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CPMT Project No.: 08-011

Pharmacokinetic Analyses of Fixed-Dose Drug Combinations for
Pediatric Tuberculosis

Prepared For:
The World Health Organization, Geneva, Switzerland

Preliminary Report Prepared:
15 December 2008

Final Report Submitted:
23 January 2009


Addendum Submitted:
30 February 2009

CPMT Project No.: 08-011

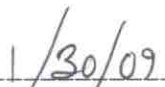
Pharmacokinetic Analyses of Fixed-Dose Drug Combinations for Pediatric Tuberculosis

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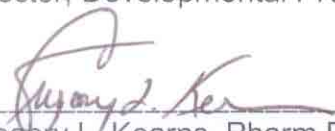
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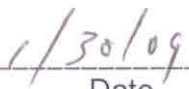
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Objectives

In July 2008, WHO convened a task force which was charged to evaluate the dosing of drugs currently recommended (by WHO) for use in the treatment of children with tuberculosis. This task force was comprised of experts in pediatrics, pediatric infectious diseases, tropical medicine and pediatric clinical pharmacology. A comprehensive review of four drugs (isoniazid, rifampin, pyrazinamide and ethambutol) was undertaken with respect to age-appropriate guidelines for their dosing and use. The task force considered the importance of adherence and compliance in drug regimens to treat pediatric tuberculosis and identified the need to produce an age-appropriate solid, combination fixed drug-dose formulation. The formulation should possess the necessary characteristics to enable age-appropriate drug dosing in a precise manner that would be suitable for administration by caregivers with minimal sophistication. The work product from this meeting included the development (by Drs. S. P. Spielberg and G. L. Kearns) of a dosing “table” constructed using a weight-based strategy that would encompass a pediatric population of infants and children ranging from 5 to 30 kg total body weight (Table 1, Appendix).

WHO commissioned this *in silico* study to explore the dose-exposure-response relationship for a fixed-strength, three-drug formulation of isoniazid (INH), rifampin (RIF) and pyrazinamide (PZA).

The two primary objectives of this report included:

1. Simulate the steady state plasma concentrations of each of the three drugs based on age-specific estimates of pharmacokinetic (PK) parameters derived from the existing medical literature. These simulations should consider relevant intrinsic factors (e.g. age, concomitant disease, pharmacogenetics) that might be expected to contribute to PK variability.
2. Explore exposure-response relationships for each of the three drugs based on appropriate pharmacodynamic (PD) surrogates previously described in the literature.

Pharmacokinetic Simulations

Simulations were performed to determine the range of pediatric exposures expected in infants and children after fixed-dosing of INH, RIF and PZA. These simulations were conducted using established pharmacokinetic methods. Each simulation used pharmacokinetic parameter estimates derived from previously conducted pediatric studies as detailed in the references section. Adult studies were used, where necessary, to derive estimates of absorption rate constant (k_a) and oral bioavailability (F). Drug concentrations were simulated according to a once-daily (i.e. every 24 hour) dosing regimen and accumulated to steady-state using a model-dependent approach with first-order absorption and mono-exponential decay. The parameter estimates employed in the simulations along with the resultant average estimates of drug exposure (+/- 90% confidence interval) are provided in the Appendix.

It should be highlighted that several important and necessary assumptions are nested in these simulations. The most relevant assumptions employed herein are detailed as follows:

1. The pharmacokinetic parameters used in these simulations (derived from primary and secondary medical literature) offer a reasonable approximation of those that would be observed in the infants and children receiving the fixed-dosing combination under evaluation.
2. The pharmacokinetic parameters employed herein represent values that approximate those that would be observed after repeated drug administration.
3. The pharmacokinetic parameters used for the simulation of any given drug represent values that approximate those that would be observed with concomitant administration of the other two drugs (i.e. no accounting for drug-drug interactions).
4. The pediatric weights used in these simulations reflect the range of weights anticipated for children (both male and female) expected to receive the fixed-dosing combination under evaluation.

5. No dose-dependent (i.e. zero-order, mixed zero-order/first-order) absorption is observed within the range of doses evaluated.
6. There are no appreciable age-dependent differences in the rate and extent of absorption between the age groups evaluated.
7. There are no appreciable age-dependent differences in the extent of drug distribution within the age groups simulated.
8. Systemic drug exposure resulting from dose escalation within any given individual is linear and does not vary with age.
9. There are no formulation specific (i.e. physicochemical) effects that would independently alter the disposition of the component drugs under evaluation.

Note: in the absence of relevant *in vivo* and *in vitro* data the validity of selected assumptions remains unconfirmed.

Pharmacokinetic/Pharmacodynamic Surrogates

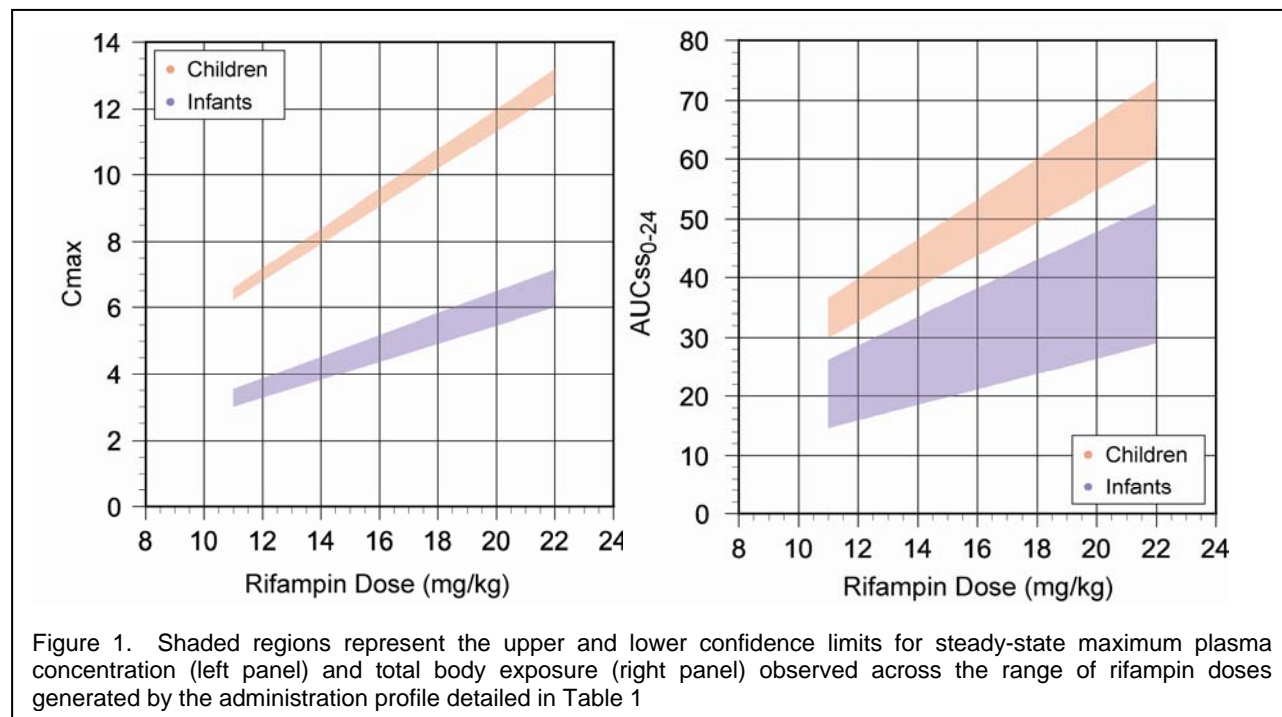
Pharmacokinetic surrogate endpoints were selected from among those described in the review by P. R. Donald (2008) as being associated with expected efficacy in the treatment of systemic infections produced by *M. tuberculosis*. In all instances, these reflected attainable plasma drug concentrations at specific post-dose time points. Pharmacodynamic surrogate endpoints [e.g. maximum plasma concentration to MIC ratio (C_{max}/MIC), area under the plasma concentration vs. time curve to MIC ratio (AUC/MIC) and percent of the dosing interval where concentrations remain above the MIC (%T>MIC)] were determined using the minimum inhibitory concentration that reflects the upper limit of susceptibility for each drug against *M. tuberculosis*. Two important caveats should be considered in the interpretation of PK/PD data from the simulations in this report: 1) PD surrogate endpoints derived from *in vitro* data represent a static, single-dimension perspective of pathogen sensitivity to a fixed concentration of drug and 2) the discussion of PD

surrogates for each drug and their potential implications do not consider additivity and/or synergy that can be achieved *in vivo* with combination therapy

Results-Rifampin

Table 2 (Appendix) details the parameter estimates used in the simulations of rifampin exposure at the dose levels detailed in Table 1 (Appendix). Tables 3 and 4 (Appendix) provide a summary of the average exposure estimates (along with the 90% confidence interval) of rifampin as well as corresponding values for rifampin pharmacokinetic/pharmacodynamic surrogates.

Across the range of doses from 11 to 22 mg/kg, average estimates of C_{max} range from 3.3 to 6.5 mcg/mL in infants and 6.4 to 12.8 mcg/mL in children (Figure 1, left). Similarly, AUC ranges between 19.8 to 39.6 mcg*hr/mL and 33.0 to 66.0 mcg*hr/mL for infants and children, respectively (Figure 1, right).



The simulated plasma concentration-vs.-time profiles suggest that infants and children spend between 33-70% of a 24-hour dosing interval above the susceptibility limit for *M. tuberculosis* (0.5 mcg/mL) when administered doses between 11 to 22 mg/kg (Figure 2). Notably, significantly more variability is anticipated in this pharmacodynamic surrogate for infants as compared with children which is

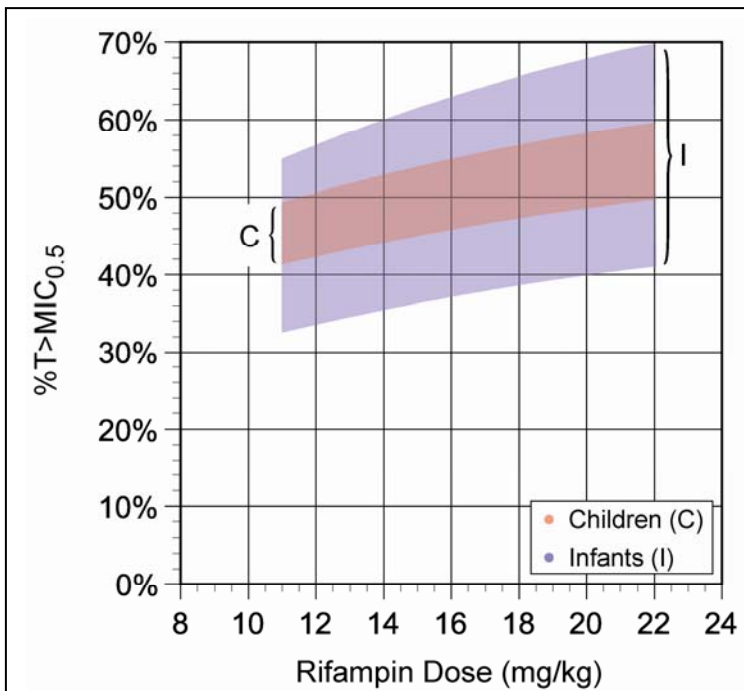


Figure 2. Shaded regions represent the upper and lower confidence limits for the percent of a 24-hour dosing interval that remains above the limit of susceptibility for a *M. tuberculosis* isolates when rifampin is dosed according to the administration profile detailed in Table 1.

