Optimizing dosing and fixed-dose combinations of rifampicin, isoniazid, and pyrazinamide in pediatric patients with tuberculosis: a prospective population pharmacokinetic study

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SUMMARY

Current pediatric dosing guidelines lead to infant rifampicin exposures much lower than in adults, while isoniazid and pyrazinamide exposures are similar. A new FDC with rifampicin/isoniazid/pyrazinamide 120/35/130 mg and weight-bands of <6, 6-13, 13-20, and 20-25 kg could improve treatment.

ABSTRACT

BACKGROUND In 2010, the WHO revised dosing guidelines for treatment of childhood tuberculosis. Our aim was to investigate first-line antituberculosis drug exposures under these guidelines, explore dose optimization using the current dispersible fixed-dose combination (FDC) table of rifampicin/isoniazid/pyrazinamide; 75/50/150 mg , and suggest a new FDC with revised weight-bands.

METHODS Children with drug-susceptible tuberculosis in Malawi and South Africa underwent pharmacokinetic sampling while receiving first-line tuberculosis drugs as single formulations according the 2010 WHO recommended doses. Nonlinear mixed-effects modelling and simulation was used to design the optimal FDC and weight-band dosing strategy for achieving the pharmacokinetic targets based on literature-derived adult $AUC_{0\text{-}24h}$ for rifampicin (38.7-72.9) isoniazid (11.6-26.3) and pyrazinamide (233-429 mg·h/L).

RESULTS 180 children (42% female; 13.9% HIV-infected; median [range] age 1.9 [0.22-12] years; weight 10.7 [3.20-28.8] kg) were administered 1, 2, 3, or 4 FDC tablets (rifampicin/isoniazid/pyrazinamide 75/50/150 mg) daily for 4-8, 8-12, 12-16, and 16-25 kg weight-bands, respectively. Rifampicin exposure (for weight and age) was up to 50% lower than in adults. Increasing the tablet number resulted in adequate rifampicin but relatively high isoniazid and pyrazinamide exposures. Administering 1, 2, 3, or 4 optimized FDC tablets (rifampicin/isoniazid/pyrazinamide 120/35/130 mg) to children <6, 6-13, 13-20 and 20-25 kg, and 0.5 tablet in <3-month-olds with immature metabolism, improved exposures to all three drugs.

CONCLUSION Current pediatric FDC doses resulted in low rifampicin exposures. Optimal dosing of all drugs cannot be achieved with the current FDCs. We propose a new FDC formulation and revised weight-bands.

Keywords: first-line tuberculosis treatment, pharmacokinetics, fixed-dose combination, rifampicin, isoniazid, pyrazinamide, NONMEM, children

INTRODUCTION

Tuberculosis (TB) remains a leading cause of death, globally. The burden of TB in children is high. In 2019, it affected an estimated 1.19 million children under the age of 15 years [1]. Although many children have minimal disease and respond well to treatment, optimized dosing is especially important in young children and children living with HIV who are prone to develop disseminated and severe disease. These children deserve treatment at least as effective as that in adults [2].

First-line treatment for children with drug susceptible TB consists of a regimen with three or four drugs (rifampicin, isoniazid, pyrazinamide with or without ethambutol) for two months followed by a 4-month regimen with two drugs (rifampicin and isoniazid). In reaction to reports of low exposure, the World Health Organization (WHO) revised the pediatric dosing guidelines in 2010, Table 1 [1,3–8]. These guidelines recommend a dose (range) of 15 (10-20) mg/kg rifampicin, 10 (7-15) mg/kg isoniazid, 35 (30-40) mg/kg pyrazinamide and 20 (15-25) mg/kg ethambutol [9]. To facilitate uptake of the revised dosing guideline a pediatric dispersible fixed-dose combination (FDC) containing 75 mg rifampicin, 50 mg isoniazid and 150 mg pyrazinamide was recommended by the WHO, and is now widely available [10,11].

Strong pharmacodynamic targets for the first-line TB drugs are lacking. Exposures observed in adults on standard dose are used as surrogate targets given that antituberculosis activity of the regimens is expected to be similar in adults and children [12]. Several studies in adults found associations between higher doses of rifampicin and pyrazinamide and improved treatment response [13–17], while the relationship between pharmacokinetics and efficacy seems to be more complex for isoniazid [16–19]. The potential for higher doses of rifampicin to shorten treatment are being investigated as a 35 mg/kg daily dose in adults, resulting in a geometric mean area-under-the-curve over 24 hours under steady state conditions ($AUC_{0\text{-}24h}$; hereafter termed exposure) of 206 mg·h/L,

has shown to be safe and reduce the time to culture conversion [20]. Increased isoniazid and pyrazinamide exposures have been linked to toxicity and increased mortality [17,21,22].

We prospectively studied the rifampicin, isoniazid, and pyrazinamide exposures in children under 12 years when dosed according to current 2010 WHO guidelines. Ethambutol is excluded from this report and will be reported elsewhere. We aimed to design improved dosing regimens using the currently available FDC and explored ways to optimize both the FDC and the weight-bands that can bring drug exposures in children in line with adult exposures.

METHODS

Study design and setting

This pharmacokinetic study enrolled HIV-infected and -uninfected children up to 12 years and weighing 1.5-30 kg receiving standard first-line antituberculosis treatment between November 2012 to June 2017, in Blantyre, Malawi and Cape Town, South Africa. Children with acute severe illness were excluded from participation. Intensive pharmacokinetic sampling was performed at least 2 weeks after starting treatment during the initial 2-month intensive phase. Before and after pharmacokinetic evaluation, the standard of care treatment was delivered using interim dosing guidelines for FDCs available in the public health sector at the time [11], with the goal to come as close as possible to the WHO 2010 guidelines [9].

