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Evaluation of dosing guidelines for childhood tuberculosis: a mathematical modeling study

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Summary

Background—Malnourished and young children are particularly vulnerable to severe forms of tuberculosis and poor treatment response. Current World Health Organization (WHO) dosing guidelines are only based on weight, which may lead to systematic underdosing and worse outcomes in these vulnerable children. We evaluate and quantify the population impact of current WHO guidelines for drug-susceptible tuberculosis in children in the 20 countries with highest disease burden.

Methods—Using an integrated model which links country-specific individual-level demographic data to pharmacokinetic, outcome, and epidemiological models, we assessed tuberculosis

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Author contributions

All authors contributed to study conception and data interpretation. KKR, ACH, and RMS collected the data. KKR, RMS, and PJD contributed to study design. KKR performed the data analysis and modeling and prepared figures and tables. The first draft was written by KKR and RMS. All authors critically revised the article and approved the final version for publication.

Declaration of interests

The authors declare no competing interests.

treatment outcomes in children under five years of age following the current WHO guidelines and two alternative dosing strategies: a simple algorithm that utilizes age, weight, and available formulations, and an individualized algorithm without dose limitations.

Findings—We estimated that 57,234/133,302 (43%) treated under-5 tuberculosis cases would be underdosed with WHO dosing and only 47% of children would reach the rifampicin exposure target. Underdosing and subtherapeutic exposures were more common among malnourished children. The simple proposed dosing approach improved estimated rifampicin target exposure attainment to 62% and equalized outcomes by nutritional status. An estimated one-third of unfavorable treatment outcomes might be resolved with this dosing strategy, saving a minimum of 2423 children in these countries annually. With individualized dosing approaches, almost all children could achieve adequate exposure for cure.

Interpretation—This work demonstrates that a simple change in dosing procedure to include age and nutritional status, requiring no additional measurements or new drug formulations, is one approach to improve tuberculosis treatment outcomes in children, especially malnourished children who are at high risk of mortality.

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Background

Childhood tuberculosis is among the top 10 killers of children under five years of age.[1] Although global reports on leading causes of child mortality historically had omitted tuberculosis, recent estimates suggest that 191,000 children younger than five years died of tuberculosis in 2015.[1] Late or missed diagnosis of tuberculosis is a primary driver of mortality among children, but evidence from clinical studies also show that even when diagnosed and treated, tuberculosis outcomes are still far from ideal in countries with high incidence.[2,3] Narrowing the treatment-response gap for children with tuberculosis will be a pivotal step toward curbing childhood mortality and will help move us towards the goal of Zero Deaths from childhood tuberculosis.[4]

Tuberculosis disease severity, compromised immune response, and suboptimal treatment all contribute to morbidity and mortality from childhood tuberculosis. Young children are vulnerable to severe forms of tuberculosis including disseminated disease (e.g., tuberculosis meningitis and miliary tuberculosis), which is more difficult to cure.[5] Likewise, comorbidities that impair immune function (e.g., HIV infection, malnutrition) have been linked with lower survival.[6,7] Early and accurate disease detection as well as initiation of appropriate supportive therapy (e.g., anti-retroviral therapy in HIV co-infection and nutritional support in undernourished) are important for proper tuberculosis disease management. Further, adequate drug exposure of anti-tuberculosis treatment is essential for optimal disease outcomes and preventing the development of drug-resistant tuberculosis, which has substantially worse outcomes.[8,9] While many factors certainly contribute to tuberculosis disease outcome, the precise impact of each factor has not been quantified. Optimizing treatment dosing for children is one known and established intervention that can be easily controlled and is an attractive, simple, and efficient strategy for tuberculosis policy change that could immediately benefit children's lives.

Pediatric dosing guidelines, including the WHO guidelines for child tuberculosis,[10] are historically derived based on weight and may leave young and malnourished children vulnerable to underdosing. Flat weight-based dosing (e.g., mg/kg for all ages) assumes a linear relationship between dose requirement and weight, neglecting basic principles of developmental pharmacology.[11] In general, weight is a good indicator of a child's capacity to distribute, metabolize, and eliminate drug if the child is well-nourished and school-aged or older. However, young children undergo dynamic changes in metabolic capacity and body composition during growth that alter drug pharmacokinetics.[11] These changes are often correlated to weight using ¾ power laws, which forms the basis for weight-based dosing where higher mg/kg doses are required in very young children. Further, weight and metabolic rate do not correlate well in malnourished children who have the same metabolic potential as healthy children of equal age. The current tuberculosis dosing guidelines do not consider allometry, age, or malnutrition, which is likely to result with systematic underexposure of young and malnourished children. For example, in the case of children one year of age, a child with a normal weight of 9 kg receives twice as much drug as a malnourished child who weighs 6 kg with WHO weight band dosing,[12] but both children would be expected to eliminate the drug at similar rates. Correcting systematically low drug exposures in the most vulnerable children by modifying drug dosing is an unrecognized and simple area of intervention that could greatly improve outcomes in all of pediatric medicine.

We conducted a modeling study to estimate the prevalence of potential underdosing of first-line anti-tuberculosis drugs and the consequent impact on drug exposures and population outcomes (including mortality) in the 20 countries with the highest burden of childhood tuberculosis. We used a novel, integrative modeling design which used real, individual-level child demographic data along with relevant population pharmacokinetic, exposure-response, and epidemiological models to minimize assumptions and to establish an environment representative of true conditions. To our knowledge, this is the first time a model such as this has been used. With this design, we estimated the impact of a revised dosing method which incorporates age and nutritional status, simply measured, on treatment outcomes compared to the current standard.

