg/day (linezolid is an AUC/minimum inhibitory concentration–driven drug) has CFR of about 94% for efficacy, and <1% for toxicity target. In toddlers and older children, however, 15 mg/kg achieves AUC_{0-24} associated with toxicity in a large portion of children; thus, we accepted the 88% CFR for 10 mg/kg for efficacy as sufficient since that dose has less toxicity in this age group.

nomogram. The figure shows that doses of 15 mg/kg/day achieve or exceed the target in >90% of patients in the 2 younger age groups. In the meantime, <10% of these children achieved target AUC_{0-24} thresholds associated with mitochondrial toxicity. On the other hand, Figure 2 shows that in children >3 months, the CFR was 88% for 10 mg/kg and 95% for 15 mg/kg. However, the later dose would raise the proportion of children achieving AUC_{0-24} associated with mitochondrial toxicity to >10%. Thus, on balance we chose 10 mg/kg/day.

Target Attainment for Moxifloxacin in 3 Age Groups

The pharmacokinetic parameter estimates in 10 000 simulated children are compared to those observed in children in Table 1. In terms of concentrations achieved, the moxifloxacin AUC_{0-24} (mg × hour/L) in the in silico children was 24.89 (24.76%) vs 25.52 (17.26%) in infants treated with 9 mg/kg, 27.59 (23.88%) vs 27.18 (19.29%) in toddlers treated with 8 mg/kg, and 20.74 (37.35%) vs 19.73 (30.53%) in school-aged children treated with a 5 mg/kg dose, respectively. Thus, the simulations faithfully recapitulated the moxifloxacin pharmacokinetics of children observed in the clinic.

Figure 3 shows the PTAs at each MIC for several moxifloxacin doses in each age group. Figure 3*A* shows the PTAs for infants; even the highest dose of 25 mg/kg/day failed to achieve the optimal exposures at MICs >0.5 mg/L. Figure 3*B* shows essentially similar results for toddlers; however, performance of the 20 mg/kg/day dose was now better. Figure 3*C* shows the same findings in school-aged (preteen) children as in toddlers. The CFRs are shown in Figure 4, which demonstrates that a dose of 25 mg/kg/day would be most optimal for infants, but 20 mg/kg/day would be adequate for all older children.

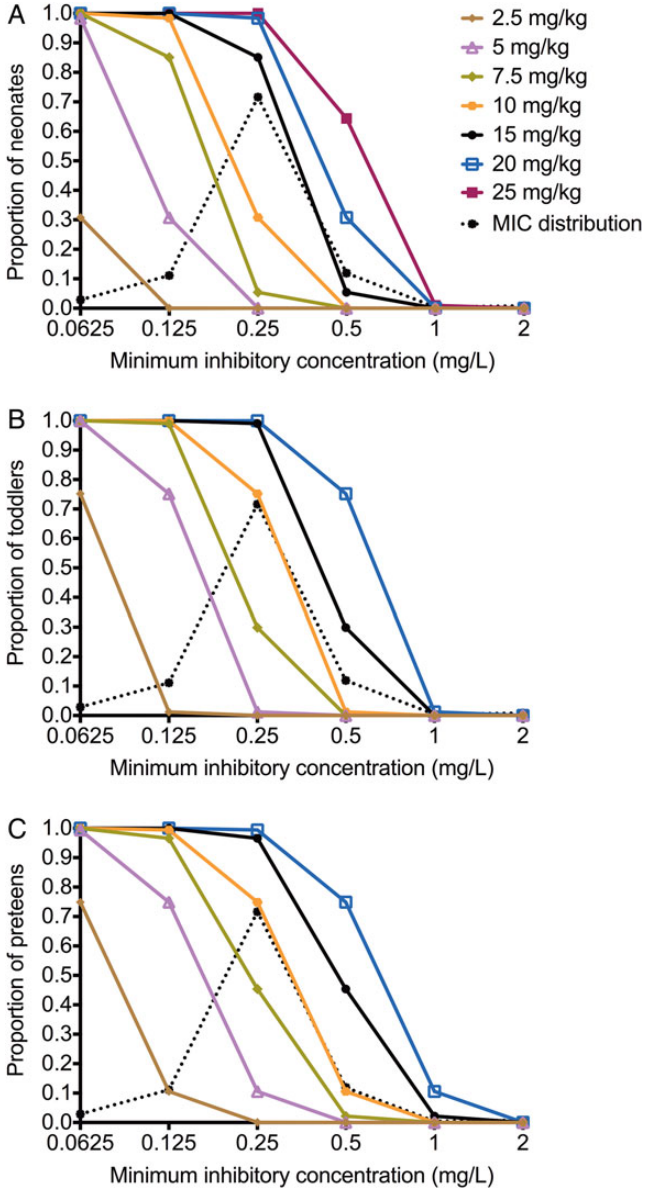

Figure 3. Moxifloxacin probability of target attainment (PTA) in children with tuberculosis. *A*, PTAs in infants. Performance of all doses falls steeply above the median minimum inhibitory concentration (MIC) of 0.25 mg/L. As a result, in this age group we also examined the effect of a dose of 25 mg/kg/day. *B*, PTAs in toddlers. As the drug clearance falls with increasing age, doses of 20 mg/kg begin to achieve optimal 0- to 24-hour area under the concentration-time curve/MICs in larger proportion of children at most MICs in the distribution. *C*, PTAs in school-aged (preteen) children.