Study procedure

At the time of the study, an FDC product providing drug ratios suited to the revised 2010 WHO recommendations was not available. Therefore, on the day of pharmacokinetic evaluation, single drug formulations were used in doses according to WHO 2010 guidelines. For rifampicin, the stringent regulatory authority (SRA) approved granulate for suspension (20mg/mL) Eremfat® (Riemser Arzneimittel, Germany) was used in 10-20 mg/kg doses. Due to an interruption in the supply, some children received either R-Cin® (Aspen Pharmacare, South Africa) suspension or the dispersible tablet in combination with isoniazid, Rimactazid® (Novartis, India). The isoniazid formulation was an SRA-approved 50-mg tablet (Riemser Arzneimittel, Germany) or Rimactazid® in 10-15 mg/kg doses, and for pyrazinamide a 150-mg tablet (Svizera Laboratories, India) complying with good manufacturing practices in a WHO certified facility was used in 30-40 mg/kg doses. Study staff observed the administration of study drugs on the day of the pharmacokinetic sampling. The drugs were crushed or dispersed in water, or given as suspension, using a syringe, or by nasogastric tube, or in older children swallowed whole. After intensive sampling, rifampicin, isoniazid, and pyrazinamide plasma concentrations were quantified using validated LC-MS/MS methods described previously [23]. The methods were validated over the concentration ranges of 0.117 to 30.0 mg/L for rifampicin, 0.0977 to 26.0 mg/L for isoniazid and 0.200 to 80.0 mg/L for pyrazinamide.

The study protocol (NCT01637558) was reviewed by the Data Safety and Monitoring Board and approved by the Health Research Ethics Committees of the Universities of Stellenbosch and Cape Town, and the College of Medicine Research Ethics Committee in Malawi. Parents or legal guardians provided written informed consent.

Population pharmacokinetic analysis

Data was analyzed using nonlinear mixed-effects modeling with the software NONMEM. One- and two-compartment models with first-order absorption and either absorption lag time or transit compartments were considered [24]. First-order elimination was investigated for all drugs as well as saturable elimination using a liver compartment for rifampicin [25]. Allometric scaling for all clearance and volume of distribution parameters was used to account for body size with exponents of 0.75 or 1, respectively, with either total body weight or fat-free mass [26]. In addition, maturation of clearance and changes in bioavailability with age were investigated for all drugs. When more than one drug formulation or administration method was used, differences in relative bioavailability and rate of absorption were explored. For isoniazid clearance, N-acetyltransferase 2 (NAT2) acetylator status was used where available, if unknown a mixture model was used to assign patients to be slow, intermediate, or fast acetylator [27]. The performance of the final model was assessed by visual predictive check (VPC) and parameter precision was measured using a non-parametric bootstrap. Detailed modeling methodology is described in the supplemental material.

Simulations

A representative population of 110,000 African pediatric patients with uniformly distributed weight between 3 and 25 kg, 50% female, aged 0 to 16 years, was constructed as described previously [28]. Figure S1 visualizes the agreement between the studied and the virtual population. NAT2 acetylator status was imputed as 44% slow, 42% intermediate, and 14% fast, as reported in a study across eight high-burden countries [29]. The final models were used to simulate exposures using SRA-approved products for three scenarios; 1) dosing under the 2010 WHO guidelines with currently available FDCs [9], 2) improved dosing with currently available FDC to optimize rifampicin exposure, and 3) dosing

with an optimized new FDC and optimized weight-bands. Additional simulations using patient characteristics from a real-life cohort of 8,130 Kenyan children diagnosed with tuberculosis assessed the performance of these dosing scenarios in a real population.

Optimization of fixed-dose combinations and weight-bands

The final models were used to optimize dosing by designing a novel FDC with optimal tablet content for each of the three drugs and new weight cut-off points where the number of FDC tablets should change. A continuous logistic function was used to estimate the weight-band breakpoints and the dose of each of the three drugs using a gradient-based estimation method, as described previously [30]. The iterative algorithm chose the optimal regimen based on a utility function that penalized (and therefore minimized) exposures outside the target range. The algorithm was restricted to allow four weight-bands with one tablet in the lowest weight-band and four tablets in the highest weight-band. Additionally, since very young infants often have a lower clearance due to immature enzymes, we investigated administering half a tablet to children <3, <6, <9 or <12 months [31]. The root mean square error (RMSE) was used to compare achievement of target exposures between the current and the optimized FDC. Further details are provided in the supplemental materials.

Exposure targets

There is no consensus in the pharmacokinetic targets for first line tuberculosis drugs in children. Therefore, we aimed to achieve exposures reported in adult patients on recommended doses of 10 and 5 mg/kg for rifampicin and isoniazid, respectively, and 1000 to 2000 mg pyrazinamide (depending on weight) [32,33]. For isoniazid and pyrazinamide, we used the lowest and highest median exposures reported in a systematic review of published studies in patients, excluding one study with outlying results for isoniazid [34], resulting in target ranges of 11.6-26.3 mg·h/L and 233-

429 mg·h/L, respectively [32]. For rifampicin, since increasing evidence supports the use of higher doses [14,15,20], we decided to target 38.73 mg·h/L to 72.94 mg·h/L, the mean estimate and highest study mean estimate, respectively, in a meta-analysis of published studies reporting steady-state pharmacokinetics [33].

