Rifampin urinary excretion to predict serum targets in children with tuberculosis: a prospective diagnostic accuracy study

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ABSTRACT

Objective Pharmacokinetic variability drives tuberculosis (TB) treatment outcomes but measurement of serum drug concentrations for personalised dosing is inaccessible for children in TB-endemic settings. We compared rifampin urine excretion for prediction of a serum target associated with treatment outcome.

Design Prospective diagnostic accuracy study.

Setting Inpatient wards and outpatient clinics, northern Tanzania.

Patients Children aged 4–17 years were consecutively recruited on initiation of WHO-approved treatment regimens.

Interventions Samples were collected after directly observed therapy at least 2 weeks after initiation in the intensive phase: serum at pre-dose and 1, 2 and 6 hours post-dose, later analysed by liquid chromatography-tandem mass spectrometry for calculation of rifampin total exposure or area under the concentration time curve (AUC_{0-24}); urine at post-dose intervals of 0–4, 4–8 and 8–24 hours, with rifampin excretion amount measured onsite by spectrophotometry.

Main outcome measures Receiver operating characteristic (ROC) curve for percentage of rifampin dose excreted in urine measured by spectrophotometry to predict serum rifampin AUC_{0-24} target of 31.7 mg*hour/L.

Results 89 children, 52 (58%) female, with median age of 9.1 years, had both serum and urine collection. Only 59 (66%) reached the serum AUC_{0-24} target, reflected by a range of urine excretion patterns. Area under the ROC curve for percentage of rifampin dose excreted in urine over 24 hours predicting serum AUC_{0-24} target was 69.3% (95% CI 56.7% to 81.8%), p=0.007.

Conclusions Urine spectrophotometry correlated with a clinically relevant serum target for rifampin, representing a step toward personalised dosing for children in TB-endemic settings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pharmacokinetic variability is an important driver of tuberculosis (TB) treatment failure, and low serum drug concentrations have been associated with delayed response to treatment, death and acquired drug resistance.

⇒ Within first-line drugs for TB, rifampin demonstrates the most pharmacokinetic variability, acts in bactericidal and sterilising capacity, and for children, recent serum rifampin targets have been associated with treatment outcome from multinational cohorts.

WHAT THIS STUDY ADDS

⇒ A urine spectrophotometric assay performed in rural Tanzania without the need for specialised laboratory capacity for chromatography or mass spectrometry and without the need for preservation of the cold chain, correlated with a serum rifampin target associated with treatment outcome among a representative population of children undergoing TB treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ With further study of dose response to a suboptimal urine detection, and optimisation toward assay automation, urine spectrophotometry could deliver point-of-care personalised dosing for children with TB currently without access to personalisation, an even more critical advance as shorter course regimens for childhood TB are trialled.

INTRODUCTION

In non-pandemic periods, tuberculosis (TB) is the leading cause of death by a single infectious disease worldwide.[1] Despite the availability of effective treatment regimens in controlled studies, TB is nonetheless responsible for the disproportionate deaths of over 200 000 children annually. Pharmacokinetic variability is an important driver of treatment failure, and low serum drug concentrations have been associated with delayed response to treatment, poor outcomes and acquired drug resistance.[2–4] Many anti-TB medications are concentration dependent in their activity with peak serum concentration (C_{max}) and total area under the concentration time curve (AUC) predictive of microbial kill and prevention of acquired resistance.[5 6] Dosing recommendations for childhood TB were previously based on adult pharmacokinetic data,

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and certain formulations of fixed combinations have demonstrated reduced bioavailability in some populations.[7] Despite the updated 2014 WHO guidelines for weight-based dosing in paediatric TB, subsequent studies have continued to document poor attainment of target C_{max} and AUC values in children.[8–11] We previously showed that among children undergoing TB treatment in rural Tanzania, the minority achieved target peak serum C_{max} for key drugs, and malnutrition, in addition to drug dose, was associated with lower drug concentration in multivariable models.[12] Further, in a more recent cohort in the same setting, we found enteropathogen burden in children treated for TB associated with lower overall serum exposure and pharmacokinetic variability.[13]