Methods

The integrated model was created by linking individual child demographic data obtained from country-specific population health surveys with pharmacokinetic, pharmacodynamic (outcome), and epidemiological models (S1 Figure).

Demographic Database

We created a database of nationally-representative child populations under five years of age from publicly accessible survey data for the 20 countries with the highest total tuberculosis incidence (Table 1). These countries account for 82% of total estimated under-5 tuberculosis incidence.[13] The Demographic and Health Surveys (DHS) Program, a standardized international survey that collects accurate and representative data on health and nutrition for more than 90 countries with large sample sizes, was used as the primary data source.[14] For eight of the 20 countries, child DHS data were unavailable, and other government

administered survey sources were used. Child-specific anthropometrics, gender, age, and nutritional status markers (height-for-age z-score [HAZ], weight-for-age z-score [WAZ], weight-for-height z-score [WHZ], and body mass index-for-age z-score [BAZ]) were extracted from each database. When unavailable from the database, nutritional markers were calculated in R 3.4.2 (R Core Team; Vienna, Austria) using the WHO's Anthro software.[15] Children with expected or actual weight less than 4 kg or physiologically implausible nutritional z-scores were excluded.[12,15]

Dosing Methods

All children were sampled from the above-mentioned database as a potential child with drug-sensitive tuberculosis disease. The WHO-recommended fixed-dose combination (FDC) formulation for intensive phase treatment (75 mg rifampicin, 50 mg isoniazid, 150 mg pyrazinamide) was used.[12] Tuberculosis treatment was simulated for each child with two different dosing methods: the current standard, and a proposed simple algorithm to account for the effects of malnutrition. A third, individualized dosing method for each child was also explored.

For the current standard dosing procedure, the most recent WHO childhood tuberculosis guidelines were used.[10] In this method, children are dosed by weight bands (4-7 kg, 8-11 kg, 12-15 kg, 16-24 kg, 25+) corresponding to incremental FDC tablet quantity and flat mg/kg dose range (S2 Table).[12]

For the new proposed dosing procedure, we chose a simple method where underweight children would receive equal drug doses as normal weight children of the same age (Figure 1). This method was derived by evaluating what dose a child would receive if they were of normal weight. In this proposed method, children with good nutritional status (WAZ ≥ 0) received weight-based dosing according to the WHO weight band algorithm.[12] Children with poor nutritional status (WAZ < 0) received age-based (i.e., expected weight-based) dosing, receiving higher doses than would be received with the current method. This method utilizes the WHO-recommended FDC formulation for children, is simple to implement in resource-limited clinical settings and minimizes the need for additional measurements. Furthermore, to facilitate using WAZ for dose determination, a simplified dosing chart resembling a child growth chart was constructed to eliminate any calculation requirements (see S3-S4 Figures for full page charts).

An individualized dosing scheme was also tested which utilized a developmental pharmacology-driven approach to define the optimal dose. Here, rifampicin, isoniazid, and pyrazinamide doses were determined separately using drug-specific target exposures and individual pharmacokinetic parameter estimates, without constraint to available formulations or rounding (appendix, page 9). This method focused on ensuring that each child reached the target exposure for each drug. With these individualized doses, we explored optimized fixed-dose formulations and dose ratios that may be required for implementing this method.

Exposure Simulations

Drug exposures were estimated for rifampicin, isoniazid, and pyrazinamide using two published and peer-reviewed population pharmacokinetic models (appendix, page 9).[16,17]

Individual child pharmacokinetic parameters were sampled from the established population distribution, defined with median values and between-child variability. Pharmacokinetic profiles were simulated in R using Monte Carlo for each drug and dosing method assuming once-daily oral administration with full adherence to represent the most promising scenario (i.e., treatment completion). For isoniazid, pharmacokinetic profiles for both slow and fast acetylators were simulated. Pharmacokinetic data were summarized as area under the curve at steady state (AUC_{ss}) by integration of the pharmacokinetic profile over a desired period (day, week, month).

Definition of Target Exposure and Outcome Predictions

The simulated pharmacokinetic profiles were linked to drug exposure targets to predict tuberculosis treatment outcome. Target exposures for children are typically based on adult reference concentrations, so the AUC_{ss} targets of 23·4 mg*h/L for isoniazid and 427 mg*h/L for pyrazinamide over 24 hours were used.[17] For rifampicin, a child-specific target defined from an exposure-response model was used, where the relationship between rifampicin AUC_{ss} over one week (AUC_{wk}) is related to the probability of unfavorable event (P_{unf}), defined as death or treatment failure, aligning with the fact that rifampicin is the most important drug in the regimen.[16] Using this model, we defined the rifampicin exposure target as $AUC_{wk} \geq 222$ mg*h/L, which results in a $P_{unf} \leq 5\%$, and predicted the P_{unf} for each child.

Linkage to Epidemiological Models

An epidemiological model was linked to the pharmacodynamic model to estimate the number of children who would experience an unfavorable outcome in the 20 countries included (appendix, page 13).[18] The country- and age-specific median P_{unf} was applied to age-disaggregated WHO tuberculosis notification data to estimate the number of unfavorable events.[13] Notified cases were assumed to represent treated cases.