RESULTS

Study population

Data from 180 children (42% female, 14% HIV-positive) was included, median (range) age 2.0 (0.22-12) years, and weight 10.9 (3.20-28.8) kg. NAT2 genotype was available in 142 (79%) children; 35/81/26 (25/57/18%) were slow/intermediate/fast acetylators. Subject characteristics are summarized in Table 2. A total of 841, 843, and 838 plasma concentrations of rifampicin, isoniazid, and pyrazinamide, respectively, were included in the analysis.

Population pharmacokinetic analysis

For rifampicin, a one-compartment model with transit compartments absorption and elimination via saturable hepatic clearance best described the data [25]. For isoniazid and pyrazinamide, two- and one-compartment disposition models, respectively, with first-order elimination and absorption with lag time described the data well. Allometry was included in the models for all drugs with fat-free mass as size descriptor and improved model fit. The maturation of clearance with age also improved the fit for all drugs, while maturation of bioavailability was identified for rifampicin and isoniazid (Figure 1). In the rifampicin model, the use of the formulation R-Cin was found to cause a 61% decrease in bioavailability, as previously reported [35]. For isoniazid, *NAT2* acetylator status significantly improved the fit by categorizing children in slow, intermediate, and fast metabolizers. The VPCs in Figure 2 show that the models are appropriately describing the data. Table 3 shows the

pharmacokinetic parameters and their precision. Additional modeling results can be found in the supplemental material.

Exposures with current FDC

Using the 2010 WHO dose recommendations and assuming bioavailability of the SRA-approved product (Table 1), median rifampicin exposure is below the target exposure for almost all weight-bands (Figure 3, panel A and Table S1). Median isoniazid exposure is within the target range for low weight children, while it is above target for most children above 8 kg and children below 3 months of age (Figure 3, panel B and Table S1). Median pyrazinamide exposure is within the target range for all weight-bands except for children below 3 months of age (Figure 3, panel C and Table S1). To increase low rifampicin exposure the dose was adjusted by adding an additional tablet of the currently available FDC in all children older than 3 months and above 5 kg (Figure 3, panels D-F and Table S1). As a result, median rifampicin exposure was within the target range, but isoniazid and pyrazinamide exposures were above the target range.

Optimization of fixed-dose combinations and weight-bands

To maximize target attainment, the optimal FDC would have a 60% higher rifampicin content (120 mg), a 30% lower isoniazid content (30 mg), and a 10% lower pyrazinamide content (135 mg) than the currently available FDC, with corresponding optimal break points between the weight-bands of 6, 13 and 20 kg (versus the currently 8, 12 and 16 kg), Table 1. Figure S2 compares the deviation from the target range (i.e., RMSE) of the three dosing regimens, the lower the deviation the better the regimen. The RMSE is considerably lower when using the new FDC and new weight-bands, indicating better target attainment than what is achieved with the current FDC. The improvement for rifampicin is most prominent in children in the lowest weight-band (<1 years-old) receiving a

single tablet where the deviation decreases from 86% with WHO dosing to approximately 30% when rifampicin dose is increased in children >3-months-of-age.

Median exposures achieved with the optimized FDC, and new weight-bands were within target range for all three drugs (Figure 3, panels G-I). Administering half a tablet in children below 3 months of age would prevent overexposure to pyrazinamide and rifampicin.

Figure 4 visualizes the probability of target attainment of the dosing scenarios. A new FDC and new weight-bands dramatically increases the percentage of children within the target range and improve the balance of under-and overdosing between the three drugs. Overall, the percentage of children that have an exposure within the target increases significantly, especially for rifampicin and isoniazid. With the current guidelines and FDC approximately 25%, 38% and 62% have exposure within the target range for rifampicin, isoniazid, and pyrazinamide, while with the optimized FDC target attainment increases to 50%, 64% and 71%, respectively. Furthermore, for rifampicin, under-exposure dropped from 73% to 27% when using the new FDC. We found similar improvements in a dataset containing patient characteristics from a real-life Kenyan population, Figure S4. The new FDC and weight-bands will also result in an acceptable isoniazid exposure in slow, intermediate, and fast acetylators (Figure S3). Especially in slow acetylators, less overexposure is expected compared with current guidelines. The optimization was performed on an AUC target but Figure S5 shows that with the new FDC and weight-bands, typical C_{max} ranges reported in adults are also achieved [36].

DISCUSSION

We found suboptimal exposures in children relative to adults in this prospective pharmacokinetic study investigating the exposure of three first-line antituberculosis drugs under the 2010 WHO guidelines. This is most worrying for rifampicin where we found that the majority of children are underdosed, even though there is sufficient evidence that higher rifampicin doses are more effective and tolerated well [13–17,20]. The smallest children who are most vulnerable to severe forms of disease were most at risk of low drug exposure [37]. Less than 10% of the children between 5 and 8 kg reached a rifampicin exposure comparable to adults. Children below 5 kg are likely to have incomplete enzyme maturation resulting in higher rifampicin exposures. However, in very young children we also found that bioavailability is reduced by 35% compared to older children. The lower exposures in young children is consistent with previous reports [38–40]. Exposure to isoniazid was found to be above the range that is seen in adults and lowering the dose could potentially result in fewer side effects, especially in slow acetylators [22]. The exposure to pyrazinamide, finally, was close to the set target range but children below 3 months of age have a much higher exposure due to incomplete enzyme maturation. Our results show that there is considerable potential to improve drug doses in all weight-bands especially for rifampicin and isoniazid but also for pyrazinamide in young infants in the lowest weight-band [41].