Current dosing strategies for paediatric TB rely on crude weight bands not because personalised dosing to reach pharmacokinetic targets is unimportant, rather that the methodology for doing so is typically accomplished by measurement of serum concentrations scheduled during the dosing interval and analysed with either high performance liquid chromatography and ultraviolet absorbance or mass spectrometry.[14] Alternatively, assays that bypass the need for cold chain preservation with serum, eliminate blood draws altogether for paediatric patients or are analysed without the need for specialised equipment could considerably expand the means for delivery of personalised dosing. In prioritising drugs for alternative assays, rifampin demonstrates the most pharmacokinetic variability and has a well-understood range for exposure increase without dose-related toxicity.[5 6]

Previously, we found that urine spectrophotometric testing could predict serum rifampin peak concentrations in a pilot study among children treated for TB in Tanzania.[15] Here, we sought to study the urine spectrophotometric assay's predictive ability among a larger cohort across an age spectrum to include adolescents and to understand performance characteristics from different urine collection intervals.

MATERIALS AND METHODS

Patient population

Paediatric patients diagnosed with confirmed or probable TB defined by the National Institutes of Health Consensus Case Definitions for TB research were enrolled in Tanzania at the Haydom Lutheran Hospital in the rural Mbulu district and the Kilimanjaro Christian Medical College Hospital in semiurban Moshi urban district in 2020–2021.[16] Ninety participants were sought for enrolment to account for potential covariates and inadequate sample collection or loss to follow-up. Females and males between ages 4 and 17 years and able to void on command without incontinence were consecutively recruited from inpatient wards and outpatient clinics near TB treatment initiation. Guardians signed written informed consent and children >7 years of age provided assent. All patients received weight-based daily doses of rifampin, isoniazid, pyrazinamide and ethambutol, per Tanzanian national guidelines, including the use of fixed-dose combination (FDC) paediatric dispersible tablets for children <25 kg, and adult FDC formulations for children >25 kg.[17] The findings were reported per the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines.[18]

Procedures

Serum and urine sample collection was performed at least 2 weeks after TB treatment initiation to allow for steady-state kinetics of rifampin. Participants arrived at the research centre to spend the night 1 day prior to sampling; anthropometrics were measured and additional demographics and clinical information collected. Children were provided with bottled water to consume prior to and throughout the day of blood/urine sampling. On the morning of blood/urine sampling, after an overnight fast, participants had witnessed TB medication administration. Venous samples were collected pre-dose, 1, 2 and 6 hours post-dose. Approximately 30 min after the first blood draw, patients were provided breakfast and encouraged to eat per usual routine. Venous blood was immediately centrifuged and serum frozen at −80°C until batch shipment on dry ice to University of Florida, USA. Prior to the medication administration, the participant voided all urine. After medication administration (time zero hour), all urine was collected for 24 hours in three separate intervals using a graded receptacle for each interval: 0–4, 4–8 and 8–24 hours. Each interval urine volume was recorded, and an aliquot from each interval was used for analysis of rifampin urine concentration using the spectrophotometric assay.

Serum drug quantification

Rifampin serum concentrations were quantified using validated liquid chromatography-tandem mass spectrometry procedures.[12] Clinical information and urine results were not available to technicians performing serum drug quantification. C_{max} was recorded as the highest of the measured rifampin concentrations during the dosing interval. Estimated total exposure, AUC over 24 hours ($AUC_{0–24}$), was determined by non-compartmental analysis using Phoenix WinNonlin V.8.3 (Certara, USA).