Analysis

All data manipulation, nutritional marker calculations, summary statistics, model simulations, and visualizations were performed in R. Children were considered underweight if WAZ < −2, stunted if HAZ < −2, and wasted if WHZ < −2. Malnutrition severity was defined based on z-score: normal ($z \geq 0$), mildly malnourished ($-2 \leq z < 0$), moderately malnourished ($-3 \leq z < -2$), or severely malnourished ($z < -3$). Children were considered underdosed by current guidelines if the WHO-recommended dose was lower than the dose that child would have received with the proposed guidelines (i.e., if the weight-based dosing resulted in lower dose than the expected weight-based dosing for an underweight child). Underexposure was defined as AUC_{ss} below the defined exposure target.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Population Characteristics

Our database included individual-level anthropometric data from 388,209 children under five years of age from 20 high-burden tuberculosis countries. Overall, 27% of children were underweight, 36% were stunted, and 15% were wasted. Stunting was prevalent in most countries (>30% in 13 countries; Table 1). Bangladesh, India, and Ethiopia had high proportions of underweight children (>30%) and wasting was critically (>15%) or seriously (10-15%) high in five countries.

Underdosing Prevalence

We estimated that 43% of children or 57,234 of 133,302 treated under-5 tuberculosis cases would be underdosed following current guidelines, based on predicted underdosing by country (Figure 2). Among underweight children only, the prevalence of underdosing was consistently high (>70%) across all countries. Following the current dosing method, the average dose was 16·0 mg/kg for rifampicin, 10·7 mg/kg for isoniazid, and 32·0 mg/kg for pyrazinamide. With the proposed dosing, average doses were 19·6 mg/kg for rifampicin, 13·1 mg/kg for isoniazid, and 39·2 mg/kg for pyrazinamide. This dosing gap was consistent across age groups.

Malnutrition Effects on Rifampicin Exposure Target Outcomes

With current dosing guidelines, only 47% of all children were predicted to reach the defined rifampicin target exposure (Figure 3). Most cases of target attainment (>75%) occurred in children of adequate weight (WAZ ≥−2). Rifampicin target exposure attainment following current dosing guidelines was lower among malnourished children and lessened with increasing malnutrition severity. The proposed dosing method improved outcomes not only for all children but also for those with poor nutritional status and equalized target outcomes across different measures of malnutrition and severity. This trend of improved exposure target outcomes with the proposed method was consistent in all 20 high burden countries (Figure 4). Target exposure trends for isoniazid and pyrazinamide are shown in S8 Figure and S9 Figure, respectively.

Population Estimate of Unfavorable Outcome

The median P_{unf} for the study population following the current dosing regimen was 3·3%. Notably, very young (median P_{unf} = 7·7%) or underweight (median P_{unf} = 4·0%) children were predicted to be particularly vulnerable to poor treatment outcomes with current guidelines. The proposed dosing method improved treatment outcomes for all children (median P_{unf} = 1·8%), with the best improvement seen in the very young (median P_{unf} = 4·7%) and underweight (median P_{unf} =1%). Estimated P_{unf} was more equal with the proposed and individualized dosing across varying WAZ (S10 Figure).

Linking the exposure-response model to tuberculosis case notification data, we found that the number of treatment failures or deaths in children under five years decreased for all 20 high-burden countries with the proposed dosing method (Table 2). Considering only treatment of notified cases, which represents 30% of the total estimated under-5 incidence in

these countries,[13] the proposed method would prevent treatment failure or death from tuberculosis in at least one-third of children predicted to have unfavorable outcome with current dosing practices (equivalent to 2423 actual cases saved per year, at minimum). This impact could be as high as 7844 children saved if all estimated cases are considered (S9 Table).

Discussion

In this study, we introduce a novel, integrative modeling approach which links pharmacologic with epidemiologic models to predict population-level outcomes for childhood tuberculosis. This is the first time that individual child demographic data, representative of true global populations, are used in this context. We included individual-level data from more than 300,000 children under five years of age from 20 high-burden tuberculosis countries, enabling true representation of malnourished children and populations at the highest risk of tuberculosis and severe disease. We compare the current WHO-recommended dosing guidelines with alternative dosing methods to show that simple modifications to dosing practices can improve anti-tuberculosis drug exposure and consequently, population outcomes for children with tuberculosis.

Effective anti-tuberculosis therapy has drastically decreased child mortality from tuberculosis disease in recent decades.[19] However, treatment failures and mortality rates are still high in many endemic areas, especially among children who are very young, malnourished, HIV infected, or have severe disease.[2,3,20] Adequate treatment exposure is essential in these children for successful disease outcomes. Our model predicted that less than half of children under five years of age would reach the rifampicin exposure target, a key drug for tuberculosis cure, with the current guidelines. Malnourished children had lower drug exposures and higher probabilities of unfavorable outcome. These findings support trends shown in clinical studies and reflect the inadequacy of current weight-based dosing recommendations that do not consider age or nutritional status.

With high malnutrition prevalence in tuberculosis-endemic countries, it is important to consider the treatment needs of malnourished children separately. Currently, the way malnourished children are distinguished from their well-nourished peers of the same age is by receiving less drug for the same disease, as evidenced by the percentage of potentially underdosed children in our model. In addition to receiving less drug, pathophysiological changes in the poor nutritional state such as malabsorption, increased renal clearance, and altered protein-binding capacity can further lead to variable and subtherapeutic drug exposures in malnourished children.[21,22] All of these well-established factors suggest that malnourished children require higher anti-tuberculosis dosages to have an equal chance of cure.