To optimize the rifampicin exposure, an additional tablet of the currently available FDC could be administered. It would result in improved rifampicin exposure across the board but with relatively high isoniazid and pyrazinamide exposures, increasing the risks of toxicity [17,20,21]. We show that a new FDC with 120, 30 and 135 mg of rifampicin, isoniazid, and pyrazinamide, respectively, with break points between the weight-bands at 6, 13, and 20 kg would result in exposures that are on average optimal for the whole weight and age range, thus potentially improving therapy, both in terms of efficacy and toxicity. The development of a new FDC is likely to take a considerable amount of time. Therefore, a temporary solution could be to use the current FDC and top up the rifampicin

dose with 75 mg (half a 150 mg rifampicin capsule) for each weight-band. Although not ideal, this will result in an improved rifampicin exposure, visualized in Figure 3D.

A study by Zvada et al., which estimated rifampicin exposures in pediatric patients on the 2010 WHO recommended doses, predicted that 75% of children below 25 kg would have an exposure below 39.5 mg·h/L [42]. Kwara *et al.* supported these results, in 2016, by reporting a median (IQR) rifampicin AUC of 31.2 mg·h/L (16.9-43.6) in 62 children [38]. Both studies show that 75% of their population has an exposure below their target which, was similar to the lower bound of the target exposure of 38.7 mg·h/L we used in this analysis. The Zvada *et al*. model has since been used to develop a method for dose optimization of FDCs [30,42]. However, this model had insufficient data to describe the saturable rifampicin clearance. In the current work, more data was available which allowed us to implement saturable clearance, hence, predictions at higher doses of rifampicin are likely to be more accurate.

Our study has some strengths and limitations that should be considered. Although we used single formulations instead of an FDC, we used formulations approved by an SRA or certified by the WHO to comply with Good Manufacturing Practices. Bioequivalence testing of a new pediatric FDC would be required, as originator products for these drugs are not available, there are potential differences in bioavailability of the drugs we measured and a new FDC that we could not account for. However, a recent study in children receiving the current FDC reported exposures in line with our predictions, indicating similar bioavailability [40]. Second, in applying the *NAT2* acetylator distributions from a study representing patients from a wide range of high burden countries, the results should serve global dosing practices, however the optimal doses of isoniazid for some geographic regions may be different. Third, the optimization procedure was performed with user-chosen constraints (e.g., 4 weight-bands, 1 tablet for the first group, half tablet for children <3 months-of-age). Consequently, the outcome is optimal for the chosen constraints but could be improved e.g., by allowing more weight-bands. The optimization procedure is flexible and can easily be adjusted to accommodate for

more, less, or different constraints, or different targets (C_{max} instead of AUC, or a combination of both). Fourth, we chose to aim for the adult exposure ranges, with above median exposure for rifampicin. However, the algorithm could readily be used to predict optimal FDCs and weight-bands for revised targets.

In conclusion, in this study we have confirmed the findings of previous reports showing low rifampicin exposures relative to adults, in children receiving the currently recommended doses. Resolving low rifampicin exposure by increasing the number of tablets of the current FDC would result in supratherapeutic exposures to isoniazid and pyrazinamide, risking adverse events. We designed a new FDC with 120/30/135 mg rifampicin/isoniazid/pyrazinamide with new weight-bands of <6, 6-13, 13-20 and 20-25 kg (Table 1), which would result in exposures in line with adult exposures for all three drugs. An extra 75 mg rifampicin in each weight-band could be used as a temporary solution against low rifampicin exposure.

NOTES

ACKNOWLEDGEMENTS

We thank all families for participation in the study. We thank the Kenyan Ministry of Health for providing demographic data of children diagnosed with tuberculosis in Kenya. Computations were performed using facilities provided by the University of Cape Town's ICTS High Performance Computing team: hpc.uct.ac.za

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FUNDING

This research was sponsored by the National Institutes of Health [NIH (Bethesda, MD, USA)] and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01HD069175). HM is funded by the Wellcome Trust (206379/Z/17/Z). EMS is supported by PanACEA, which is part of the European and Developing Countries Clinical Trials Partnership (EDCTP) 2 programme supported by the European Union (grant number TRIA2015-1102-PanACEA). HZ is supported by the SA-MRC. Research reported in this publication was also supported by National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (Award nos. UM1 AI068634, UM1 AI068636 and UM1 AI106701). The content is solely the responsibility of the authors and does not necessarily represent the official views of the sponsors.

CONFLICTS OF INTEREST

HR reports support paid to their institution to conduct PK work from DNDi, during the conduct of the study; support from NIH (part of CTU paid to the institution); payment for lectures and travel support for conference attendance from ABBVIE, outside the submitted work. None of the other authors have any conflicts of interest to disclose.

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TABLES AND FIGURES

Table 1 Drug content and weight-bands for the WHO recommended FDC and the optimized FDC and weight-bands.

	WHO	Optimized FDC and weight-bands
Rifampicin (mg)	75	120
Isoniazid (mg)	50	30
Pyrazinamide (mg)	150	135
1st weight-band (1 tablet) (kg)	4 - 8	3 - 6
2nd weight-band (2 tablet) (kg)	8 - 12	6 - 13
3rd weight-band (3 tablet) (kg)	12 - 16	13 - 20
4th weight-band (4 tablet) (kg)	16 - 25	20 - 25

WHO, World Health Organization; FDC, fixed-dose combination

Table 2 Patient demographics

	South Africa			Malawi	
	Desmond Tutu TB Centre (N=40)	**Red Cross Children's Hospital (N=106)**	**Tygerberg Hospital (N=6)**	**Queen Elizabeth Central Hospital (N=28)**	**Total (N=180)**
Age (years)					
Median	0.572	2.49	1.42	6.55	2.03
[Min - Max]	[0.219 - 0.991]	[0.263 - 10.2]	[0.890 - 3.00]	[1.63 - 11.9]	[0.219 - 11.9]
Height (cm)					
Median	63.1	84.9	72.0	98.4	80.6
[Min - Max]	[49.9 - 74.0]	[59.0 - 134]	[70.0 - 86.2]	[71.6 - 135]	[49.9 - 135]
Weight (kg)					
Median	6.50	12.2	10.0	14.1	10.9
[Min - Max]	[3.20 - 10.2]	[5.91 - 28.8]	[8.10 - 13.0]	[6.70 - 26.7]	[3.20 - 28.8]
Fat-free mass (kg)					
Median	5.16	9.59	7.49	11.4	8.40
[Min - Max]	[2.76 - 7.77]	[4.72 - 21.3]	[6.45 - 10.1]	[5.54 - 22.7]	[2.76 - 22.7]