Table 1 Demographic and clinical characteristics (N=89)

Parameter	Median or n (N=89)	IQR or %
Sex (female)	52	57.8
Age (years)	9.1	5.8–12.9
Weight (kg)	21.1	15.9–31.8
Height (cm)	123.7	105.5–144.5
MUAC (cm)	15.2	14.1–18.0
BMI-for-age z-score*	−1.34	−2.3 to −0.41
BCG vaccinated	84	93.3
Prior TB disease	7	7.8
HIV seropositivity	3 of 90	3.3
Diabetes	0	0
Asthma	1	1.1
TB location		
Pulmonary	54	61
Pleural	1	1
Spine/bone	5	6
Lymph node	51	57
Pericarditis	1	1
Anti-TB medications on day of assay		
Rifampin dose (mg)	300	225–450
Isoniazid dose (mg)	150	112.5–225
Pyrazinamide dose (mg)	600	450–1200
Ethambutol dose (mg)	412.5	300–825
Laboratory values on day of assay		
Serum creatinine (µmol/L)	34.85	27.7–44
Blood urea nitrogen (mmol/L)	2.73	2.1–3.43
Haemoglobin (g/dL)	11.3	10–13.3

*N=86 with calculable BMI (body mass index).
MUAC, mean upper arm circumference; TB, tuberculosis.

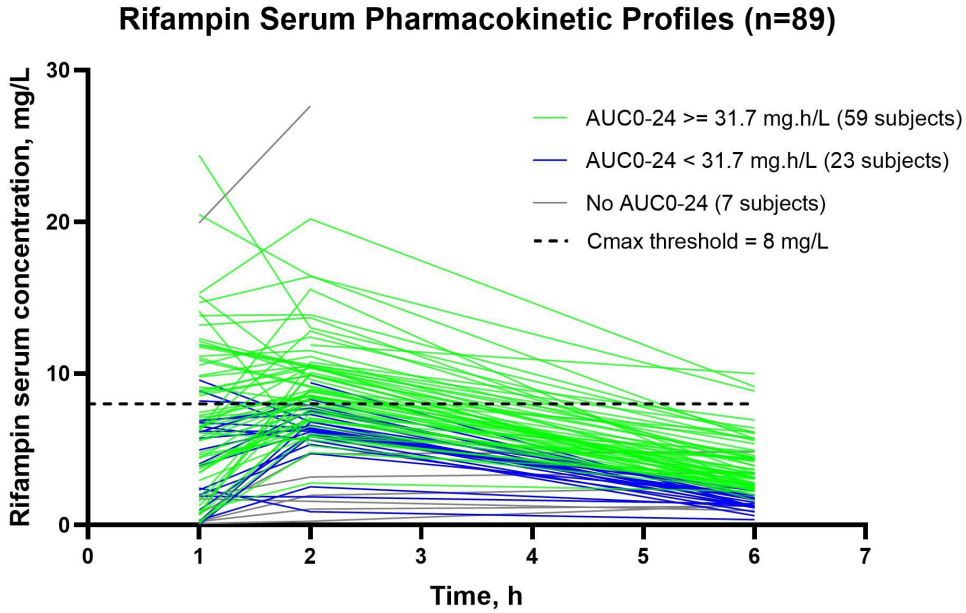


Figure 1 Rifampin serum pharmacokinetic profiles after standard tuberculosis regimen dose administration. AUC0–24, calculated area under the concentration time curve over 24 hours, coloured for those meeting or failing to meet the threshold previously associated with treatment failure in paediatric cohorts; C_{max}, peak serum concentration with 8 mg/L identified as typical minimal range for peak in application of serum therapeutic drug monitoring.

Urine spectrophotometric assay

The Sunahara method was followed to extract total rifamycins in urine.[19] Clinical information and serum results were not available to technicians performing the urine spectrophotometric assay. For a working volume of 500 µL of urine, 250 µL of phosphate buffer (pH 7, Sigma-Aldrich) and 500 µL of isoamyl alcohol (Sigma-Aldrich) were added. Samples were vortexed for 20 s and centrifuged at 13 000 rpm for 5 min at room temperature. Next, 100 µL of the aqueous phase was removed and added to a 96-well plate, and the optical density was measured at 475 nm using a spectrophotometer (Bio-Rad, iMark Microplate Absorbance Reader #1681130). A seven-point calibration curve was constructed with 1000 and 31.2 µg/mL as upper and lower limits of calibration. We have previously documented interday and intraday agreement, as well as the stability of the assay in various environmental conditions including prolonged light exposure and differing urine protein and pH measurements.[15]

The amount of rifampin excreted in urine over the following intervals was calculated: 0–4, 4–8, 0–8, 8–24 and 0–24 hours.