The simple dosing method proposed here shows that accounting for malnutrition could improve tuberculosis treatment outcomes in underweight children by delivering adequate drug exposure. With the proposed dosing method, more children reached target exposures compared to the current guidelines in all 20 countries evaluated, even those with low malnutrition prevalence. This method is a simple change from current guidelines that can be

readily implemented in clinical practice. It would be easy-to-use by tuberculosis clinicians, even in remote settings, as it requires only the measurement of weight, age, gender, and estimation of nutritional status (i.e., WAZ for which a simple dosing chart could be used).

When considering dose increases, the risk of toxicity must also be assessed. These drugs have high therapeutic margins and are well-tolerated in children even at higher doses, as routinely prescribed in tuberculosis meningitis.[3,23,24] Additionally, no studies have reported decreased clearance of these drugs with malnutrition. Therefore, any concerns regarding administering higher doses to underweight children are likely unjustified. Without established upper limits of exposure associated with toxicity, the benefit of higher dosages will likely outweigh any potential risk. Regardless, the risk/benefit ratio should be considered for malnourished children who are extremely vulnerable to death.

Even with the proposed dosing method, treatment success was still far below desired targets (~90%). Further, drug exposure outcomes in normal weight children were suboptimal with both dosing methods. The proposed method is based on the minimum change required to make a sizeable impact. We constrained dosing to WHO-recommended dose ranges and FDC formulations, which may not be appropriate for all individuals. Precision dosing algorithms, which account for additional patient and/or disease factors that impact exposure (e.g., HIV infection, SLCO1B1 genotype, and NAT2 acetylator status), will likely be needed to achieve WHO targets with current therapeutics.[20,22,25-27] Optimized FDC formulations were explored based on the individualized doses, but drug doses and dose ratios varied by pharmacokinetic model and isoniazid metabolizing capacity. Our work along with others[16,28] suggests that higher anti-tuberculosis doses and new FDC formulations are needed to ensure optimal outcomes. However, it remains unclear from current pediatric pharmacologic data whether a single global FDC formulation can meet the needs of all children. One simple intermediate solution would be to develop a stand-alone, child-friendly rifampicin formulation to supplement current FDC tablets when higher dosages are necessary.

Drug exposures were simulated using two pharmacokinetic models from distinct populations (India and South Africa) and applied in regionally and demographically similar populations. Outcomes were predicted for all children with a pharmacodynamic model representative of an Indian population alone. These assumptions were made due to the lack of country-specific pharmacologic models and are a limitation of the study. Still, these models represent the only pediatric pharmacokinetic and pharmacodynamic models in the countries of interest and are of the highest quality. The two pharmacokinetic models differed slightly. Genetic diversity or other differences in patient demographics may explain the slight inequality we observed. However, whether the pharmacology truly does differ by region remains unclear as these questions were either not considered in the original trial design or lacked sufficient power to detect differences. It is imperative that future multi-regional studies are conducted and data sharing between countries is improved in order to fully understand dose-concentration-response relationships in children across the globe.

Our study focused on evaluating tuberculosis treatment and obtaining adequate exposure for cure. The effects of non-pharmacological interventions for malnutrition, HIV co-infection,

and extrapulmonary disease, independent of drug exposure, were not included in our model. These children at high risk of poor outcomes may require even higher doses and/or additional interventions to overcome a poor immune response or severe disease in order to have an equal chance of cure. Future pediatric studies should be designed to include these high-risk cohorts in order to establish drug efficacy targets for vulnerable populations and efficacy of additional pharmacological and non-pharmacological interventions if we hope to cure tuberculosis in all.

Our epidemiological model accounted for age-related differences in disease risk, but malnutrition and HIV infection, both known to impact disease progression, were not included. Malnutrition impacts the immune system, increasing a child's risk of progression to active tuberculosis, and the disease further exacerbates the child's nutritional state.[29] While the relationship between tuberculosis and malnutrition is well-known, the relative risk of disease progression in malnourished children has not been quantified. We assumed that the malnutrition prevalence among tuberculosis cases in our model matched the prevalence in our demographic database. In tuberculosis disease, we would expect more malnourished children than the general population, implying that our population-level estimates with the proposed dosing algorithm are conservative. Further, HIV status information was sparse in the demographic datasets, limiting our analysis to an HIV uninfected population. While we cannot make unique dose recommendations or predict outcomes for HIV co-infected children from this study, we would expect that the proposed dosing would improve exposure outcomes in HIV co-infected children, as these children are often malnourished.