Target Attainment of Different Faropenem Dosages

In our simulations, the median peak concentration and the AUC_{0-4} were 15.93 mg/L and 23.05 mg × hour/L with 7.5 mg/kg oral dosing, compared with 16.5 mg/L and 20.4 mg × hour/L identified in an unrelated study of 179 children [54]. Thus, our simulations reflect clinical reality. We examined target attainment in several doses in different dosing frequencies, with

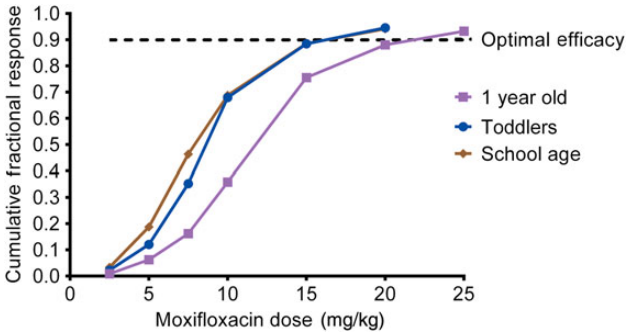

Figure 4. Cumulative fraction of response for moxifloxacin efficacy. The dosing nomograms for the 2 older age groups are virtually the same, and show the optimal dose as 20 mg/kg/day. In infants, the faster clearance led to an optimal dose of 25 mg/kg/day.

results shown in Figure 5. In Figure 5*A*, which is an in silico dose-ranging study with a twice-daily dosing schedule, none of the doses up to 40 mg/kg achieved a PTA of 90% at any MIC. Thus, the twice-daily dosing schedule would be inadvisable for children. Figure 5*B* shows performance of the thrice-daily dosing schedule, with PTAs >90% in the 2 highest doses at low MICs. Moreover, the 40 mg/kg dose barely improved on the 30 mg/kg doses, so that the curves virtually overlapped. Figure 5*C* shows the 4 times a day dosing schedule, for which both 30 mg/kg and 40 mg/kg performed relatively well until MIC of 4 mg/L, beyond which the PTA fell. Given that we did not have an MIC distribution, the CFR could not be calculated. However, the dose of 30 mg/kg 3–4 times daily seems most optimal.

DISCUSSION

While exposures at site of infection are the most accurate predictors of microbial kill, clinicians in tuberculosis programs nevertheless treat children using specific doses. Because pharmacokinetic/pharmacodynamic exposures and relationships are invariant across systems, they can be used as a means to translate results from the laboratory to the clinic. Monte Carlo simulations have been used to translate such exposures to doses in the tuberculosis field starting more than a decade ago with moxifloxacin monotherapy exposures from the HFS model [47]. Here, we completed a similar step for children, but this time focusing on exposures identified as at least additive, and not antagonistic, in a combination therapy regimen. In other words, we designed new doses and dosages for a combination regimen that are not dependent on observations in adults. In the case of linezolid, for which there are concerns of concentration-dependent toxicity, we identified doses that optimize efficacy while minimizing concentration-related toxicity. For faropenem, doses of 30–40 mg/kg have been administered to children in the past, even with a thrice-daily dosing frequency, without toxicity concerns [58]. With regard to