Statistical analysis

Simple frequencies were used to quantify demographic characteristics at baseline. Body mass index (BMI) for age z-scores were calculated in R software using anthro and childsds packages.[20 21] We anticipated that paediatric subjects significantly varied in age and body weight which altered rifampin dose, noting the fraction of rifampin dose excreted unchanged into urine (Fe) has been reported as approximately 30%.[22] We therefore assumed that Fe is independent of the body weight and age (additionally, no such correlations were later found), and that the total amount excreted into urine over 24 hours would be proportional to the dose. Thus, urinary excretion amount for each individual was normalised by dose, effectively converting urine

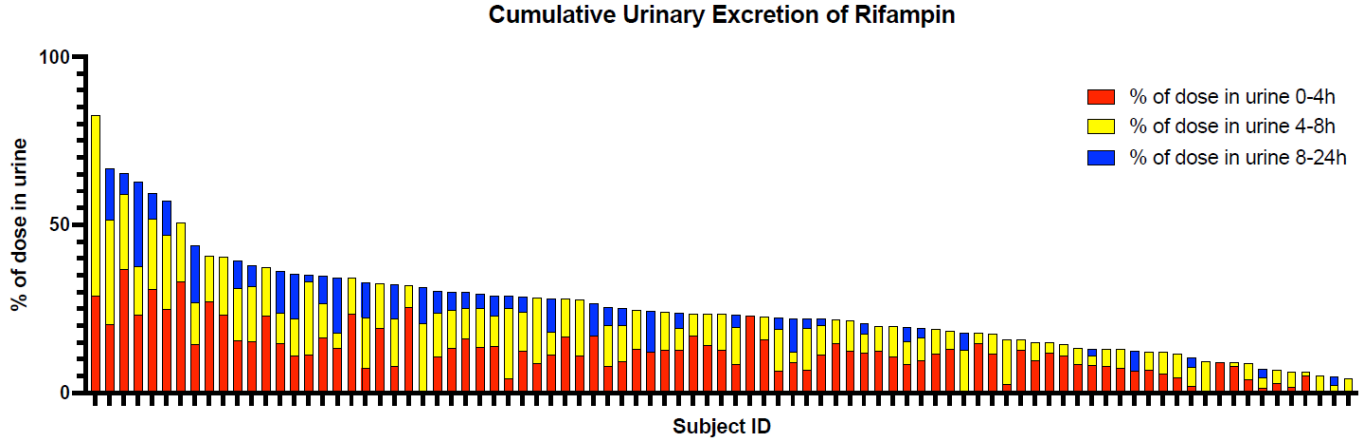
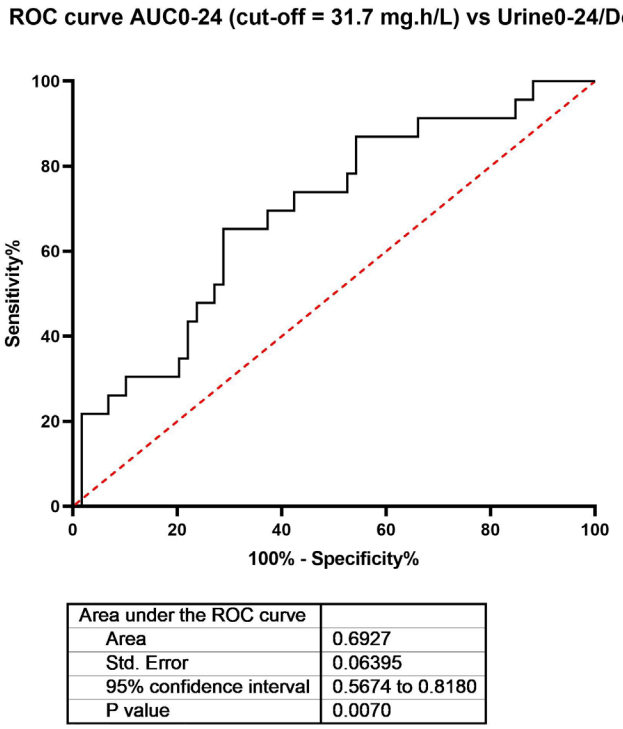


Figure 2 Cumulative urinary excretion of rifampin over 24 hours as measured by urine spectrophotometry and presented as percentage of dose with peak of each bar representing the total % of dose excreted in 24 hours and coloured bands for percentages within each time period within the interval. Y-axis represents each individual patient in the study (N=89).