Less than half of the estimated one million child tuberculosis cases per year are represented in WHO notification data.[13] Case detection is extremely low in children under five years of age due to diagnostic challenges and under-reporting.[18] Clearly, finding and diagnosing children with tuberculosis is the highest priority for decreasing disease burden. However, this work shows that even with access to the correct treatment, an impact can be made by optimizing dosing. The minimum impact of implementing the proposed dosing strategy is 2423 fewer treatment failures or deaths annually in children under five years in these 20 high-burden countries, based on notified cases. Unfavorable outcomes could be reduced from 23,510 to 15,666 per year if we assume all estimated under-5 tuberculosis cases in these countries are diagnosed and treated. It is clear that while the proposed dosing method improves outcomes, treatment failures and deaths still occur. Future studies that evaluate the impact of all key factors such as treatment, malnutrition, HIV status, etc. are imperative. Only by carefully studying and understanding the quantitative impact of all factors and unbiased efficacy predictions of targeted interventions can we move closer to achieving zero childhood deaths from tuberculosis. Acting on discoveries that could lead to simple adjustments in how we treat the most vulnerable of children is an important first step.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Research in Context

Evidence before this study

We searched PubMed for studies published before Dec 1, 2018 with the search terms "child*" AND "tuberc*" AND ("outcome" OR "exposure" OR "pharmaco*") AND ("dose*" OR "dosing" OR "treatment") in the title or abstract. Our search identified 652 studies, most of which pertained to diagnosis, latent tuberculosis or prevention, and drug-resistant forms were not considered. We also reviewed our personal files for additional relevant articles. Since the release of the first WHO child tuberculosis guidelines in 2006, 30 studies have reported tuberculosis treatment outcomes in children. In 20 of these studies, unfavorable outcomes, including treatment failure or death, were greater than 10%. Young age (< 5 years), malnutrition, HIV infection, and extra-pulmonary tuberculosis (e.g., meningitis) have all been associated with worse outcomes. Underdosing or subtherapeutic drug levels have been reported in >50% of child subjects in 17 studies, 8 of which utilized the current WHO dosing guidelines. No clinical studies in children with tuberculosis have been conducted with alternative dosing approaches to the standard weight-based method (i.e., mg/kg); however, several studies conclude that improved dosing is required to adequately treat children.

Added value of this study

To our knowledge, this is the first study to use an integrative modeling approach which links pharmacological with epidemiological models to evaluate the population-level impact of tuberculosis dosing in children. We utilized individual child demographic data (n>300,000) from 20 countries with high tuberculosis incidence to predict individual drug exposure profiles and link them to treatment response and epidemiological outcomes. Our innovative approach enables true representation of populations vulnerable to treatment failure in realistic proportions, including very young children and children who are malnourished. Furthermore, we compare drug exposure and treatment outcomes following the current WHO dosing guidelines, which are based solely on a child's weight, with a newly proposed dosing approach that incorporates age and nutritional status. Our study is the first to show that a weight-based approach is inadequate for tuberculosis treatment where many ill children are malnourished. To that end, a simple change in dosing approach can drastically improve tuberculosis treatment outcomes in the most vulnerable children.

Implications of all the available evidence

The current WHO dosing recommendations for children with drug-sensitive tuberculosis are not sufficient to cure disease in all children, especially in malnourished and young children who are particularly vulnerable to severe forms, poor treatment outcomes, and death. The dosing method proposed in this study is simple, directly implementable, would not require any additional measurements by tuberculosis care providers, utilizes currently available fixed-dose combination formulations, and would save many children's lives. Importantly, this work can advise future dosing recommendations for young children with tuberculosis.

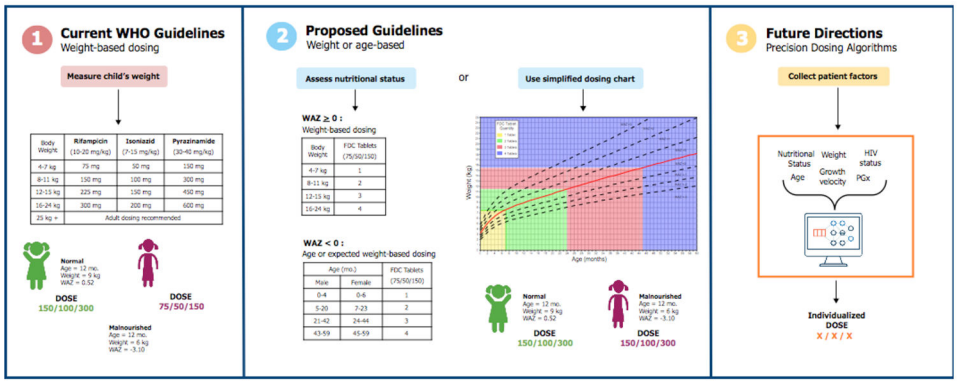

Figure 1. Childhood tuberculosis dosing schematic.

For the proposed guidelines, dosing is stratified by nutritional status (WAZ ≥ 0, use weight-based dosing; WAZ < 0, use age or expected weight dosing). Alternatively, a simplified dosing chart can be used to determine dose. WAZ = weight-for-age z-score. PGx = pharmacogenomics. FDC = fixed dose combination.