Weight-for-age z-score					
Median	-2.09	-0.607	-0.482	-3.07	-0.829
[Min - Max]	[-5.25 - 1.22]	[-3.43 - 2.19]	[-2.52 - 0.350]	[-6.08 - 0.369]	[-6.08 - 2.19]
Height-for-age z-score					
Median	-2.43	-1.34	-2.41	-2.82	-1.87
[Min - Max]	[-6.51 - 1.26]	[-4.84 - 1.90]	[-4.68 - - 0.943]	[-7.70 - - 0.189]	[-7.70 - 1.90]
Sex					
Male	27 (67.5%)	59 (55.7%)	4 (66.7%)	16 (57.1%)	106 (58.9%)
Female	13 (32.5%)	47 (44.3%)	2 (33.3%)	12 (42.9%)	74 (41.1%)
HIV Status					
Negative	35 (87.5%)	97 (91.5%)	0 (0%)	18 (64.3%)	150 (83.3%)
Positive	5 (12.5%)	5 (4.7%)	6 (100%)	9 (32.1%)	25 (13.9%)
Missing	0 (0%)	4 (3.8%)	0 (0%)	1 (3.6%)	5 (2.8%)
Antiretroviral					
NA	35 (87.5%)	102 (96.2%)	0 (0%)	19 (67.9%)	156 (86.7%)
Lopinavir/ritonavir	5 (12.5%)[#]	2 (1.9%)[*]	6 (100%)[*]	0 (0%)	13 (7.2%)
Efavirenz	0 (0%)	1 (0.9%)	0 (0%)	5 (17.9%)	6 (3.3%)
Nevirapine	0 (0%)	1 (0.9%)	0 (0%)	4 (14.3%)	5 (2.8%)
Administration method					
Whole	0 (0%)	23 (21.7%)	0 (0%)	20 (71.4%)	43 (23.9%)
Crushed and swallowed	0 (0%)	50 (47.2%)	6 (100%)	3 (10.7%)	59 (32.8%)
Crushed and syringe	1 (2.5%)	33 (31.1%)	0 (0%)	4 (14.3%)	38 (21.1%)
Crushed and nasogastric tube	39 (97.5%)	0 (0%)	0 (0%)	1 (3.6%)	40 (22.2%)
Rifampin formulation					
Eremfat	15 (37.5%)	78 (73.6%)	0 (0%)	22 (78.6%)	115 (63.9%)

R-Cin	25 (62.5%)	28 (26.4%)	0 (0%)	6 (21.4%)	59 (32.8%)
Rimactazid	0 (0%)	0 (0%)	6 (100%)	0 (0%)	6 (3.3%)
Rifampin dose (mg)					
Median	80.0	240	120	240	160
[Min - Max]	[40.0 - 166]	[80.0 - 300]	[120 - 180]	[80.0 - 300]	[40.0 - 300]
Isoniazid dose (mg)					
Median	75.0	150	120	150	150
[Min - Max]	[37.5 - 150]	[75.0 - 300]	[120 - 180]	[100 - 300]	[37.5 - 300]
Pyrazinamide dose (mg)					
Median	225	450	250	450	450
[Min - Max]	[113 - 375]	[188 - 900]	[250 - 500]	[225 - 900]	[113 - 900]
Rifampin dose (mg/kg)					
Median	15.4	15.5	13.6	16.0	15.5
[Min - Max]	[10.1 - 20.5]	[10.1 - 20.0]	[11.8 - 14.8]	[11.2 - 20.0]	[10.1 - 20.5]
Isoniazid dose (mg/kg)					
Median	12.8	11.9	13.6	11.2	12.0
[Min - Max]	[10.3 - 15.4]	[10.1 - 14.9]	[11.8 - 14.8]	[10.0 – 21.5]	[10.0 – 21.5]
Pyrazinamide dose (mg/kg)					
Median	34.1	34.6	30.9	33.5	34.1
[Min - Max]	[28.5 - 38.5]	[28.3 - 41.7]	[24.5 - 38.5]	[27.9 - 40.9]	[24.5 - 41.7]
NAT2 Status					
Slow	7 (17.5%)	28 (26.4%)	0 (0%)	0 (0%)	35 (19.4%)
Intermediate	23 (57.5%)	58 (54.7%)	0 (0%)	0 (0%)	81 (45.0%)
Fast	8 (20.0%)	18 (17.0%)	0 (0%)	0 (0%)	26 (14.4%)
Not available	2 (5.0%)	2 (1.9%)	6 (100%)	28 (100%)	38 (21.1%)
SLCO1B1 gene *(rs4149032)*					