Area under the ROC curve	
Area	0.6927
Std. Error	0.06395
95% confidence interval	0.5674 to 0.8180
P value	0.0070

Figure 3 Receiver operator characteristic (ROC) curve for rifampin urinary dose excretion over 24 hours and calculated serum area under the concentration time curve (AUC_{0-24}) threshold value previously associated with tuberculosis treatment outcome in paediatric cohorts.

rifampin amounts to a percentage of the dose excreted. Pearson's correlations were generated using serum rifampin AUC_{0-24} and percentage of the dose excreted in urine from each collection interval. Rifampin AUC_{0-24} was then categorised as at or above a target level of 31.7 mg*hour/L, based on a previous multi-country model of child-specific targets derived from AUC over 1 week (AUC_{wk}) and probability of death or treatment failure (AUC_{wk} ≥222 mg *hour/L resulted ≤5% probability of poor outcome).[23] Receiver operator characteristic (ROC) curves were generated, and the area under the ROC curve calculated. Sensitivity and specificity costs were displayed with either fixed sensitivity or specificity of 80%. Data were analysed in R software (V.3.6.1, http://r-project.org), with ROC analysis performed using the pROC package.[24]

RESULTS

A total of 90 children were enrolled, with 89 (99%) completing both serum and urine collection per protocol and available for analysis (table 1). There were no adverse events related to serum or urine collection. Of the 89 participants included, the median age was 9.1 years, 52 (58%) were female. Undernourishment affected 51 (59.2%) of participants, including 23 (26.7%) with mild undernourishment (BMI for age z-score <-1), 15 (17.4%) with moderate undernourishment (BMI for age z-score <-2) and 13 (15.1%) with severe undernourishment (BMI for age z-score <-3).

Serum pharmacokinetics

Figure 1 displays the individual serum pharmacokinetic curves. Forty-seven (53%) reached a conventional serum C_{max} target of 8 mg/L, while 59 (66%) reached the paediatric cohort derived serum AUC_{0-24} target of 31.7 mg*hour/L. Online supplemental figure 1 demonstrates the expected correlation of serum C_{max} and serum AUC_{0-24}.

Urine excretion pattern and spectrophotometric results

Using the spectrophotometer to measure absorbance, extraction of rifampin using the Sunahara method demonstrated a linear relationship between rifampin concentration from 31.2 to 1000 mg/L (r=1). A total of 534 total urine samples were analysed from 89 participants. The proportion of rifampin dose excreted in the urine varied significantly among participants and the mean urinary excretion percentage over 24 hours for the cohort was 25.65% (±14.81%). Based on visual inspection of