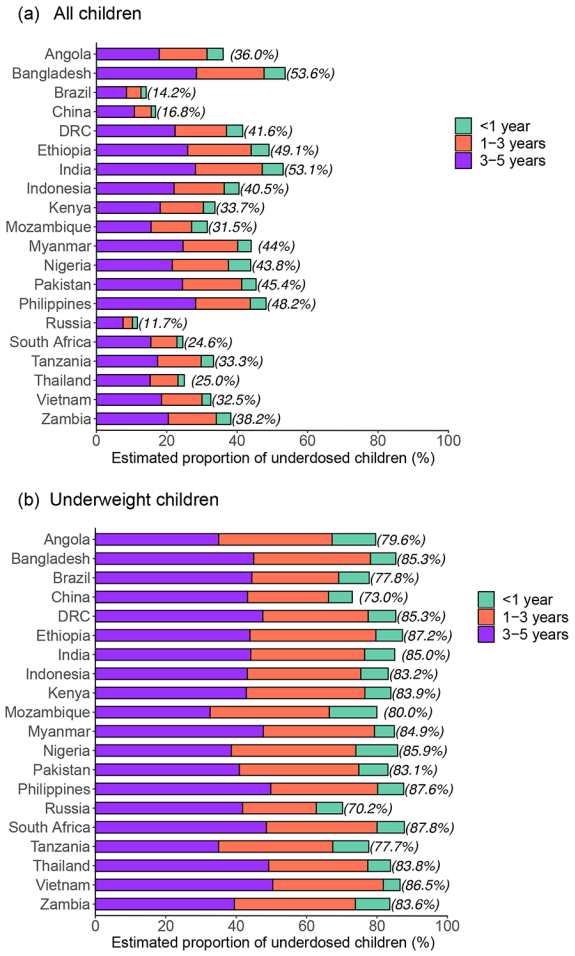

Figure 2. Underdosing prevalence with current WHO treatment guidelines.

Bar segments represent the contribution of each age group to the overall underdosing prevalence in all (a) or underweight (b) children. DRC = Democratic Republic of the Congo.

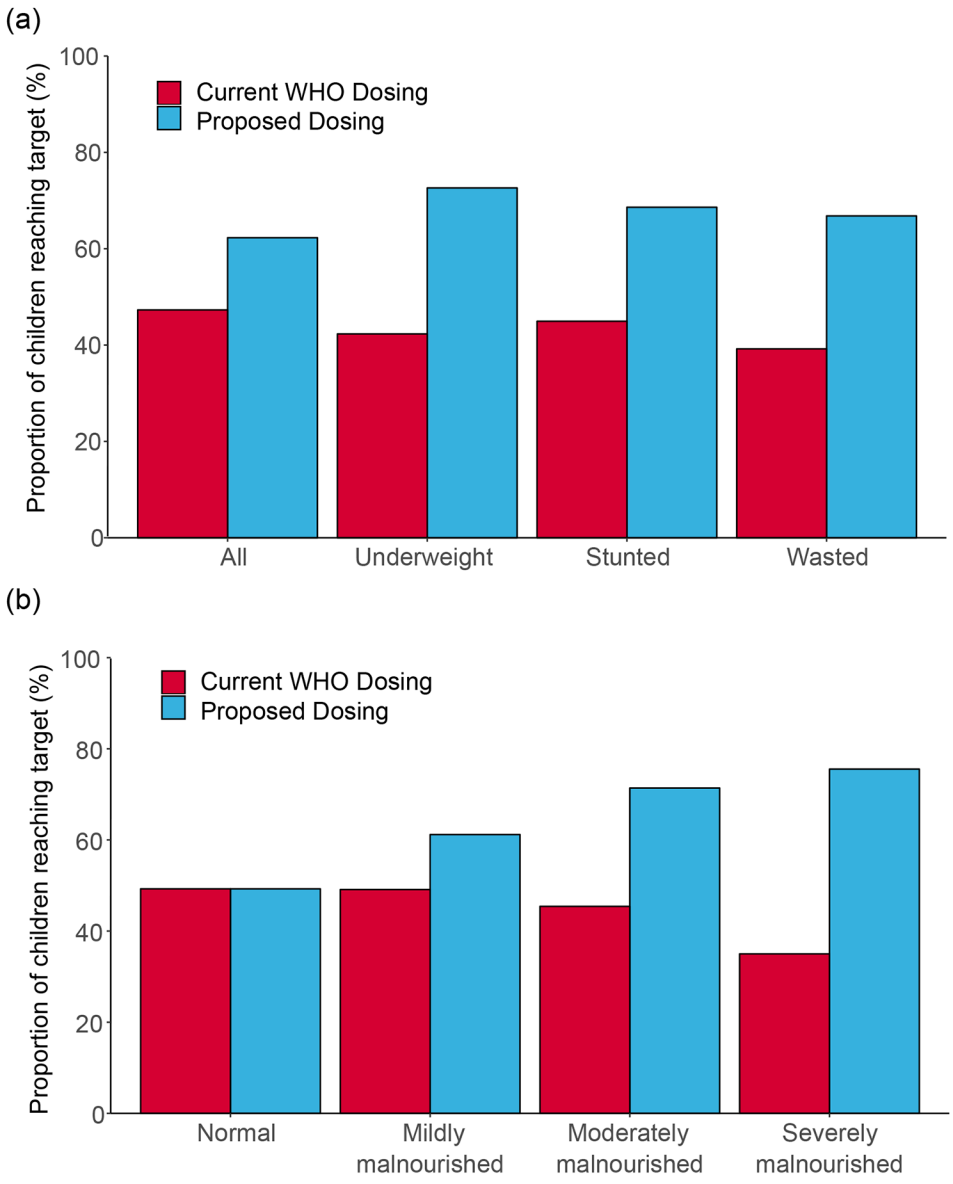

Figure 3. Impact of malnutrition on rifampicin exposure target outcomes.

Target outcomes are shown with respect to different measures of nutritional status (a) and severity of malnourishment, determined by weight-for-age z-score (b).