Wild type (TT)	0 (0%)	62 (58.5%)	0 (0%)	0 (0%)	62 (34.4%)
TC	0 (0%)	31 (29.2%)	0 (0%)	0 (0%)	31 (17.2%)
CC	0 (0%)	8 (7.5%)	0 (0%)	0 (0%)	8 (4.4%)
Not available	40 (100%)	5 (4.7%)	6 (100%)	28 (100%)	79 (43.9%)
Arylacetamide deacetylase *(rs1803155)*					
Wild type (AA)	0 (0%)	72 (67.9%)	0 (0%)	0 (0%)	72 (40.0%)
AG	0 (0%)	32 (30.2%)	0 (0%)	0 (0%)	32 (17.8%)
GG	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not available	40 (100%)	2 (1.9%)	6 (100%)	28 (100%)	76 (42.2%)

* These patients received an increased dose of 3 times a day lopinavir/ritonavir
# These patients received lopinavir with super boosted ritonavir

Table 3 Pharmacokinetic parameter estimates for the final models of Rifampicin, Isoniazid and Pyrazinamide

	Typical values (95% CI)[a]		
Parameter	Rifampicin	Isoniazid	Pyrazinamide
Clearance[b] (L/h) Slow Intermediate Fast	54.5 (33.2–74.5) - - -	- 3.00 (2.70–3.44) 4.65 (4.24–5.22) 5.90 (4.98–7.06)	1.03 (0.982–1.10) - - -
Volume[b] (L)	12.3 (10.4–14.2)	10.5 (9.60–11.6)	8.96 (8.70–9.19)
Q[b] (L/h)	-	0.364 (0.291–0.453)	-
V_p[b] (L)	-	3.04 (2.33–4.49)	-
Bioavailability – F ( )	1 FIXED	1 FIXED	1 FIXED
MTT (h)	0.589 (0.397–0.736)	-	-
NN ( )	9.70 (5.89–14.4)	-	-
Lag time (h)	-	0.123 (0.0244–0.440)	0.106 (0.0121–0.262)
K_a (1/h)	1.82 (1.24–3.47)	2.83 (2.28–4.50)	3.36 (2.50–4.15)
Q_h[e](L/h)	90 FIXED	-	-
V_h[e](L)	1 FIXED	-	-
f_u ( )	0.2 FIXED	-	-
K_m (mg/L)	8.25 (4.45–17.8)	-	-
Formulation on F[f] (%)	-61.5 (-52.8– -71.0)	-	-
Yesterday's F (%)	-	-	-34.2 (-21.6– -44.6)
Maturation of CL[d]			
PMA_{50} (years)	1.04 (0.856–1.15)	0.829 (0.777–0.898)	0.922 (0.808–1.03)
γ ()	3.22 (3.03–3.45)	3.35 (3.13–3.52)	3.56 (3.34–3.89)
Maturation of F			
F at birth ( )	0.655 (0.141–0.759)	0.740 (0.609–0.855)	-
Age_{full_F} (years)	2.72 (0.607–4.08)	1.63 (1.18–3.36)	-
BSV (CV%)[c]			

Clearance	41.8 (34.3–53.1)	30.8 (26.2–34.8)	24.8 (20.9–28.1)
BOV (CV%)[c]			
Bioavailability	45.1 (37.5–68.6)	31.1 (25.9–36.1)	17.8 (13.3–22.1)
K_a	111 (75.6–155)	48.7 (28.9–76.7)	58.8 (39.2–88.1)
MTT	58.8 (43.1–78.8)	-	-
Lag time	-	132 (48.0–269)	147 (58.8–309)
Residual variability			
Proportional error (%)	13.7 (11.4–16.4)	8.19 (6.25–10.0)	7.28 (6.09–8.36)
Additive error[g] (mg/L)	0.023 FIXED	0.0610 (0.0364–0.0794)	1.33 (1.10–1.59)

V_p, peripheral volume of distribution; Q, inter-compartmental clearance between the central and peripheral volume of distribution; MTT, mean transition time; NN, number of transit compartments; K_a, absorption rate constant; Q_h, hepatic blood flow; f_u, unbound fraction; V_h, volume of distribution of the hepatic compartment; K_m, Michaelis-Menten constant; PMA_{50}, postmenstrual age at which maturation of clearance is 50% complete; γ, shape factor for maturation of clearance; F, bioavailability; Age_{full}, age at which bioavailability is 1; BSV, between subject variability; BOV, between occasion variability; CV, coefficient of variance.

[a] Based on n=500 bootstraps

[b] These parameters were allometrically scaled with fat-free mass (FFM) and the typical values reported refer to a 9-kg FFM individual. For rifampicin, the value reported is the maximum intrinsic clearance (i.e. intrinsic clearance at concentrations<<K_m, see supplementary methods)

[c] CV% was calculated as $\sqrt{(\omega^2)}$

[d] A prior was included to estimate these parameters, details can be found in the supplemental materials

[e] These values are for an adult male of 70-kg male corresponding with 56-kg of FFM. Then it was allometrically scaled with FFM.

[f] This effect was for the R-Cin formulation only.

[g] Additive error estimates include an value of 20% of the respective lower limit of quantification for each drug.

Figure Legends:

Figure 1 Maturation of clearance (solid line) and bioavailability (dashed line) of rifampicin, isoniazid, and Pyrazinamide. The vertical lines in the bottom indicate the ages for which we have observations

Figure 2 Visual predictive check of the rifampicin, isoniazid, and pyrazinamide concentrations versus time after dose, stratified for children below and above 1 year-of-age. The solid and dashed lines represent the 5th, 50th, and 95th percentiles of the observed data, while the shaded areas represent the model-predicted 95% confidence intervals for the same percentiles. The dots are the observed concentrations. Model predicted concentrations below the limit of quantification (BLQ) were set to half the lower limit, which is in line with how observed BLQ concentrations were handled.