Table 2 Sensitivity and specificity for subtarget serum rifampin

Threshold	Serum AUC_{0-24}, cut-off 31.7 mg*hour/dL			Estimated peak serum at 2 hours (C_{2hr}), cut-off 8 mg/L		
	Urine dose excretion interval	Specificity* % (95% CI) n/n	Sensitivity* % (95% CI) n/n	Urine dose excretion interval	Specificity* % (95% CI) n/n	Sensitivity* % (95% CI) n/n
≥80% specificity (eg, less severely ill, more monitoring capabilities)	0–4 hours (n=79)	0.80 (0.46 to 0.95) 45/56	0.26 (0.09 to 0.48) 6/23	0–4 hour (n=84)	0.80 (0.56 to 0.96) 36/45	0.31 (0.15 to 0.49) 12/39
	0–8 hours (n=82)	0.81 (0.66 to 0.98) 48/59	0.30 (0.13 to 0.70) 7/23	0–8 hour (n=89)	0.81 (0.57 to 0.94) 38/47	0.38 (0.19 to 0.57) 16/42
	0–24 hours (n=82)	0.81 (0.69 to 1.00) 48/59	0.30 (0.13 to 0.70) 7/23	0–24 hour (n=89)	0.81 (0.64 to 1.00) 38/47	0.33 (0.19 to 0.62) 14/42
≥80% sensitivity (eg, severely ill, fewer monitoring capabilities)	0–4 hours (n=79)	0.21 (0.11 to 0.39) 12/56	0.83 (0.61 to 1.00) 19/23	0–4 hour (n=84)	0.29 (0.07 to 0.49) 13/45	0.82 (0.56 to 0.95) 32/39
	0–8 hours (n=82)	0.41 (0.15 to 0.64) 24/59	0.83 (0.61 to 0.96) 19/23	0–8 hour (n=89)	0.43 (0.13 to 0.62) 20/47	0.81 (0.60 to 0.90) 34/42
	0–24 hours (n=82)	0.46 (0.10 to 0.68) 27/59	0.83 (0.61 to 1.00) 19/23	0–24 (n=89)	0.30 (0.11 to 0.64) 14/47	0.81 (0.64 to 0.93) 34/42

*Sensitivity/specificity true positive or true negative set at the lowest number required to meet the ≥0.8 threshold.
AUC_{0-24}, serum area under the concentration time curve over the 24-hour dosing interval.

the variation in excretion across dosing intervals (figure 2), the urine 0–24 interval was prioritised for further comparison to serum targets.

Urinary excretion for prediction of serum AUC_{0-24} target

Online supplemental figure 2 demonstrates the correlation of the different urine time points and serum AUC_{0-24} with and without adjustment for dose. The ROC curve for the 24-hour urinary excretion to identify patients with subtarget serum rifampin AUC_{0-24} is shown in figure 3. Using the AUC_{0-24} target of 31.7 mg*hour/L, the area under the ROC curve was 69.3% (95% CI 56.7% to 81.8%), p=0.007. Altering serum rifampin AUC_{0-24} targets based on other previously published studies or the quartile values within the current population did not significantly alter the area under the ROC curve (range 68.4–73.6%; online supplemental figure 3).

A serum C_{2hr} value is frequently operationalised in clinical care to estimate rifampin C_{max} and approximation of total serum exposure. Importantly, we found that the serum C_{2hr} value only modestly outperformed the 0–24 hour urine and 0–8 hour urine intervals of the spectrophotometric assay despite being a direct component of measuring AUC_{0-24} (online supplemental figure 4). Under certain circumstances, a higher specificity for the urine spectrophotometric assay may be targeted, whereas in a child with severe illness and fewer monitoring capabilities, a higher sensitivity may be desired to not miss the need for dose increase. Table 2 demonstrates the performance of the spectrophotometric assay in those scenarios with notable cost to sensitivity or specificity, and using the conventional serum C_{2hr} value as comparator.

DISCUSSION

The major finding of this study was that urine spectrophotometry correlated with a clinically relevant serum rifampin pharmacokinetic target among children with TB providing a potential alternative to the equipment and laboratory capacity necessary for conventional testing. A 24-hour urine collection interval performed best due to the unexpected interindividual variability in the timing of urine rifampin excretion and the minimal rifampin excretion detected in urine for some participants. Nevertheless, this is to our knowledge the largest study of urine rifampin excretion in children with TB from an endemic setting and led to several important observations.