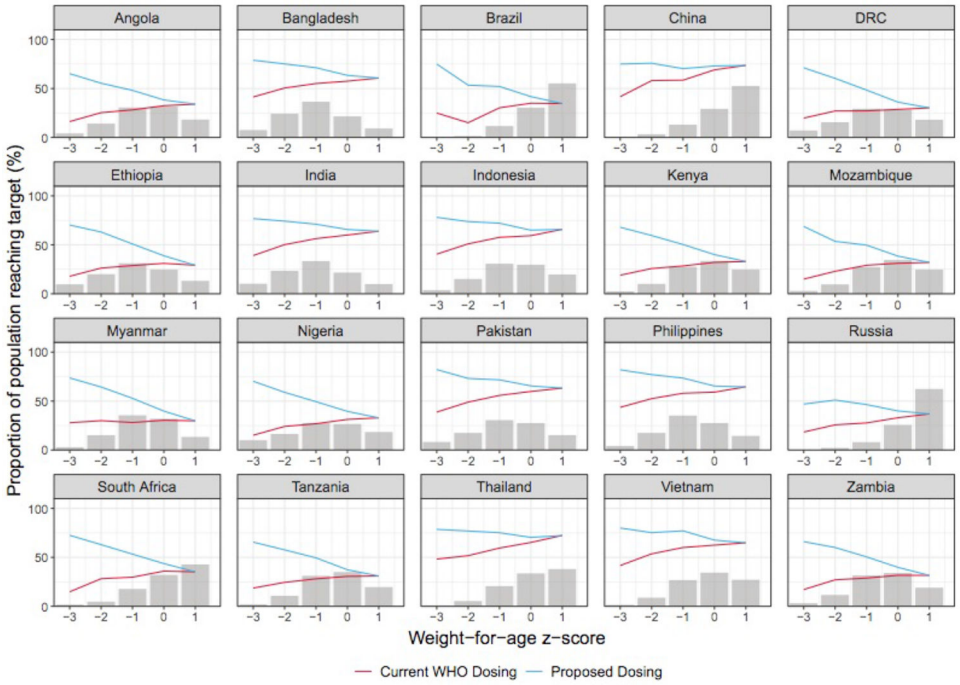

Figure 4. Rifampicin target exposure outcomes in high-burden tuberculosis countries.

The proportion of children reaching the rifampicin exposure target across weight-for-age z-score (WAZ) is shown for each dosing scheme. Histogram shows the population distribution. DRC = Democratic Republic of the Congo.

Table 1.

Study Population.

Country	N	Nutritional Status, n (%)			Survey, Year(s)
		Underweight	Stunted	Wasted	
Angola	6135	1139 (19)	2309 (38)	305 (5)	DHS, 2015
< 1 year	1310	202 (15)	275 (21)	93 (7)	
1-3 years	2528	518 (20)	1149 (45)	136 (5)	
3-5 years	2297	419 (18)	885 (39)	76 (3)	
Bangladesh	6857	2225 (32)	2522 (37)	972 (14)	DHS, 2011
< 1 year	1236	216 (17)	203 (16)	202 (16)	
1-3 years	2862	974 (34)	1162(41)	405 (14)	
3-5 years	2759	1035 (38)	1157 (42)	365 (13)	
Brazil	4288	81 (2)	311 (7)	62 (1)	PNDS, 2006
< 1 year	801	15 (2)	35 (4)	24 (3)	
1-3 years	1721	29 (2)	149 (9)	21 (1)	
3-5 years	1766	37 (2)	127 (7)	17 (1)	
China	1729	74 (4)	220 (13)	76 (4)	CHNS, 2006
< 1 year	233	7 (3)	35 (15)	13 (6)	
1-3 years	708	28 (4)	95 (13)	32 (5)	
3-5 years	788	39 (5)	90 (11)	31 (4)	
DRC	7913	1835 (23)	3515 (44)	613 (8)	DHS, 2013
< 1 year	1608	213 (13)	303 (19)	181 (11)	
1-3 years	3275	725 (22)	1513 (46)	268 (8)	
3-5 years	3030	897 (30)	1699 (56)	164 (5)	
Ethiopia	9482	2850 (30)	4043 (43)	1095 (12)	DHS, 2011
< 1 year	1839	289 (16)	243 (13)	307 (17)	
1-3 years	3654	1253 (34)	1816 (50)	461 (13)	
3-5 years	3989	1308 (33)	1984 (50)	327 (8)	
India	221,113	75,869 (34)	85,069 (38)	44,323 (20)	DHS, 2015
< 1 year	37,970	9541 (25)	8018 (21)	9968 (26)	
1-3 years	90,396	31,759 (35)	38,196 (42)	18,274 (20)	
3-5 years	92,747	34,569 (37)	38,855 (42)	16,081 (17)	
Indonesia	4398	850 (19)	1582 (36)	411 (9)	IFLS, 2006, 2007
< 1 year	767	100 (13)	206 (27)	92 (12)	
1-3 years	1805	366 (20)	729 (40)	182 (10)	
3-5 years	1826	384 (21)	647 (35)	137 (8)	
Kenya	18,424	2427 (13)	4995 (27)	989 (5)	DHS, 2014
< 1 year	3478	233 (7)	437 (13)	192 (6)	
1-3 years	7639	1102 (14)	2522 (33)	407 (5)	
3-5 years	7307	1092 (15)	2036 (28)	390 (5)	
Mozambique	9142	1178 (13)	3604 (39)	450 (5)	DHS, 2011
< 1 year	1873	228 (12)	463 (25)	133 (7)	