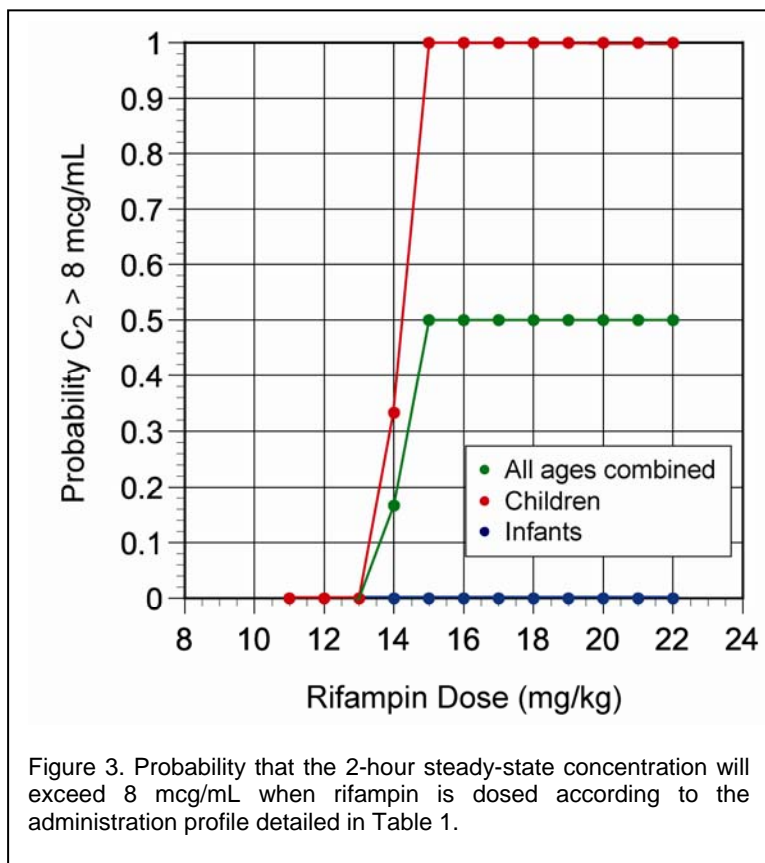


Figure 3. Probability that the 2-hour steady-state concentration will exceed 8 mcg/mL when rifampin is dosed according to the administration profile detailed in Table 1.

accounted for, in part, by the larger degree of inter-individual variability in drug elimination observed in this population. (Figure 2).

In no instance did infants who would receive an 11-22 mg/kg rifampin dose achieve the pharmacokinetic surrogate (i.e. plasma concentrations 2 hours post-dose that equal or exceed 8 mcg/mL) described as desirable by Peloquin (1992) (Figure 3). In

contrast, the average child achieved a C_2 of 8 mcg/mL with doses equal to, or in excess of, 15 mg/kg (Figure 3). When the dosing strategy detailed in Table 1 is applied without regard for age, less than half of pediatric recipients will achieve this particular pharmacokinetic target (Figure 3). However, this surrogate remains to be validated in children.

Results-Pyrazinamide

Table 5 (Appendix) details the parameter estimates used in the simulations of pyrazinamide at the dose levels detailed in Table 1 (Appendix). Tables 6 and 7 (Appendix) provide a summary of the average estimates (along with the 90% confidence interval) of pyrazinamide exposure and pyrazinamide pharmacokinetic/pharmacodynamic surrogates.

Of note, two distinct subpopulations with respect to pyrazinamide absorption have been described in the literature (Wilkins 2006). The pyrazinamide absorption rate constant was demonstrated to be bimodal in a population of South African tuberculosis patients (with an equal fraction of individuals characterized as fast or slow

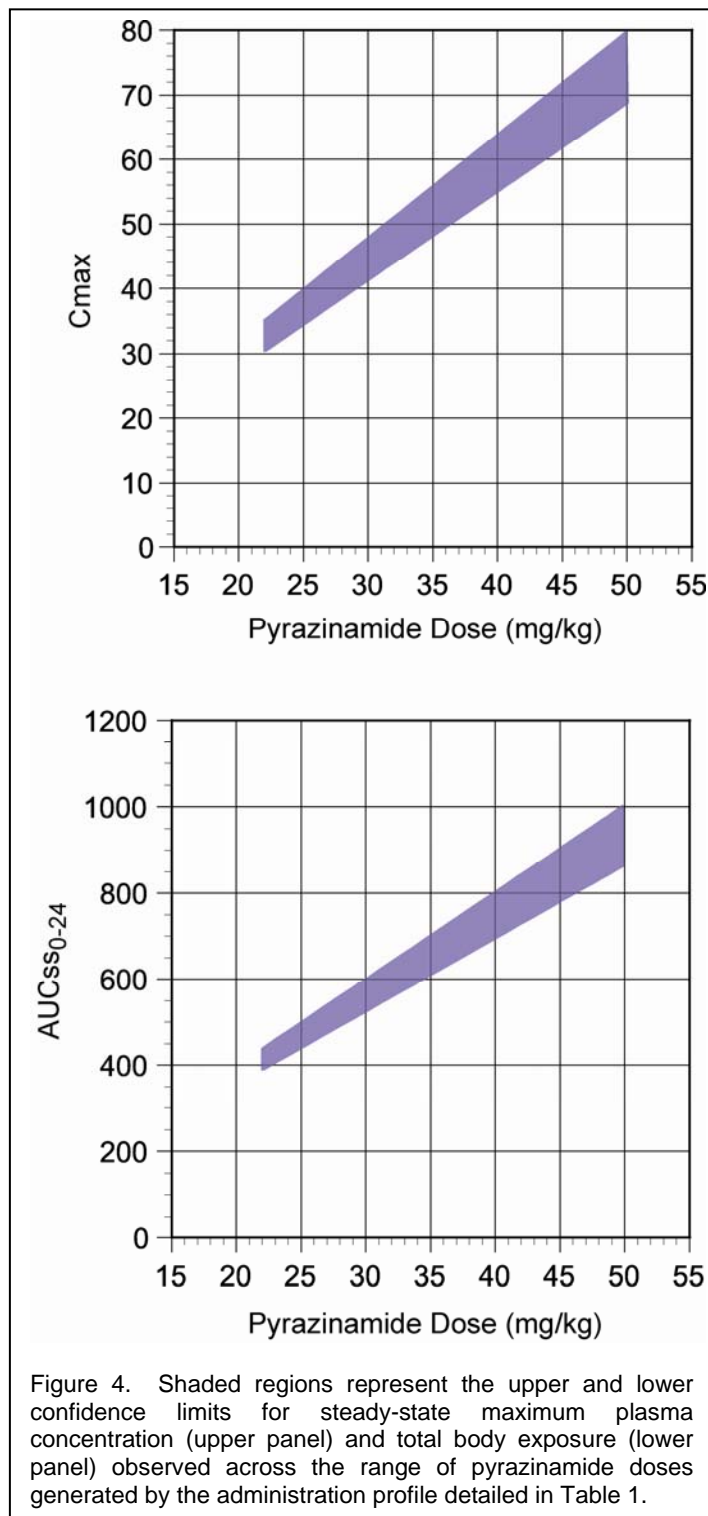
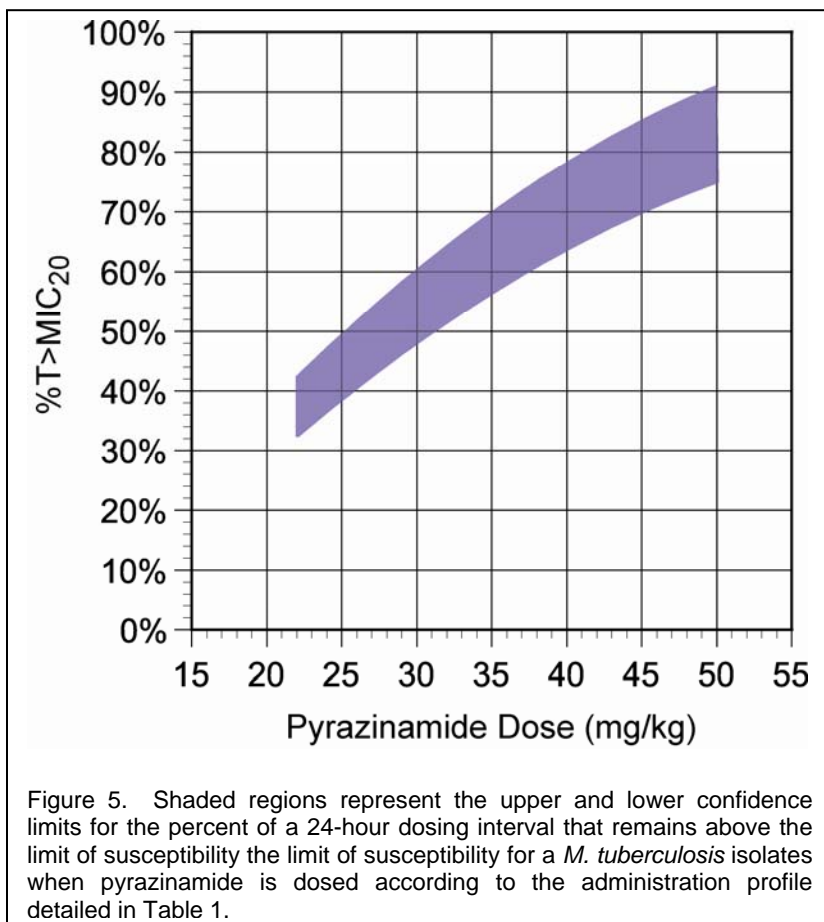


Figure 4. Shaded regions represent the upper and lower confidence limits for steady-state maximum plasma concentration (upper panel) and total body exposure (lower panel) observed across the range of pyrazinamide doses generated by the administration profile detailed in Table 1.

absorbers). Absorber status could not be predicted based on the demographic or formulation-dependent covariates examined in the investigation. As such, this report simulates the pharmacokinetic profile for infants and children with parameter estimates derived from both slow and fast absorbers in attempts to more completely reflect the variability that might be expected following oral administration.

Across the range of doses from 22 to 50 mg/kg, average estimates of C_{max} range from 31.3 to 77.5 mcg/mL (Figure 4, upper). Estimates of AUC ranged from between 406.6 to 937.8 mcg*hr/mL (Figure 4, lower). There were no significant difference in pharmacokinetic parameters between slow and fast absorbers (although the latter, as expected, was associated slightly higher C_{max} values and slightly lower estimates of total body exposure). Consequently, the composite data are reflected in Figure 4.