Despite weight-based dosing with fixed dose combination pills, adequate lag-days from treatment initiation to pharmacokinetic testing to establish steady-state kinetics and directly observed medication administration, only two-thirds of the population reached a target rifampin serum AUC_{0-24} associated with successful treatment outcome.[23] While seven (7.9%) participants did not have a calculated serum AUC_{0-24} due to a lack of terminal slope (figure 1), at least six of those had pharmacokinetic profiles highly unlikely to have translated to an AUC_{0-24} above target. This relatively high frequency of suboptimal serum exposure also occurred in an outpatient cohort that was less undernourished and of an older age compared with prior cohorts where serum pharmacokinetics have been measured in this setting.[12] The ongoing frequency of suboptimal serum exposures suggests a more persistent mechanism of malabsorption, such as enteropathogen burden or enteropathy,[13] which may have contributed not only to the frequency of diminished serum C_{max} but also altered timing of C_{max} and subsequent pattern of observed urinary excretion.[25 26] Thus, the urinary rifampin dose percentage as a correlate to serum exposure may perform differently in populations with a more consistent pattern of urinary excretion.

Even with the pattern of urinary rifampin excretion, the ROC analyses of a 0–24 hour or a 0–8 hour collection suggested a clinically actionable test. The 8-hour interval in particular may enable a single-day collection in a clinic or home-based setting. We envision a clinical application where a binary urine spectrophotometric result is reported as 'adequate exposure' or 'inadequate exposure, consider dose increase'. The proportionality of dose increase in response to a result of inadequate exposure will require further study, but similar approaches have been applied in practice for adults with serum testing for rifampin and a single C_{2hr} value.[27] In the more likely scenario of use of the urine colorimetric assay in ill children in TB endemic settings, specificity is limited at the cost of higher sensitivity needed to minimise missing subtarget rifampin exposure (table 2). Such an approach would lead to dose increase in some patients with adequate serum exposures. However, rifampin dose escalation well-beyond current WHO-recommended doses is tolerated,[28] and rifampin doses of 35–60 mg/kg were found safe in children from South Africa in design of a treatment shortening regimen.[29] As shorter course regimens are implemented in diverse paediatric populations removed from their original trials,[30] assuring adequate pharmacokinetic exposure of cornerstone drugs will be critical. As with the case of urine lipoarabinomannan, an assay for TB diagnosis, implementation of a test with only moderate accuracy to guide treatment among high-risk groups, such as hospitalised children, can still have impact in reducing adverse outcomes and mortality.[31]

A potential limitation of the assay for rifampin is that it spectrophotometrically detects all rifamycins including the metabolised deacetyl-rifampin. Separate rifampin metabolites were not quantified from the urine in this study but may ultimately prove of better correlation with serum targets. Further study can determine if this precision is required, or even if spectrophotometry can be substituted by colour reader applications present on mobile phones.[15] The study also tested urine spectrophotometric methods for isoniazid which has a more predictable early serum C_{max}, and for pyrazinamide where metabolites are excreted in greater proportion in the urine compared with rifampin,[6] and will be reported separately. Yet the difference in processing steps of the urine do not currently favour a multiplexed assay for all three common anti-TB drugs. Furthermore, given the age and weight-based approach to rifampin dosing in the paediatric population, we also found it necessary to normalise the urine colorimetric results by dose which may not be needed for other populations such as adults. The current findings may also differ when the assay is applied to populations with more significantly impaired kidney function.

In summary, urine spectrophotometry should not replace serum quantification for rigorous pharmacokinetic studies of rifampin; however, the use of urinary excretion to predict serum concentrations below a threshold that would trigger dose increase is a step forward to personalised dosing for children in TB-endemic settings. Further study should determine urinary excretion and serum concentrations following dose change.

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Correction notice This paper has been amended since it was first published. We have corrected the spelling of author Yingda L Xie.

Contributors SH, TT, CV and EM conceptualised and designed the study. PR, SS, TT and SH verified the source data. SS, PM, EM and BM managed patient recruitment and oversaw the study sites. CAP analysed pharmacokinetic data. PR and RM performed urinary assays. SS, DA, HP, BM, KPdG and DH contributed to data collection. TT, LK, CV, YX and SH interpreted the data. SY, AS, LK and RR performed statistical analysis. SY, AS, LK and RR produced figures. TT, PR and SH wrote the first draft of the manuscript. SH was the author responsible for overall content guarantee. All authors revised and edited the final version of the manuscript. All authors had final responsibility for the decision to submit for publication.

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Patient consent for publication Not applicable.

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