Figure 3 Simulated exposures in 110,000 children between 3 and 25 kg below (blue) and above (red) 3 months-of-age to rifampicin (first column), isoniazid (second column) and pyrazinamide (third column) under 2010 WHO dose recommendation (first row), augmented doses of the current FDC to optimize the rifampicin exposure (second row) and on a new FDC and new weight-bands to optimize exposure to all drugs (third row). The dashed lines represent the weight-bands, the green shaded is the target range. The boxes represent the 25^{th}, 50^{th} and the 75^{th} percentile and the whiskers represent the 5^{th} and 95^{th} percentile. The red stars indicate that the 95^{th} percentile is outside of the plot range. The blue dashed boxplots in the bottom row represent the exposure in children <3 months old when receiving a full tablet instead of half a tablet. The underlying data are shown in Table S1 in the supplemental material.

Figure 4 Percentage of individuals within (green), below (yellow) or above (red) the target range of rifampicin (first column), isoniazid (second column) and pyrazinamide (third column) under 2010 WHO dose recommendation (first row), augmented doses of the current FDC to optimize the rifampicin exposure (second row) and on a new FDC and new weight-bands to optimize exposure to all drugs (third row).

Figure 1

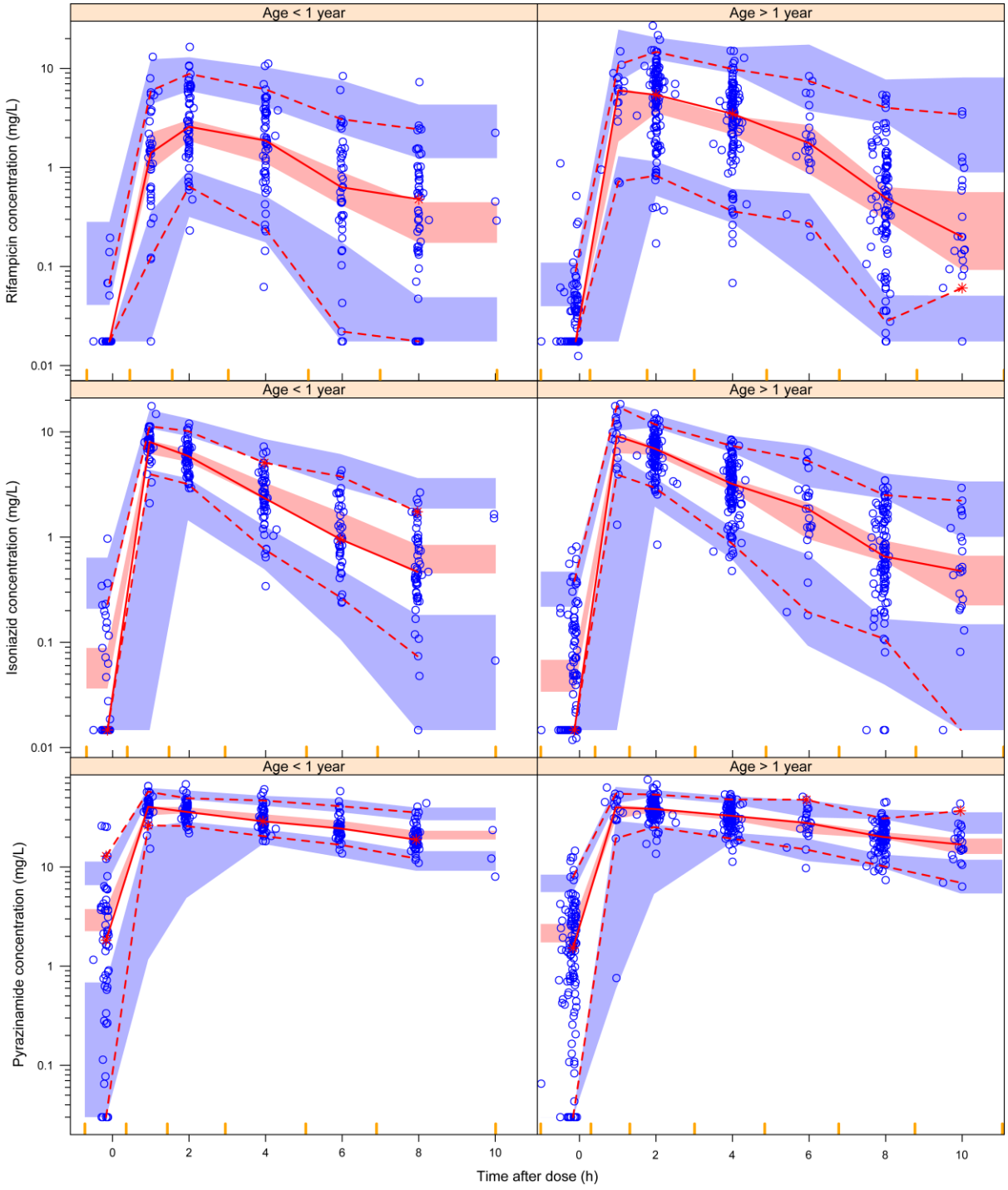

Figure 2

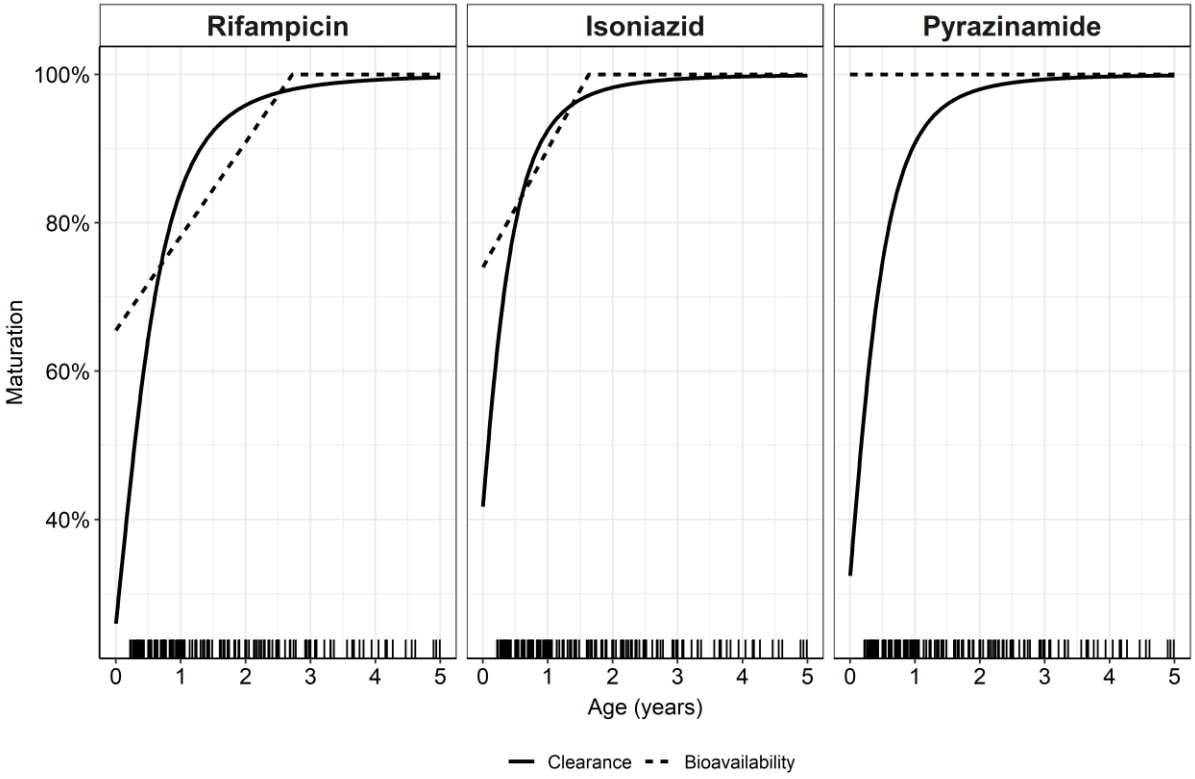

Figure 3

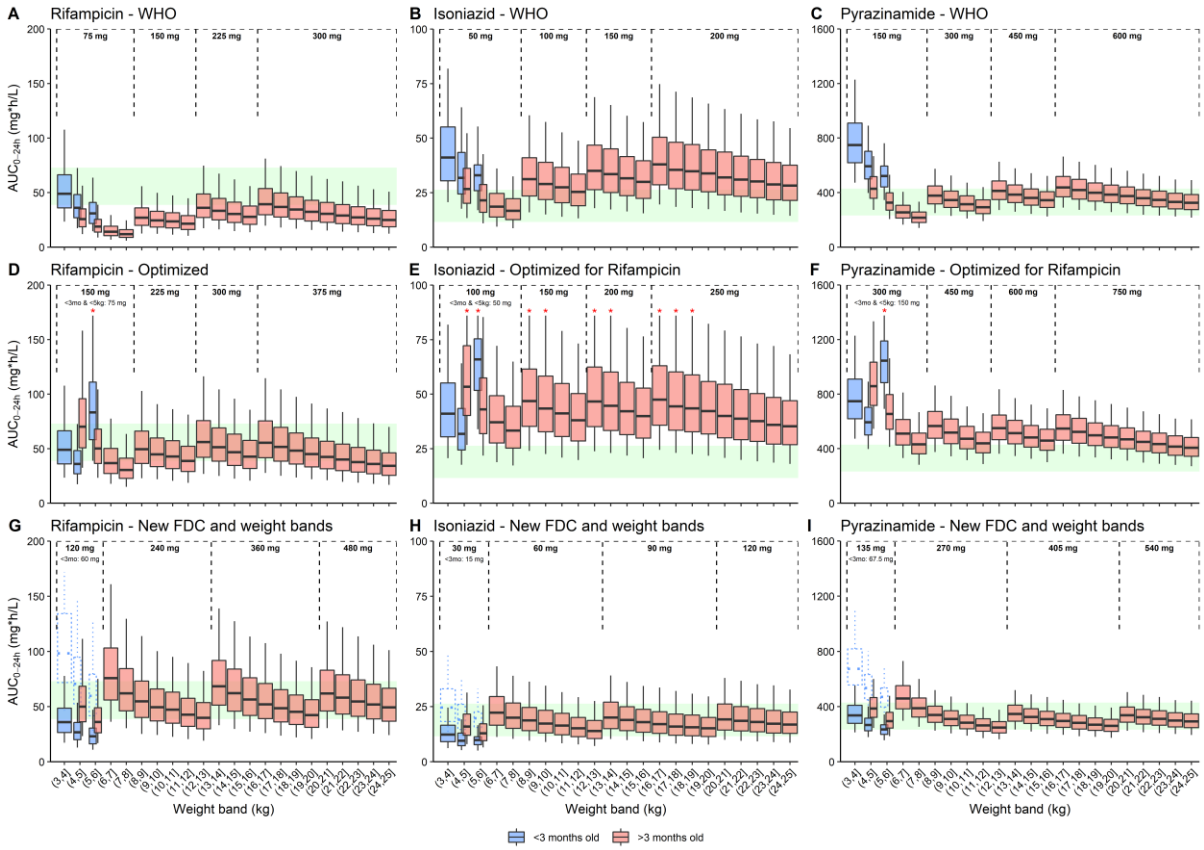

Figure 4