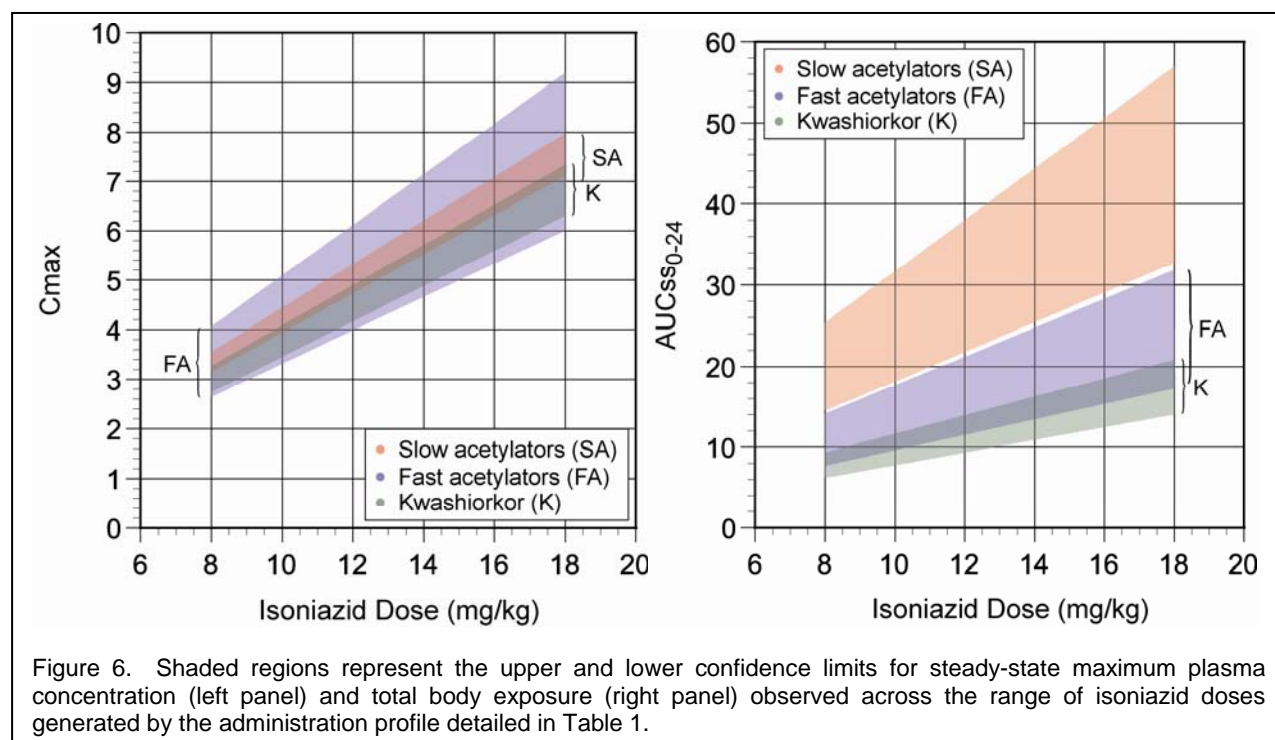


These simulated plasma concentration-vs.-time profiles suggest that infants and children spend between 32-91% of a 24-hour dosing interval above the susceptibility limit for *M. tuberculosis* (20 mcg/mL) when administered doses between 22 to 50 mg/kg (Figure 5). In every instance, infants and children administered pyrazinamide

according to the dosing strategy detailed in Table 1 achieved the pharmacokinetic surrogate (i.e. plasma concentrations at 2 hours post-dose that equal or exceed 20 mcg/mL) described as desirable by Peloquin (1992). These findings should be considered in the context of reports concerning possible dose-dependent toxicity with pyrazinamide.

Results-Isoniazid

Table 8 (Appendix) details the parameter estimates used in the simulations of isoniazid at the dose levels detailed in Table 1 (Appendix). Tables 9 through 13 (Appendix) provide a summary of the average estimates (along with the 90% confidence interval) of isoniazid exposure and isoniazid pharmacokinetic/pharmacodynamic surrogates. Both nutritional status (reflective of severe protein/calorie malnutrition) and N-acetyltransferase phenotype (i.e. acetylator status) were taken into account in these simulations. Given that acetylator, and in some cases nutritional, status are not known at the time of dosing, figures detailing the pharmacokinetic/pharmacodynamic surrogates are represented in both segregated and pooled fashion.



Across the range of doses from 8 to 18 mg/kg, average estimates of C_{max} range from 2.8 to 8.7 mcg/mL (Figure 6, left) and estimates of AUC range from 8.6 to 48.7 mcg*hr/mL (Figure 6, right). As would be expected, slow acetylators demonstrate larger estimates of total body

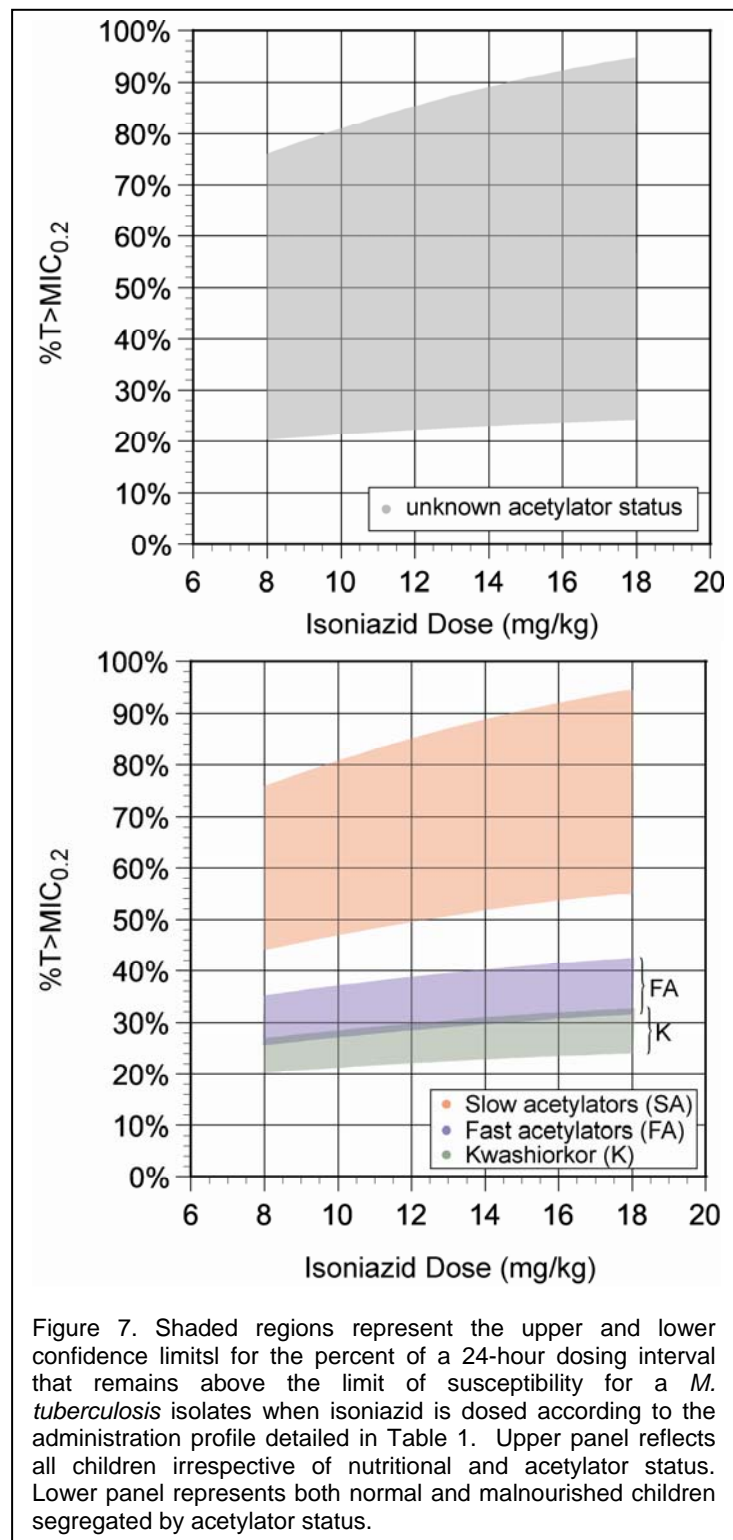


Figure 7. Shaded regions represent the upper and lower confidence limits for the percent of a 24-hour dosing interval that remains above the limit of susceptibility for a *M. tuberculosis* isolates when isoniazid is dosed according to the administration profile detailed in Table 1. Upper panel reflects all children irrespective of nutritional and acetylator status. Lower panel represents both normal and malnourished children segregated by acetylator status.

exposure as compared with fast acetylators (Figure 6, right); however, the range of C_{max} values observed between metabolizer phenotypes overlaps between the populations (Figure 6, left). Notably, children with Kwashiorkor would be expected to have total body exposure estimates that are comparable to or lower than those observed in children that are rapid metabolizers (Figure 6, right).

The simulated plasma concentration-vs.-time profiles suggest that infants and children administered isoniazid at doses between 8 and 18 mg/kg can spend as little as 20% or as much as 95% of a 24-hour dosing interval above the susceptibility limit for *M. tuberculosis* (0.2 mcg/mL) (Figure 7, upper). As illustrated, the extent to which this pharmacodynamic surrogate is attained is markedly

dependent on both nutritional and acetylase status (Figure 7, lower).

The probability that infants and children administered 8-18 mg/kg of isoniazid achieve the pharmacokinetic surrogate described as desirable by Mitchell & Bell (1957), Peloquin (1992), and Donald et al. (2004, 2007) (i.e. plasma concentrations 2-hours post-dose around 3 mcg/mL) is illustrated in Figure 8. When all children are considered without regard for nutritional or acetylase status, the majority will achieve the desired pharmacokinetic target with the dosing strategy detailed in Table 1 (Figure 8, upper). Given that metabolizer phenotype is unlikely to be available *a priori*, the probability that this surrogate is achieved according to nutritional status alone across all metabolizer phenotypes is also depicted (Figure 8, lower). As illustrated, infants and children with Kwashiorkor are at greatest risk for