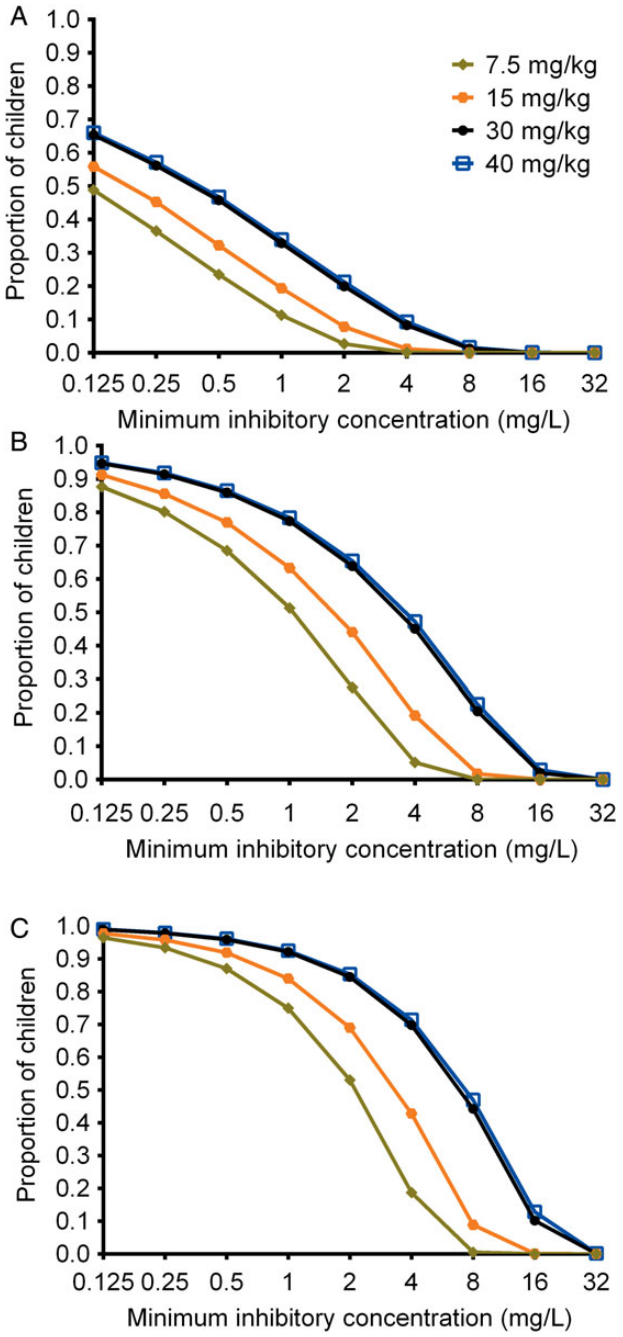

Figure 5. Probability of target attainment (PTA) of different faropenem doses and dosages. *A*, Twice-daily dosing is suboptimal at any dose. *B*, For the 3 times daily dosing, the performance of 30 mg/kg is virtually the same as 40 mg/kg. However, PTA falls steeply once minimum inhibitory concentrations (MICs) are at 1 mg/L. *C*, For the 4 times daily dosage, good PTA is extended to MICs >2 mg/L, making this dosing frequency better at high MICs. However, the faropenem MIC distribution for *Mycobacterium tuberculosis* clinical isolates is currently unknown.

moxifloxacin, concentration-dependent toxicity in children is yet to be studied.

We took into account drug penetration into such sites as the subarachnoid space, so that the doses we identified would be

considered as worst-case-scenario doses. However, given that the exposures we identified for use in combination are higher than those we identified in the same regimen for the treatment of cavitary pulmonary tuberculosis (manuscript in preparation), our doses will be able to work as well even if the children also have pulmonary disease. In addition, the FLAME regimen and the doses we identified are expected to be as effective in MDR tuberculosis as in drug-susceptible disease, so that taken together we have identified a treatment regimen for all different tuberculosis syndromes regardless of presence of resistance for first-line drugs. Thus, the regimen is expected to be tested for use in children with tuberculosis.

Finally, the doses of drugs that we identified are specific to the current FLAME regimen. If each of these drugs was to be used in different combination regimens, work would be needed to first identify exposures associated with additivity in children to avoid the situation in current short-course chemotherapy [20]. Further work is ongoing with congeners of the current pharmacophores of methoxyquinolones, oxazolidinones, and other penems, which may have better safety profiles or could kill *Mtb* faster. Optimal exposures of such congeners will be identified using the current program [31]. On the other hand, faropenem medoxomil is not available in some countries with high tuberculosis burdens, but in others it is already on prescription for otitis media and both upper and lower respiratory infections in children. Thus, it may be difficult to obtain where most needed.

In summary, we identified an optimal linezolid dose of 15 mg/kg for full-term neonates and infants aged 28 days to 3 months, and 10 mg/kg for toddlers, administered once daily for disseminated tuberculosis. The moxifloxacin dose was 20 mg/kg/day for toddlers and school-aged children, and 25 mg/kg/day for infants. The faropenem optimal dosage was 30 mg/kg 3–4 times daily. These doses and dosages should now be examined in a clinical trial of the FLAME regimen vs current standard of care.

Notes

Author contributions. Study conception and design: T. G., E. N.; acquisition of target concentrations: S. S., D. D., J. G. P.; population pharmacokinetic analyses: J. G. P., T. G.; Monte Carlo simulations: T. G.; analysis and interpretation of data: G. R., J. G. P., S. S., D. D., T. G., E. N., S. S.; wrote manuscript: S. S., D. D., J. G. P., D. D., E. N., S. S., T. G.

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