Country	N	Nutritional Status, n (%)			Survey, Year(s)
		Underweight	Stunted	Wasted	
1-3 years	3893	545 (14)	1770 (45)	237 (6)	
3-5 years	3376	405 (12)	1371 (41)	80 (2)	
Myanmar	4138	763 (18)	1268 (31)	263 (6)	DHS, 2015
< 1 year	786	67 (9)	73 (9)	60 (8)	
1-3 years	1661	319 (19)	574 (35)	114 (7)	
3-5 years	1691	377 (22)	621 (37)	89 (5)	
Nigeria	24,076	6444 (27)	8720 (36)	3936 (16)	DHS, 2013
< 1 year	4893	1027 (21)	921 (19)	1171 (24)	
1-3 years	9631	2880 (30)	3930 (41)	1698 (18)	
3-5 years	9552	2537 (27)	3869 (41)	1067 (11)	
Pakistan	3011	787 (26)	1350 (45)	304 (10)	DHS, 2012
< 1 year	520	110 (21)	115 (22)	73 (14)	
1-3 years	1203	344 (29)	603 (50)	139 (12)	
3-5 years	1288	333 (26)	632 (49)	92 (7)	
Philippines	15,922	3510 (22)	5506 (35)	1043 (7)	FNRI-NNS, 2015
< 1 year	2593	322 (12)	343 (13)	246 (9)	
1-3 years	6089	1379 (23)	2322 (38)	451 (7)	
3-5 years	7240	1809 (25)	2841 (39)	346 (5)	
Russia	9665	282 (3)	919 (10)	828 (9)	RLMS-HSE, 2006-2015
< 1 year	1803	87 (5)	208 (12)	142 (8)	
1-3 years	4020	76 (2)	395 (10)	272 (7)	
3-5 years	3842	119 (3)	316 (8)	414 (11)	
South Africa	9691	671 (7)	2573(27)	406 (4)	NIDS, 2008-2014
< 1 year	859	65 (8)	171 (20)	80 (9)	
1-3 years	4012	265 (7)	1310 (33)	158 (4)	
3-5 years	4820	341 (7)	1092 (23)	168 (3)	
Tanzania	8735	1177 (13)	2961 (34)	400 (5)	DHS, 2015
< 1 year	1773	169 (10)	310 (17)	128 (7)	
1-3 years	3808	569 (15)	1525(40)	170 (4)	
3-5 years	3154	439 (14)	1126 (36)	102 (3)	
Thailand	8688	593 (7)	1187 (14)	516 (6)	MICS, 2012
< 1 year	987	67 (7)	140 (14)	84 (9)	
1-3 years	3722	223 (6)	559 (15)	177 (5)	
3-5 years	3979	303 (8)	488 (12)	255 (6)	
Vietnam	3515	379 (11)	758 (22)	135 (4)	MICS, 2010
< 1 year	592	26 (4)	44 (7)	32 (5)	
1-3 years	1500	157 (10)	353 (24)	48 (3)	
3-5 years	1423	196 (14)	361 (25)	55 (4)	
Zambia	11,287	1687 (15)	4493 (40)	693 (6)	DHS, 2014
< 1 year	2103	220 (10)	480 (23)	175 (8)	
1-3 years	4669	782 (17)	2269 (49)	284 (6)	

Country	N	Nutritional Status, n (%)			Survey, Year(s)
		Underweight	Stunted	Wasted	
3-5 years	4515	685 (15)	1744 (39)	234 (5)	

Underweight = weight-for-age z-score (WAZ)< −2; Stunted = height-for-age z-score (HAZ)< −2; Wasted = weight-for-height z-score (WHZ)< −2. CHNS = Chinese Health and Nutrition Surveys; DHS = Demographic and Health Surveys Program; DRC = Democratic Republic of the Congo; FNRI-NNS = Food and Nutrition Research Institute-National Nutrition Survey; IFLS = Indonesia Family Life Survey; MICS = Multiple Indicator Cluster Surveys; NIDS = National Income Dynamics Study; PNDS = Pesquisa Nacional de Demografia e Saude; RLMS = Russia Longitudinal Monitoring Survey- Higher School of Economics.

Table 2.

Estimated number of treatment failures or deaths from tuberculosis per year in children under five years of age.

Country	Notified tuberculosis cases	Estimated treatment failures or deaths		Estimated number saved from treatment failure or death
		Current Dosing	Proposed Dosing	
Angola*	102	7	5	2
Bangladesh	957	51	27	24
Brazil	888	54	48	6
China	261	9	8	1
DRC	5607	398	283	114
Ethiopia	3452	244	161	83
India	26,063	1442	799	643
Indonesia	22,203	970	676	294
Kenya	3903	253	195	57
Mozambique	3841	257	186	71
Myanmar	13,176	880	626	254
Nigeria	2517	184	116	68
Pakistan	16,880	846	558	288
Philippines	16,573	836	529	307
Russia	1025	62	56	6
South Africa	9254	563	456	107
Tanzania	4899	327	252	75
Thailand	318	14	10	3
Vietnam	589	22	18	5
Zambia	794	55	39	15
Total	133,302	7470	5047	2423

Predictions were calculated using median probability of unfavorable outcome (P_{unf}) and number of under-five notified tuberculosis cases (WHO), disaggregated by age.

*=2016 notification data.