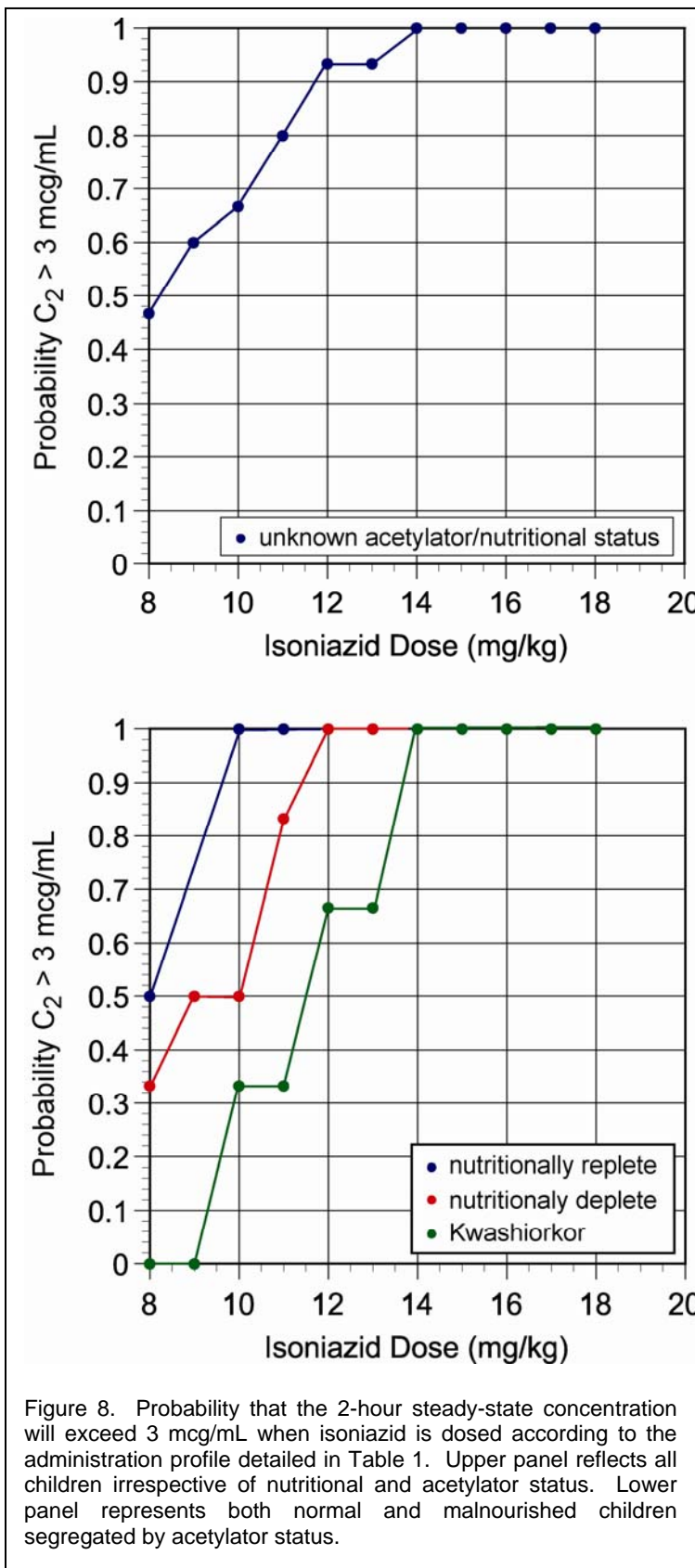


Figure 8. Probability that the 2-hour steady-state concentration will exceed 3 mcg/mL when isoniazid is dosed according to the administration profile detailed in Table 1. Upper panel reflects all children irrespective of nutritional and acetylase status. Lower panel represents both normal and malnourished children segregated by acetylase status.

failing to attain this surrogate at the recommended dosing scheme followed by malnourished infants/children as compared with nutritionally replete children.

Summary/Conclusions

Rifampin: Consequent to significant and expected variability in the clearance of RIF, the degree of systemic exposure attained with the administration of any given dose in the range simulated (11-22 mg/kg) is equally variable. With respect to the pharmacodynamic (PD) implications associated with this pharmacokinetic (PK) variability, the greatest possible concern related to adequacy of dosing resides with infants; a point illustrated by our finding that no infants from the simulations would have attained a 2-hour post-dose plasma concentration greater than or equal to 8.0 mg/L (presumed target efficacy surrogate previously reported in literature but not validated for children). Despite the potential for PD additivity in a 3 drug combination containing RIF, PZA and INH, it appears reasonable to reconsider the adequacy of the RIF dose for infants currently suggested in the dosing table.

Pyrazinamide: In contrast to RIF, the variability in predicted systemic exposure produced by the range of PZA doses suggested by the dosing table is less and portends predicted efficacy when the PD surrogate of attainment of plasma concentration greater than 20 mg/L is used. Further evaluation of the adequacy of the PZA doses in the table should consider any evidence of concentration-associated PZA toxicity.

Isoniazid: When the entire population of children is considered, the 8 to 18 mg/kg range of doses contained in the dosing table achieves the putative PD surrogate (time above the MIC) anywhere from 20 to 95% of a dosing interval. This variability appears to result from a combination of factors which includes acetylator phenotype and in some instances, nutritional status (eg., Kwashiorkor, acute malnutrition). It should be noted that the MIC evaluated herein

reflects the upper limit of susceptibility and thus the most conservative estimate of PD adequacy. A priori knowledge of the acetylator phenotype would have the impact of markedly improving INH dose selection given the differences in dose-exposure profile between patients who are fast and slow acetylators.

Recommendations / Future Directions

The results from these initial simulations should be further considered by WHO professional staff, the WHO subcommittee tasked to evaluate paediatric TB therapy (a group containing experts in antimycobacterial treatment, paediatric infectious disease and paediatric clinical pharmacology and pharmacy) and the paediatric subcommittee of the WHO Expert Committee on Essential Medicines. After this review, the simulations can be re-visited as necessary (eg., performance of additional simulations, use of refined PK parameter estimates based on more current data) and/or modifications to the proposed dosing table can be made. Additionally, a simulation exercise exploring the dose-concentration-effect relationship for Ethambutol in pediatric patients should be conducted.

Addendum

Upon review of the preliminary report as related to our findings for rifampin, WHO requested that we explore (through simulation) a higher dose for the drug. These were conducted using a

rifampin total dose of 250 mg in the proposed fixed dose, three drug combination. The method by which the simulations were conducted, and all of the assumptions nested therein, are as described above. Table 14 (Appendix) details the revisions to the proposed dosing strategy for a single-dose, fixed-strength formulation containing isoniazid, rifampin and pyrazinamide.

Tables 15 and 16 (Appendix) provide a summary of the average rifampin exposure estimates (along with the 90% confidence interval) in addition to the corresponding values for rifampin pharmacokinetic/ pharmacodynamic surrogates for the new rifampin dose.

At doses ranging from 14 to 31 mg/kg, average estimates of C_{max} ranged from 4.2 to 9.2 mcg/mL in infants and 8.1 to 18.0 mcg/mL in children (Figure 9, upper). Area under the curve

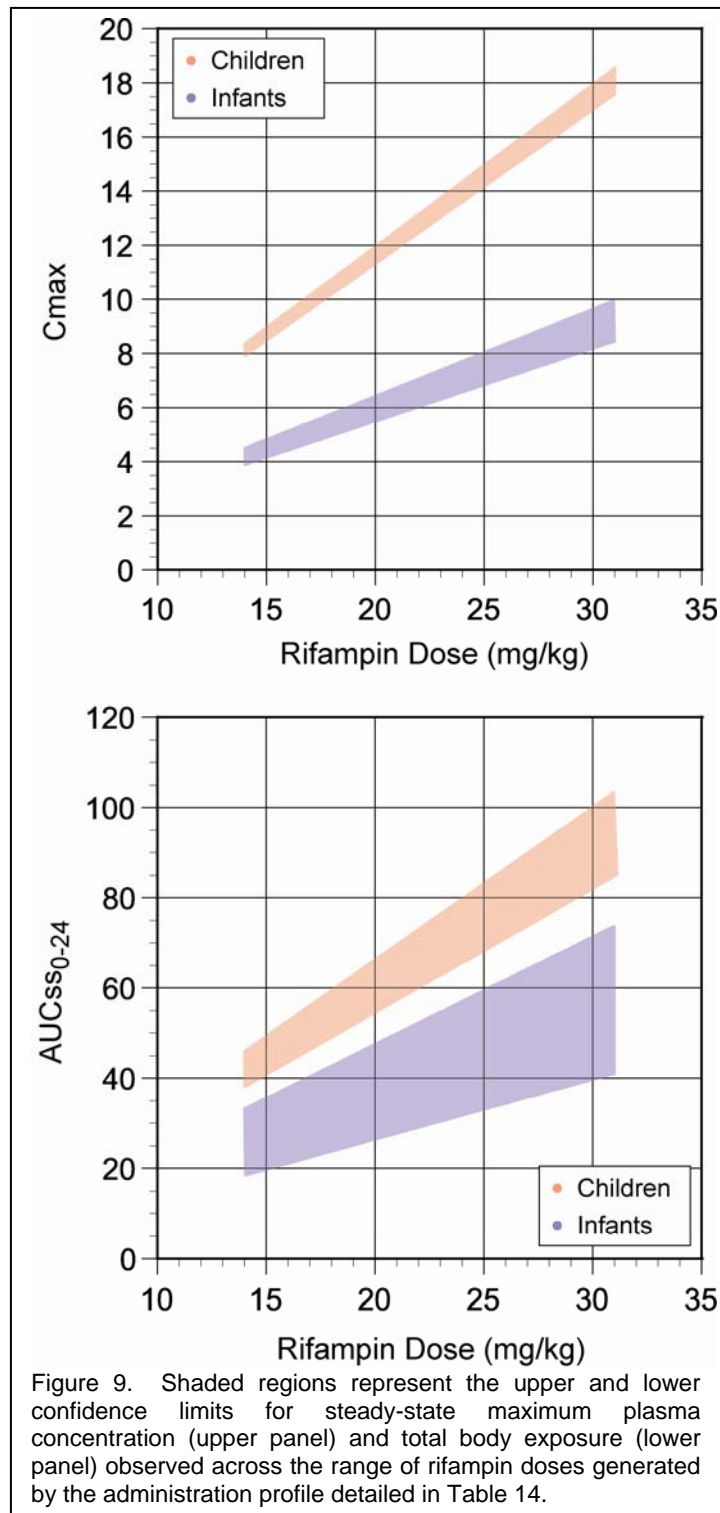
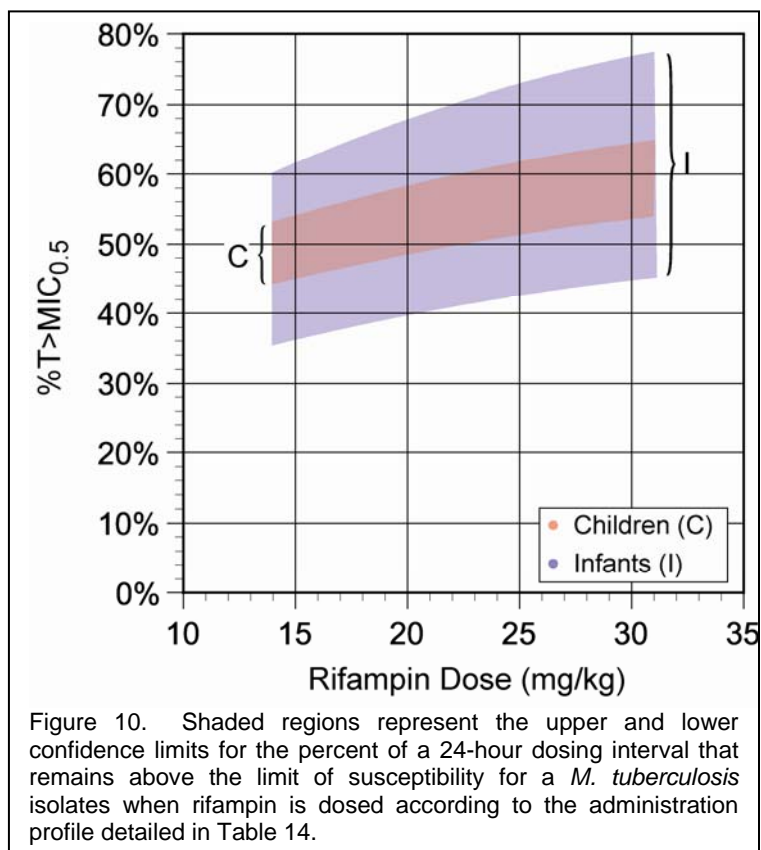


Figure 9. Shaded regions represent the upper and lower confidence limits for steady-state maximum plasma concentration (upper panel) and total body exposure (lower panel) observed across the range of rifampin doses generated by the administration profile detailed in Table 14.

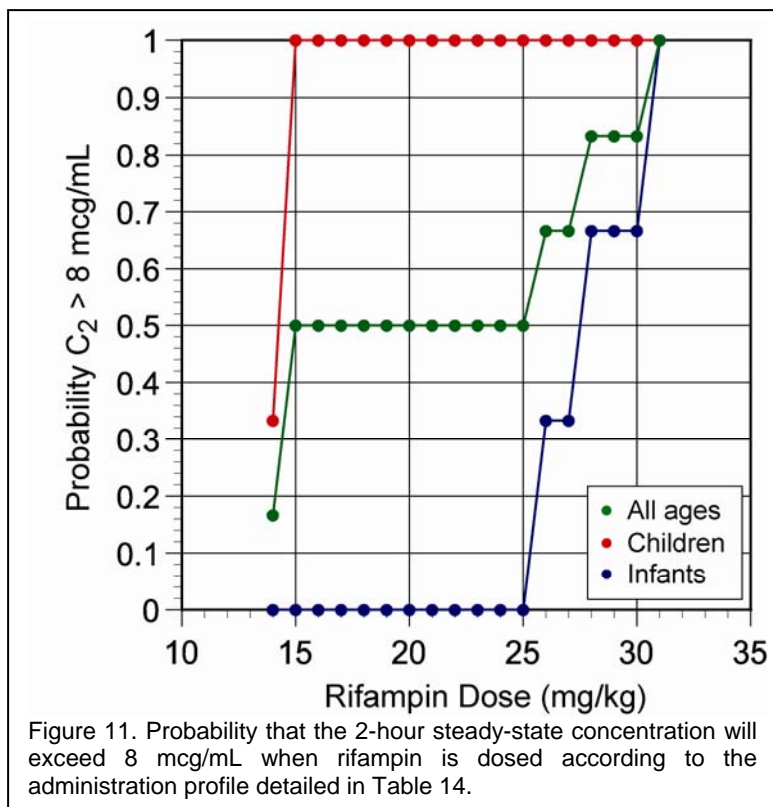
ranges from 25.2 to 55.8 mcg*hr/mL and 42.0 to 93.0 mcg*hr/mL for infants and children, respectively (Figure 9, lower).

The simulated steady-state plasma concentration-vs.-time profiles suggest that infants and children at the revised rifampin dose (14 to 31 mg/kg based upon patient weight and a fixed dose of 250 mg rifampin per tablet of ideal formulation) spend between 35-77% of a 24-hour



dosing interval above the published susceptibility limit for *M. tuberculosis* (0.5 mcg/mL) (Figure 10). As discussed above, significantly more variability is anticipated in this pharmacodynamic surrogate for infants (vs. children) owing to the larger degree of inter-individual variability in drug elimination observed in this population.

With the exception of children receiving the lowest dose (i.e. 14 mg/kg), all children administered rifampin according to the dosing scheme detailed in Table 14 achieved plasma concentrations 2 hours post-dose that equal or exceed 8 mcg/mL (Figure 11). Conversely, the simulations predicted that only infants receiving greater than 25 mg/kg achieved this pharmacokinetic surrogate (Figure 11). When the dosing strategy detailed in Table 14 is applied without regard for age, over half of pediatric patients administered the formulation containing a total of 250 mg of rifampin would be predicted to achieve 2-hour plasma concentrations that



satisfy this target (Figure 3). As alluded to above, caution is warranted when relying on this surrogate as it remains to be validated in children.

Additionally, it should be noted that by increasing the amount of rifampin in the ideal formulation to 250 mg per “tablet” would result in some patients receiving a daily rifampin dose in excess of the 20

mg/kg/day currently recommended by standard compendia. The potential impact of this excessive rifampin dose on the adverse effect profile for this drug is not known and to our knowledge, cannot be reliably predicted. On a theoretical basis, the autoinduction of rifampin biotransformation that would be expected to occur consequent to multiple dosing would have the effect to reduce systemic drug exposure; something not accounted for in our simulations (as the extent of autoinduction for a given patient is highly variable and virtually impossible to predict *a priori*).

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Table 1. Proposed dosing strategies for a single-dose, fixed-strength formulation containing isoniazid, rifampin and pyrazinamide at the dosage strengths delineated.

Product		INH 150 mg	Rifampin 200 mg	Pyrazinamide 400 mg
Weight	Dose			
5 kg	½ pill	15 mg/kg	20 mg/kg	40 mg/kg
6 kg	½ pill	12.5	16.7	33.3
7 kg	½ pill	10.7	14.3	28.5
8 kg	½ pill	9.4	12.5	25
9 kg	½ pill	8.8	11.1	22
8 kg	1 pill	18.7	25	50
9 kg	1 pill	16.7	22.2	44
10 kg	1 pill	15	20	40
11 kg	1 pill	13.5	18	36.4
12 kg	1 pill	12.5	16.6	33.3
13 kg	1 pill	11.5	15.4	30.1
14 kg	1 pill	10.7	14.3	28.6
15 kg	1 pill	10	13.3	26.6
16 kg	1 ½ pills	14.1	18.8	37.5
17 kg	1 ½ pills	13.2	17.6	35.3
18 kg	1 ½ pills	12.6	16.6	33.3
19 kg	1 ½ pills	11.8	15.8	31.6
20 kg	1 ½ pills	11.2	15	30
21 kg	1 ½ pills	10.7	14.3	28.5
21 kg	2 pills	14.8	19	38
22 kg	2 pills	13.6	18.2	36.4
23 kg	2 pills	13	17.4	34.8
24 kg	2 pills	12.5	16.6	33.3
25 kg	2 pills	12	16	32
26 kg	2 pills	11.5	15.4	30.1
27 kg	2 pills	11.1	14.8	29.6
28 kg	2 pills	10.7	14.3	28.5
29 kg	2 pills	10.4	13.8	27.5
30 kg	2 pills	10	13.3	26.6

Table 2. Rifampin parameter estimates used in the simulations [Acocella 1978, Holdiness 1984, Koup 1986, Mahajan 1997, McCracken 1980, Nahata 1990, Wilkins 2008].

	Infants	Children
Tau (hr)	24	24
bioavailability (%)	0.5	0.5
Volume (L/kg)	1.1	0.53
ka (1/hr)	1.15	1.15
kel (1/hr)	0.25	0.31
lag time (hr)	0	0
MIC (mcg/mL)	0.5	0.5

Tau- dosing interval, ka- absorption rate constant, kel- terminal elimination rate constant, MIC- minimum inhibitory concentration

Table 3. Rifampin PK/PD estimates calculated for Infants (average [90% CI])

Dose mg/kg	Cmax (mcg/mL)	AUC_{ss0-24} (mcg*hr/mL)	C₂ >8mcg/mL	AUC/MIC_{0.5}	%T>MIC_{0.5}	Cmax/MIC_{0.5}
11	3.26 [3.00, 3.54]	19.80 [14.5, 26.2]	No [No, No]	39.60 [29.0, 52.3]	43% [33%, 55%]	6.53 [6.00, 7.08]
12	3.56 [3.27, 3.86]	21.60 [15.79, 28.54]	No [No, No]	43.20 [31.59, 57.1]	44% [34%, 57%]	7.12 [6.54, 7.72]
13	3.86 [3.54, 4.18]	23.40 [17.11, 30.91]	No [No, No]	46.80 [34.22, 61.83]	45% [35%, 58%]	7.71 [7.09, 8.37]
14	4.15 [3.82, 4.51]	25.20 [18.42, 33.29]	No [No, No]	50.40 [36.85, 66.58]	47% [35%, 60%]	8.31 [7.63, 9.01]
15	4.45 [4.09, 4.83]	27.00 [19.74, 35.67]	No [No, No]	54.00 [39.48, 71.34]	48% [36%, 62%]	8.90 [8.18, 9.65]
16	4.75 [4.36, 5.15]	28.80 [21.06, 38.05]	No [No, No]	57.60 [42.11, 76.10]	49% [37%, 63%]	9.49 [8.72, 10.30]
17	5.04 [4.64, 5.47]	30.60 [22.37, 40.43]	No [No, No]	61.20 [44.75, 80.85]	50% [38%, 64%]	10.09 [9.27, 10.94]
18	5.34 [4.91, 5.79]	32.40 [23.69, 42.80]	No [No, No]	64.80 [47.38, 85.61]	51% [39%, 66%]	10.68 [9.82, 11.59]
19	5.64 [5.18, 6.11]	34.20 [25.00, 45.18]	No [No, No]	68.40 [50.01, 90.36]	52% [39%, 67%]	11.27 [10.36, 12.23]
20	5.93 [5.45, 6.44]	36.00 [26.32, 47.56]	No [No, No]	72.00 [52.64, 95.12]	52% [40%, 68%]	11.87 [10.91, 12.87]
21	6.23 [5.73, 6.76]	37.80 [27.64, 49.94]	No [No, No]	75.61 [55.27, 99.88]	53% [40%, 69%]	12.46 [11.45, 13.52]
22	6.53 [6.00, 7.08]	39.60 [28.95, 52.32]	No [No, No]	79.21 [57.91, 104.63]	54% [41%, 70%]	13.05 [12.00, 14.16]

Cmax- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC- AUC to MIC ratio, %T>MIC- percent of the dosing interval (Tau) that remains above the MIC, Cmax/MIC- Cmax to MIC ratio

Dose mg/kg	C _{max} (mcg/mL)	AUC _{ss0-24} (mcg*hr/mL)	C ₂ >8mcg/mL	AUC/MIC _{0.5}	%T>MIC _{0.5}	C _{max} /MIC _{0.5}
11	6.40 [6.22, 6.58]	33.02 [30.20, 36.62]	No [No, No]	66.03 [60.39, 73.25]	45% [41%, 49%]	12.80 [12.45, 13.16]
12	6.98 [6.79, 7.18]	36.02 [32.78, 39.95]	No [No, No]	72.04 [65.55, 79.91]	46% [43%, 51%]	13.96 [13.58, 14.35]
13	7.56 [7.36, 7.78]	39.02 [35.69, 43.28]	No [No, No]	78.04 [71.38, 86.57]	47% [44%, 52%]	15.12 [14.71, 15.55]
14	8.14 [7.92, 8.37]	42.02 [38.24, 46.61]	No [No, Yes]	84.04 [76.48, 93.22]	48% [44%, 53%]	16.29 [15.84, 16.75]
15	8.72 [8.49, 8.97]	45.02 [41.18, 49.94]	Yes [Yes, Yes]	90.05 [82.36, 99.88]	49% [45%, 54%]	17.45 [16.98, 17.94]
16	9.31 [9.05, 9.57]	48.02 [43.70, 53.27]	Yes [Yes, Yes]	96.05 [87.41, 106.54]	50% [46%, 55%]	18.61 [18.11, 19.14]
17	9.89 [9.62, 10.17]	51.03 [46.67, 56.60]	Yes [Yes, Yes]	102.05 [93.34, 113.20]	51% [47%, 56%]	19.78 [19.24, 20.34]
18	10.47 [10.19, 10.77]	54.03 [49.17, 59.93]	Yes [Yes, Yes]	108.05 [98.33, 119.86]	52% [48%, 57%]	20.94 [20.37, 21.53]
19	11.05 [10.75, 11.36]	57.03 [52.16, 63.26]	Yes [Yes, Yes]	114.06 [104.32, 126.52]	52% [48%, 57%]	22.10 [21.50, 22.73]
20	11.63 [11.32, 11.96]	60.03 [54.63, 66.59]	Yes [Yes, Yes]	120.06 [109.26, 133.18]	53% [49%, 58%]	23.26 [22.64, 23.92]
21	12.21 [11.88, 12.56]	63.03 [57.65, 69.92]	Yes [Yes, Yes]	126.06 [115.30, 139.84]	54% [49%, 59%]	24.43 [23.77, 25.12]
22	12.80 [12.45, 13.16]	66.03 [60.09, 73.25]	Yes [Yes, Yes]	132.07 [120.18, 146.49]	54% [50%, 60%]	25.59 [24.90, 26.32]

C_{max}- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC- AUC to MIC ratio, %T>MIC- percent of the dosing interval (Tau) that remains above the MIC, C_{max}/MIC- C_{max} to MIC ratio

Table 5. Pyrazinamide parameter estimates used in the simulations [Graham 2006, Holdiness 1984, Wilkins 2006].

	Infants/Children (slow absorbers)	Infants/Children (fast absorbers)
Tau (hr)	24	24
bioavailability (%)	0.8	0.8
Volume (L/kg)	0.57	0.57
ka (1/hr)	1.25	3.56
kel (1/hr)	0.075	0.075
lag time (hr)	0	0
MIC (mcg/mL)	20	20

Tau- dosing interval, ka- absorption rate constant, kel- terminal elimination rate constant, MIC- minimum inhibitory concentration

Table 6. Pyrazinamide PK/PD estimates calculated for Infants/Children that are slow absorbers (average [90% CI])

Dose mg/kg	C _{max} mcg/mL	AUC _{ss0-24} mcg*hr/mL	C ₂ > 20mcg/mL	AUC/MIC ₂₀	%T>MIC ₂₀	C _{max} /MIC ₂₀
22	31.3 [30.3, 32.4]	412.61 [386.72, 442.12]	Yes [Yes, Yes]	20.63 [19.34, 22.11]	38% [35%, 42%]	1.56 [1.51, 1.62]
24	34.1 [33.0, 35.3]	450.12 [421.88, 482.31]	Yes [Yes, Yes]	22.51 [21.09, 24.12]	43% [39%, 47%]	1.71 [1.65, 1.77]
26	36.9 [35.8, 38.3]	487.63 [457.04, 522.50]	Yes [Yes, Yes]	24.38 [22.85, 26.13]	48% [44%, 52%]	1.85 [1.79, 1.91]
28	39.8 [38.5, 41.2]	525.14 [492.19, 562.69]	Yes [Yes, Yes]	26.26 [24.61, 28.13]	52% [47%, 57%]	1.99 [1.93, 2.06]
30	42.6 [41.3, 44.1]	562.65 [527.35, 602.89]	Yes [Yes, Yes]	28.13 [26.37, 30.14]	55% [51%, 61%]	2.13 [2.07, 2.21]
32	45.5 [44.1, 47.1]	600.16 [562.51, 643.08]	Yes [Yes, Yes]	30.01 [28.13, 32.15]	59% [54%, 65%]	2.27 [2.20, 2.35]
34	48.3 [46.8, 50.0]	637.67 [597.66, 683.27]	Yes [Yes, Yes]	31.88 [29.88, 34.16]	62% [58%, 68%]	2.42 [2.34, 2.50]
36	51.2 [49.6, 53.0]	675.18 [632.82, 723.46]	Yes [Yes, Yes]	33.76 [31.64, 36.17]	66% [61% 72%]	2.56 [2.48, 2.65]
38	54.0 [52.3, 55.9]	712.69 [667.98, 763.65]	Yes [Yes, Yes]	35.63 [33.40, 38.18]	69% [63%, 75%]	2.70 [2.62, 2.80]
40	56.8 [55.1, 58.9]	750.20 [703.13, 803.85]	Yes [Yes, Yes]	37.51 [35.16, 40.19]	71% [66%, 78%]	2.84 [2.75, 2.94]
42	59.7 [57.8, 61.8]	787.71 [738.29, 844.04]	Yes [Yes, Yes]	39.39 [36.91, 42.20]	74% [69%, 81%]	2.98 [2.89, 3.09]
44	62.5 [60.6, 64.7]	825.22 [773.45, 884.23]	Yes [Yes, Yes]	41.26 [38.67, 44.21]	77% [71%, 84%]	3.13 [3.03, 3.24]
46	65.4 [63.3, 67.7]	862.73 [808.60, 924.42]	Yes [Yes, Yes]	43.14 [40.43, 46.22]	79% [73%, 86%]	3.27 [3.17, 3.38]
48	68.2 [66.1, 70.6]	900.24 [843.76, 964.62]	Yes [Yes, Yes]	45.01 [42.19, 48.23]	82% [76%, 89%]	3.41 [3.30, 3.53]
50	71.0 [68.8, 73.6]	937.75 [878.92, 1004.81]	Yes [Yes, Yes]	46.89 [43.95, 50.24]	84% [78%, 91%]	3.55 [3.44, 3.68]

C_{max}- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC- AUC to MIC ratio, %T>MIC- percent of the dosing interval (Tau) that remains above the MIC, C_{max}/MIC- C_{max} to MIC ratio

Table 7. Pyrazinamide PK/PD estimates calculated for Infants/Children that are fast absorbers (average [90% CI])

Dose	C _{max}	AUC _{ss0-24}	C ₂ > 20mcg/mL	AUC/MIC ₂₀	%T>MIC ₂₀	C _{max} >MIC ₂₀
22	34.1 [33.2, 35.1]	406.55 [380.78, 435.93]	Yes [Yes, Yes]	20.33 [19.04, 21.80]	36% [32%, 40%]	1.71 [1.66, 1.76]
24	37.2 [36.3, 38.3]	443.51 [415.39 475.56]	Yes [Yes, Yes]	22.18 [20.77, 23.78]	40% [37%, 45%]	1.86 [1.81, 1.92]
26	40.3 [39.3, 41.5]	480.47 [450.01, 515.19]	Yes [Yes, Yes]	24.02 [22.50, 25.76]	45% [41%, 49%]	2.02 [1.96, 2.07]
28	43.4 [42.3, 44.7]	517.43 [484.62, 54.82]	Yes [Yes, Yes]	25.87 [24.23, 27.74]	49% [45%, 54%]	2.17 [2.11, 2.23]
30	46.5 [45.3, 47.9]	554.39 [519.24, 594.45]	Yes [Yes, Yes]	27.72 [25.96, 29.72]	53% [48%, 58%]	2.33 [2.27, 2.39]
32	49.6 [48.3, 51.1]	591.35 [553.86, 634.08]	Yes [Yes, Yes]	29.57 [27.69, 31.70]	56% [52%, 62%]	2.48 [2.42, 2.55]
34	52.7 [51.4, 54.3]	628.30 [588.47, 673.71]	Yes [Yes, Yes]	31.42 [29.42, 33.69]	60% [55%, 65%]	2.64 [2.57, 2.71]
36	55.8 [54.4, 57.5]	665.26 [623.09, 713.34]	Yes [Yes, Yes]	33.26 [31.15, 35.67]	63% [58%, 69%]	2.79 [2.72, 2.87]
38	58.9 [57.4, 60.6]	702.22 [657.70, 752.97]	Yes [Yes, Yes]	35.11 [32.89, 37.65]	66% [61%, 72%]	2.95 [2.87, 3.03]
40	62.0 [60.4, 63.8]	739.18 [692.32, 792.60]	Yes [Yes, Yes]	36.96 [34.62, 39.63]	69% [63%, 75%]	3.10 [3.02, 3.19]
42	65.1 [63.4, 67.0]	776.14 [726.94, 832.23]	Yes [Yes, Yes]	38.81 [36.35, 41.61]	71% [66%, 78%]	3.26 [3.17, 3.35]
44	68.2 [66.5, 70.2]	813.10 [761.55, 871.86]	Yes [Yes, Yes]	40.65 [38.08, 43.59]	74% [68%, 81%]	3.41 [3.32, 3.51]
46	71.3 [69.5, 73.4]	850.06 [796.17, 911.49]	Yes [Yes, Yes]	42.50 [39.81, 45.57]	77% [71%, 83%]	3.57 [3.47, 3.67]
48	74.4 [72.5, 76.6]	887.02 [830.78, 951.12]	Yes [Yes, Yes]	44.35 [41.54, 47.56]	79% [73%, 86%]	3.72 [3.63, 3.83]
50	77.5 [75.5, 79.8]	923.98 [865.40, 990.75]	Yes [Yes, Yes]	46.20 [43.27, 49.54]	81% [75%, 88%]	3.88 [3.78, 3.99]

C_{max}- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC_{0.5}- AUC to MIC ratio, %T>MIC_{0.5}- percent of the dosing interval (Tau) that remains above the MIC, C_{max}/MIC- C_{max} to MIC ratio

Table 8. Isoniazid parameter estimates used in the simulations [Ansari 2003, Buchanan 1979, Holdiness 1984, Kergueris 1986, Pariente-Khayat 1997, Rey 2001, Shcaff 2005, Seifart 1995].

	Infants/Children (fast acetylators)	Infants/Children (slow acetylators)	Malnourished Infants/Children (fast acetylators)
Tau (hr)	24	24	24
bioavailability (%)	0.9	0.9	0.9
Volume (L/kg)	1.06	1.56	1.5
ka (1/hr)	1.57	1.57	1.57
kel (1/hr)	0.54	0.21	0.53
lag time (hr)	0	0	0
MIC (mcg/mL)	0.2	0.2	0.2

Table 8 cont'd. Isoniazid parameter estimates used in the simulations.

	Malnourished Infants/Children (slow acetylators)	Infants/Children with kwashiorkor
Tau (hr)	24	24
bioavailability (%)	0.9	0.9
Volume (L/kg)	1.5	1.22
ka (1/hr)	1.57	1.57
kel (1/hr)	0.26	0.73
lag time (hr)	0	0
MIC (mcg/mL)	0.2	0.2
Tau- dosing interval, ka- absorption rate constant, kel- terminal elimination rate constant, MIC- minimum inhibitory concentration		

Table 9. Isoniazid PK/PD estimates calculated for Infants/Children with a fast acetylator phenotype (average [90% CI])

Dose mg/kg	C _{max} mcg/mL	AUC _{ss0-24} mcg*hr/mL	C ₂ > 3mcg/mL	AUC/MIC _{0.2}	%T>MIC _{0.2}	C _{max} /MIC _{0.2}
8	3.88 [3.70, 4.07]	11.95 [10.30, 14.17]	Yes [No, Yes]	59.75 [51.49, 70.84]	30% [27%, 35%]	19.40 [18.52, 20.33]
9	4.36 [4.17, 4.57]	13.44 [11.59, 15.94]	Yes [Yes, Yes]	67.22 [57.93, 79.70]	31% [28%, 36%]	21.82 [20.83, 22.87]
10	4.85 [4.63, 5.08]	14.94 [12.87, 17.71]	Yes [Yes, Yes]	74.69 [64.37, 88.55]	32% [29%, 37%]	24.25 [23.15, 25.41]
11	5.33 [5.09, 5.59]	16.43 [14.16, 19.48]	Yes [Yes, Yes]	82.16 [70.80, 97.41]	33% [29%, 38%]	26.67 [25.46, 27.96]
12	5.82 [5.55, 6.10]	17.93 [15.45, 21.25]	Yes [Yes, Yes]	89.63 [77.24, 106.26]	34% [30%, 39%]	29.10 [27.77, 30.50]
13	6.30 [6.02, 6.61]	19.42 [16.73, 23.02]	Yes [Yes, Yes]	97.10 [83.67, 115.12]	34% [30%, 39%]	31.52 [30.09, 33.04]
14	6.79 [6.48, 7.12]	20.91 [18.02, 24.79]	Yes [Yes, Yes]	104.57 [90.11, 123.97]	35% [31%, 40%]	33.95 [32.40, 35.58]
15	7.27 [6.94, 7.62]	22.41 [19.31, 26.57]	Yes [Yes, Yes]	112.04 [96.55, 132.83]	35% [31%, 41%]	36.37 [34.72, 38.12]
16	7.76 [7.41, 8.13]	23.90 [20.60, 28.34]	Yes [Yes, Yes]	119.51 [102.98, 141.68]	36% [32%, 41%]	38.80 [37.03, 40.66]
17	8.24 [7.87, 8.64]	25.40 [21.88, 30.11]	Yes [Yes, Yes]	126.98 [109.42, 150.54]	36% [32%, 42%]	41.22 [39.35, 43.20]
18	8.73 [8.33, 9.15]	26.89 [23.17, 31.88]	Yes [Yes, Yes]	134.45 [115.86, 159.39]	37% [33%, 42%]	43.64 [41.66, 45.75]

C_{max}- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC- AUC to MIC ratio, %T>MIC- percent of the dosing interval (Tau) that remains above the MIC, C_{max}/MIC- C_{max} to MIC ratio

Table 10. Isoniazid PK/PD estimates calculated for Infants/Children with a slow acetylator phenotype (average [90% CI])

Dose mg/kg	C _{max} mcg/mL	AUC _{ss0-24} mcg*hr/mL	C ₂ > 3mcg/mL	AUC/MIC _{0.2}	%T>MIC _{0.2}	C _{max} /MIC _{0.2}
8	3.41 [3.33, 3.54]	21.66 [19.73, 25.35]	Yes [Yes, Yes]	108.29 [98.67, 126.73]	65% [60%, 76%]	17.04 [16.66, 17.69]
9	3.83 [3.75, 3.98]	24.36 [22.20, 28.51]	Yes [Yes, Yes]	121.82 [111.00, 142.57]	68% [62%, 79%]	19.17 [18.74, 19.90]
10	4.26 [4.17, 4.42]	27.07 [24.67, 31.68]	Yes [Yes, Yes]	135.36 [123.34, 158.41]	70% [64%, 81%]	21.30 [20.83, 22.11]
11	4.69 [4.58, 4.86]	29.78 [27.13, 34.85]	Yes [Yes, Yes]	148.90 [135.67, 174.25]	72% [66%, 83%]	23.43 [22.91, 24.32]
12	5.11 [5.00, 5.31]	32.49 [29.60, 38.02]	Yes [Yes, Yes]	162.43 [148.01, 190.09]	73% [67%, 85%]	25.56 [24.99, 26.54]
13	5.54 [5.41, 5.75]	35.19 [32.07, 41.19]	Yes [Yes, Yes]	175.97 [160.34, 205.93]	75% [69%, 87%]	27.69 [27.07, 28.75]
14	5.96 [5.83, 6.19]	37.90 [34.53, 44.36]	Yes [Yes, Yes]	189.50 [172.67, 221.78]	76% [70%, 89%]	29.82 [29.16, 30.96]
15	6.39 [6.25, 6.63]	40.61 [37.00, 47.52]	Yes [Yes, Yes]	203.04 [185.01, 237.62]	78% [71%, 90%]	31.95 [31.24, 33.17]
16	6.82 [6.66, 7.08]	43.32 [39.47, 50.69]	Yes [Yes, Yes]	216.58 [197.34, 253.46]	79% [72%, 92%]	34.08 [33.32, 35.38]
17	7.24 [7.08, 7.52]	46.02 [41.93, 53.86]	Yes [Yes, Yes]	230.11 [209.67, 269.30]	80% [73%, 93%]	36.21 [35.41, 37.59]
18	7.67 [7.50, 7.96]	48.73 [44.40, 57.03]	Yes [Yes, Yes]	243.65 [222.01, 285.14]	81% [75%, 95%]	38.34 [37.49, 39.80]

C_{max}- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC- AUC to MIC ratio, %T>MIC- percent of the dosing interval (Tau) that remains above the MIC, C_{max}/MIC- C_{max} to MIC ratio

Table 11. Isoniazid PK/PD estimates calculated for Malnourished Infants/Children with a fast acetylator phenotype (average [90% CI])

Dose mg/kg	C _{max} mcg/mL	AUC _{ss0-24} mcg*hr/mL	C ₂ > 3mcg/mL	AUC/MIC _{0.2}	%T>MIC _{0.2}	C _{max} /MIC _{0.2}
8	2.76 [2.66, 2.86]	8.62 [7.68, 9.79]	No [No, No]	43.08 [38.39, 48.94]	28% [26%, 31%]	13.79 [13.31, 14.28]
9	3.10 [3.00, 3.21]	9.69 [8.64, 11.01]	No [No, No]	48.46 [43.19, 55.05]	29% [27%, 32%]	15.51 [14.98, 16.07]
10	3.45 [3.33, 3.57]	10.77 [9.60, 12.23]	No [No, No]	53.85 [47.99, 61.17]	30% [27%, 33%]	17.24 [16.64, 17.85]
11	3.79 [3.66, 3.93]	11.85 [10.56, 13.46]	Yes [No, Yes]	59.23 [52.79, 67.29]	31% [28%, 34%]	18.96 [18.31, 19.64]
12	4.14 [3.99, 4.28]	12.92 [11.52, 14.68]	Yes [Yes, Yes]	64.62 [57.59, 73.41]	31% [29%, 35%]	20.68 [19.97, 21.42]
13	4.48 [4.33, 4.64]	14.00 [12.48, 15.90]	Yes [Yes, Yes]	70.00 [62.39, 79.52]	32% [29%, 36%]	22.41 [21.64, 23.21]
14	4.83 [4.66, 5.00]	15.08 [13.44, 17.13]	Yes [Yes, Yes]	75.39 [67.19, 85.64]	33% [30%, 36%]	24.13 [23.30, 25.00]
15	5.17 [4.99, 5.36]	16.15 [14.40, 18.35]	Yes [Yes, Yes]	80.77 [71.99, 91.76]	33% [30%, 37%]	25.85 [24.96, 26.78]
16	5.52 [5.33, 5.71]	17.23 [15.36, 19.58]	Yes [Yes, Yes]	86.16 [76.79, 97.88]	34% [31%, 37%]	27.58 [26.63, 28.57]
17	5.86 [5.66, 6.07]	18.31 [16.32, 20.80]	Yes [Yes, Yes]	91.54 [81.59, 103.99]	34% [31%, 38%]	29.30 [28.29, 30.35]
18	6.20 [5.99, 6.43]	19.39 [17.28, 22.02]	Yes [Yes, Yes]	96.93 [86.39, 110.11]	35% [31%, 39%]	31.02 [29.96, 32.14]

C_{max}- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC- AUC to MIC ratio, %T>MIC- percent of the dosing interval (Tau) that remains above the MIC, C_{max}/MIC- C_{max} to MIC ratio

Table 12. Isoniazid PK/PD estimates calculated for Malnourished Infants/Children with a slow acetylator phenotype (average [90% CI])

Dose mg/kg	C _{max} mcg/mL	AUC _{ss0-24} mcg*hr/mL	C ₂ > 3mcg/mL	AUC/MIC _{0.2}	%T>MIC _{0.2}	C _{max} /MIC _{0.2}
8	3.36 [3.16, 3.54]	18.10 [14.62, 22.52]	Yes [No, Yes]	90.50 [73.08, 112.62]	54% [44%, 66%]	16.78 [15.80, 17.72]
9	3.78 [3.56, 3.99]	20.36 [16.44, 25.34]	Yes [Yes, Yes]	101.81 [82.22, 126.70]	56% [46%, 68%]	18.88 [17.78, 19.94]
10	4.20 [3.95, 4.43]	22.63 [18.27, 28.15]	Yes [Yes, Yes]	113.13 [91.35, 140.77]	57% [47%, 70%]	20.98 [19.75, 22.15]
11	4.62 [4.35, 4.87]	24.89 [20.10, 30.97]	Yes [Yes, Yes]	124.44 [100.49, 154.85]	59% [49%, 72%]	23.08 [21.73, 24.37]
12	5.04 [4.74, 5.32]	27.15 [21.92, 33.79]	Yes [Yes, Yes]	135.75 [109.62, 168.93]	60% [50%, 74%]	25.18 [23.70, 26.58]
13	5.45 [5.14, 5.76]	29.41 [23.75, 36.60]	Yes [Yes, Yes]	147.06 [118.76, 183.01]	62% [51%, 76%]	27.27 [25.68, 28.80]
14	5.87 [5.53, 6.20]	31.68 [25.58, 39.42]	Yes [Yes, Yes]	158.38 [127.89, 197.08]	63% [52%, 77%]	29.37 [27.65, 31.01]
15	6.29 [5.93, 6.65]	33.94 [27.41, 42.23]	Yes [Yes, Yes]	169.69 [137.03, 211.16]	64% [53%, 79%]	31.47 [29.63, 33.23]
16	6.71 [6.32, 7.09]	36.20 [29.23, 45.05]	Yes [Yes, Yes]	181.00 [146.16, 225.24]	65% [53%, 80%]	33.57 [31.60, 35.45]
17	7.13 [6.72, 7.53]	38.46 [31.06, 47.86]	Yes [Yes, Yes]	192.31 [155.30, 239.32]	66% [54%, 81%]	35.67 [33.58, 37.66]
18	7.55 [7.11, 7.98]	40.73 [32.89, 50.68]	Yes [Yes, Yes]	203.63 [164.43, 253.39]	67% [55%, 82%]	37.76 [35.55, 39.88]

C_{max}- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC- AUC to MIC ratio, %T>MIC- percent of the dosing interval (Tau) that remains above the MIC, C_{max}/MIC- C_{max} to MIC ratio

Table 13. Isoniazid PK/PD estimates calculated for Infants/Children with Kwashiorkor (average [90% CI])

Dose mg/kg	C _{max} mcg/mL	AUC _{ss0-24} mcg*hr/mL	C ₂ > 3mcg/mL	AUC/MIC _{0.2}	%T>MIC _{0.2}	C _{max} /MIC _{0.2}
8	3.02 [2.81, 3.26]	7.48 [6.22, 9.27]	No [No, No]	37.40 [31.12, 46.36]	23% [20%, 27%]	15.10 [14.04, 16.28]
9	3.40 [3.16, 3.66]	8.42 [7.00, 10.43]	No [No, No]	42.08 [35.01, 52.15]	24% [21%, 28%]	16.99 [15.79, 18.31]
10	3.78 [3.51, 4.07]	9.35 [7.78, 11.59]	No [No, Yes]	46.75 [38.90, 57.95]	24% [21%, 28%]	18.88 [17.55, 20.34]
11	4.15 [3.86, 4.48]	10.29 [8.56, 12.75]	No [No, Yes]	51.43 [42.79, 63.74]	25% [22%, 29%]	20.77 [19.30, 22.38]
12	4.53 [4.21, 4.88]	11.22 [9.34, 13.91]	Yes [No, Yes]	56.10 [46.68, 69.54]	25% [22%, 30%]	22.66 [21.05, 24.41]
13	4.91 [4.56, 5.29]	12.16 [10.11, 15.07]	Yes [No, Yes]	60.78 [50.57, 75.33]	26% [23%, 30%]	24.54 [22.81, 26.45]
14	5.29 [4.91, 5.70]	13.09 [10.89, 16.22]	Yes [Yes, Yes]	65.45 [54.46, 81.12]	26% [23%, 31%]	26.43 [24.56, 28.48]
15	5.66 [5.26, 6.10]	14.03 [11.67, 17.38]	Yes [Yes, Yes]	70.13 [58.35, 86.92]	26% [23%, 31%]	28.32 [26.32, 30.52]
16	6.04 [5.61, 6.51]	14.96 [12.45, 18.54]	Yes [Yes, Yes]	74.81 [62.25, 92.71]	27% [24%, 32%]	30.21 [28.07, 32.55]
17	6.42 [5.97, 6.92]	15.90 [13.23, 19.70]	Yes [Yes, Yes]	79.48 [66.14, 98.51]	27% [24%, 32%]	32.10 [29.83, 34.58]
18	6.80 [6.32, 7.32]	16.83 [14.01, 20.86]	Yes [Yes, Yes]	84.16 [70.03, 104.30]	28% [24%, 32%]	33.98 [31.58, 36.62]

C_{max}- maximum plasma concentration, AUC_{ss0-24}- area under the plasma concentration vs. time curve from 0-24 hours at steady-state, AUC/MIC- AUC to MIC ratio, %T>MIC- percent of the dosing interval (Tau) that remains above the MIC, C_{max}/MIC- C_{max} to MIC ratio

Table 14. Proposed dosing strategies (revised) for a single-dose, fixed-strength formulation containing isoniazid, rifampin and pyrazinamide at the dosage strengths delineated.

Product		INH	Rifampin	Pyrazinamide
		150 mg	250 mg	400 mg
Weight	Dose			
5 kg	½ pill	15 mg/kg	25.0 mg/kg	40 mg/kg
6 kg	½ pill	12.5	20.8	33.3
7 kg	½ pill	10.7	17.9	28.5
8 kg	½ pill	9.4	15.6	25
9 kg	½ pill	8.8	13.9	22
8 kg	1 pill	18.7	31.3	50
9 kg	1 pill	16.7	27.8	44
10 kg	1 pill	15	25.0	40
11 kg	1 pill	13.5	22.7	36.4
12 kg	1 pill	12.5	20.8	33.3
13 kg	1 pill	11.5	19.2	30.1
14 kg	1 pill	10.7	17.9	28.6
15 kg	1 pill	10	16.7	26.6
16 kg	1 ½ pills	14.1	23.4	37.5
17 kg	1 ½ pills	13.2	22.1	35.3
18 kg	1 ½ pills	12.6	20.8	33.3
19 kg	1 ½ pills	11.8	19.7	31.6
20 kg	1 ½ pills	11.2	18.8	30
21 kg	1 ½ pills	10.7	17.9	28.5
21 kg	2 pills	14.8	23.8	38
22 kg	2 pills	13.6	22.7	36.4
23 kg	2 pills	13	21.7	34.8
24 kg	2 pills	12.5	20.8	33.3
25 kg	2 pills	12	20.0	32
26 kg	2 pills	11.5	19.2	30.1
27 kg	2 pills	11.1	18.5	29.6
28 kg	2 pills	10.7	17.9	28.5
29 kg	2 pills	10.4	17.2	27.5
30 kg	2 pills	10	16.7	26.6

Table 15. Rifampin PK/PD estimates calculated for Infants (average [90% CI]).

Dose mg/kg	C _{max} (mcg/mL)	AUC _{ss0-24} (mcg*hr/mL)	C ₂ >8mcg/mL	AUC/MIC _{0.5}	%T>MIC _{0.5}	C _{max} /MIC _{0.5}
14	4.15 [3.82, 4.51]	25.20 [18.42, 33.29]	No [No, No]	50.40 [36.85, 66.58]	47% [35%, 60%]	8.31 [7.63, 9.01]
15	4.45 [4.09, 4.83]	27.00 [19.74, 35.67]	No [No, No]	54.00 [39.48, 71.34]	48% [36%, 62%]	8.90 [8.18, 9.65]
16	4.75 [4.36, 5.15]	28.80 [21.06, 38.05]	No [No, No]	57.60 [42.11, 76.10]	49% [37%, 63%]	9.49 [8.72, 10.30]
17	5.04 [4.64, 5.47]	30.60 [22.37, 40.43]	No [No, No]	61.20 [44.75, 80.85]	50% [38%, 64%]	10.09 [9.27, 10.94]
18	5.34 [4.91, 5.79]	32.40 [23.69, 42.80]	No [No, No]	64.80 [47.38, 85.61]	51% [39%, 66%]	10.68 [9.82, 11.59]
19	5.64 [5.18, 6.11]	34.20 [25.00, 45.18]	No [No, No]	68.40 [50.01, 90.36]	52% [39%, 67%]	11.27 [10.36, 12.23]
20	5.93 [5.45, 6.44]	36.00 [26.32, 47.56]	No [No, No]	72.00 [52.64, 95.12]	52% [40%, 68%]	11.87 [10.91, 12.87]
21	6.23 [5.73, 6.76]	37.80 [27.64, 49.94]	No [No, No]	75.61 [55.27, 99.88]	53% [40%, 69%]	12.46 [11.45, 13.52]
22	6.53 [6.00, 7.08]	39.60 [28.95, 52.32]	No [No, No]	79.21 [57.91, 104.63]	54% [41%, 70%]	13.05 [12.00, 14.16]
23	6.82 [6.27, 7.40]	41.40 [30.27, 54.69]	No [No, No]	82.81 [60.54, 109.39]	55% [42%, 71%]	13.65 [12.54, 14.80]
24	7.12 [6.54, 7.72]	43.20 [31.59, 57.07]	No [No, No]	86.41 [63.17, 114.14]	56% [42%, 72%]	14.24 [13.09, 15.45]
25	7.42 [6.82, 8.05]	45.00 [32.90, 59.45]	No [No, No]	90.01 [65.80, 118.90]	56% [43%, 73%]	14.83 [13.63, 16.09]
26	7.71 [7.09, 8.37]	46.80 [34.22, 61.83]	No [No, Yes]	93.61 [68.43, 123.66]	57% [43%, 74%]	15.43 [14.18, 16.73]
27	8.01 [7.36, 8.69]	48.60 [35.53, 64.21]	No [No, Yes]	97.21 [71.07, 128.41]	57% [44%, 74%]	16.02 [14.72, 17.38]
28	8.31 [7.63, 9.01]	50.40 [36.85, 66.58]	Yes [No, Yes]	100.81 [73.70, 133.17]	58% [44%, 75%]	16.61 [15.27, 18.02]
29	8.60 [7.91, 9.33]	52.20 [38.17, 68.96]	Yes [No, Yes]	104.41 [76.33, 137.92]	59% [44%, 76%]	17.21 [15.81, 18.66]
30	8.90 [8.18, 9.65]	54.00 [39.48, 71.34]	Yes [No, Yes]	108.01 [78.96, 142.68]	59% [45%, 77%]	17.80 [16.36, 19.31]
31	9.20 [8.45, 9.98]	55.80 [40.80, 73.72]	Yes [Yes, Yes]	111.61 [81.59, 147.44]	60% [45%, 77%]	18.39 [16.90, 19.95]

Dose mg/kg	C _{max} (mcg/mL)	AUC _{ss0-24} (mcg*hr/mL)	C ₂ >8mcg/mL	AUC/MIC _{0.5}	%T>MIC _{0.5}	C _{max} /MIC _{0.5}
14	8.14 [7.92, 8.37]	42.02 [38.24, 46.61]	No [No, Yes]	84.04 [76.48, 93.22]	48% [44%, 53%]	16.29 [15.84, 16.75]
15	8.72 [8.49, 8.97]	45.02 [41.18, 49.94]	Yes [Yes, Yes]	90.05 [82.36, 99.88]	49% [45%, 54%]	17.45 [16.98, 17.94]
16	9.31 [9.05, 9.57]	48.02 [43.70, 53.27]	Yes [Yes, Yes]	96.05 [87.41, 106.54]	50% [46%, 55%]	18.61 [18.11, 19.14]
17	9.89 [9.62, 10.17]	51.03 [46.67, 56.60]	Yes [Yes, Yes]	102.05 [93.34, 113.20]	51% [47%, 56%]	19.78 [19.24, 20.34]
18	10.47 [10.19, 10.77]	54.03 [49.17, 59.93]	Yes [Yes, Yes]	108.05 [98.33, 119.86]	52% [48%, 57%]	20.94 [20.37, 21.53]
19	11.05 [10.75, 11.36]	57.03 [52.16, 63.26]	Yes [Yes, Yes]	114.06 [104.32, 126.52]	52% [48%, 57%]	22.10 [21.50, 22.73]
20	11.63 [11.32, 11.96]	60.03 [54.63, 66.59]	Yes [Yes, Yes]	120.06 [109.26, 133.18]	53% [49%, 58%]	23.26 [22.64, 23.92]
21	12.21 [11.88, 12.56]	63.03 [57.65, 69.92]	Yes [Yes, Yes]	126.06 [115.30, 139.84]	54% [49%, 59%]	24.43 [23.77, 25.12]
22	12.80 [12.45, 13.16]	66.03 [60.09, 73.25]	Yes [Yes, Yes]	132.07 [120.18, 146.49]	54% [50%, 60%]	25.59 [24.90, 26.32]
23	13.38 [13.02, 13.76]	69.03 [63.14, 76.58]	Yes [Yes, Yes]	138.07 [126.28, 153.15]	55% [51%, 60%]	26.75 [26.03, 27.51]
24	13.96 [13.58, 14.35]	72.04 [65.55, 79.91]	Yes [Yes, Yes]	144.07 [131.11, 159.81]	55% [51%, 61%]	27.92 [27.16, 28.71]
25	14.54 [14.15, 14.95]	75.04 [68.63, 83.24]	Yes [Yes, Yes]	150.08 [137.26, 166.47]	56% [52%, 62%]	29.08 [28.29, 29.91]
26	15.12 [14.71, 15.55]	78.04 [71.02, 86.57]	Yes [Yes, Yes]	156.08 [142.03, 173.13]	57% [52%, 62%]	30.24 [29.43, 31.10]
27	15.70 [15.28, 16.15]	81.04 [74.12, 89.89]	Yes [Yes, Yes]	162.08 [148.24, 179.79]	57% [52%, 63%]	31.41 [30.56, 32.30]
28	16.29 [15.84, 16.75]	84.04 [76.48, 93.22]	Yes [Yes, Yes]	168.08 [152.96, 186.45]	58% [53%, 63%]	32.57 [31.69, 33.49]
29	16.87 [16.41, 17.35]	87.04 [79.61, 96.55]	Yes [Yes, Yes]	174.09 [159.22, 193.11]	58% [53%, 64%]	33.73 [32.82, 34.69]
30	17.45 [16.98, 17.94]	90.05 [81.94, 99.88]	Yes [Yes, Yes]	180.09 [163.89, 199.77]	58% [54%, 64%]	34.90 [33.95, 35.89]
31	18.03 [17.54, 18.54]	93.05 [85.10, 103.21]	Yes [Yes, Yes]	186.09 [170.20, 206.42]	59% [54%, 65%]	36.06 [35.08, 37.08]