Presentation and outcome of culture-confirmed isoniazid-resistant rifampicin-susceptible tuberculosis in children

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DECLARATION

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ABSTRACT

Setting: Isoniazid-resistant rifampicin-susceptible (HRRS) tuberculosis (TB) is the most prevalent form of drug-resistant TB globally, and may be a risk factor for poor outcomes. HRRS-TB in children has been poorly described.

Objective: To characterize the clinical presentation, treatment, and clinical and microbiological outcomes, and factors associated with poor outcomes among children with culture-confirmed HRRS-TB.

Design: Retrospective hospital-based cohort study.

Results: Of the 72 children included, median age 50.1 months (IQR 21.5-102.5), 42% were male. Forty-four (51%) had a potential source case; only 13 were confirmed HRRS-TB. Twelve of 66 tested (17%) were HIV-infected, and 36 of 60 (60%) with pulmonary TB had severe disease. Seventy had treatment data; median total duration was 11.3 months (IQR 9-12.3); 25 (36%) initiated treatment with a 3-drug intensive phase; 52 (74%) received a fluoroquinolone. Of 63 with known outcome, 55 (88%) had a favourable outcome; 1 died and 3 had treatment failure. Ten had positive follow-up cultures at ≥2 months after starting treatment (17% of all PTB and 27% of those with follow-up culture data); older age (p=0.008), previous TB treatment (p=0.023) and severe PTB (p=0.018) were associated with failure to culture-convert at ≥2 months.

Conclusions: Although overall outcomes were good, prolonged culture positivity and cases of treatment failure emphasize the need for additional attention to clinical management of children with HRRS-TB.

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INTRODUCTION

Children account for 10-15% of the global tuberculosis (TB) disease burden,[1] resulting in an estimated 550,000 to 1,000,000 cases yearly, and an estimated 80,000 deaths in HIV-uninfected children globally in 2013.[2, 3] Substantial resources are being invested in addressing the global problem of multidrug-resistant (MDR)-TB, defined as *Mycobacterium tuberculosis* resistant to isoniazid (INH) and rifampicin (RIF), however limited attention has been given to TB that is INH-resistant but RIF-susceptible (HRRS-TB).

The 2014 Global TB Report of the World Health Organization (WHO) estimated that HRRS-TB represented on average 9.5% of all cases, including 8.1% of new cases and 14.0% of previously treated cases, with substantial regional variation.[2] Data on HRRS-TB prevalence in children is limited. Recent estimates suggest that 12.1% of incident TB cases in children globally were INH-resistant in 2010, with many of these likely being HRRS depending on the setting.[4] In Cape Town, South Africa, ongoing enhanced hospital-based surveillance showed that between 2003-2011, 5.1-7.7% of children <13 years with culture-confirmed TB had HRRS-TB.[5]

With a high early bactericidal activity, INH is responsible for a rapid initial reduction in mycobacterial burden, potentially decreasing patients' infectiousness, hastening clinical improvement,[6, 7] and protecting against resistance development in other drugs in the regimen.[7] Current adult and paediatric guidelines recommend treating HRRS-TB with 6-12 months of RIF, pyrazinamide (PZA), and ethambutol (EMB), with the addition of a fluoroquinolone for extensive disease.[8-12] Evidence for these recommendations is low quality, and no controlled trials have evaluated regimens for HRRS-TB in adults or children.[13, 14] A systematic review and meta-analysis showed variable but substantial rates of treatment failure, relapse, and acquired drug resistance in adults with HRRS-TB .[15] Children with HRRS-TB may be at particular risk for poor treatment outcomes as they may be treated with a standard 3 drug intensive phase containing RIF, INH, and PZA, (RHZ) which is likely inadequate in the context of INH resistance. The clinical presentation, treatment, and outcomes of children with HRRS-TB are poorly described,[16] and more data on this important TB disease entity in children is needed.

The Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), a new molecular diagnostic tool for rapid detection of TB and RIF resistance in clinical specimens,[17] is increasingly used globally for TB diagnosis, including in children.[18 19] The inability to test for INH resistance means the roll-out of Xpert MTB/RIF may have important implications for the detection and management of HRRS-TB in children, since this entity would be under-detected using Xpert MTB/RIF only.

This study aimed to characterize the clinical presentation, treatment and clinical and microbiological outcomes in children with culture-confirmed HRRS-TB; we also investigate factors associated with poor treatment outcomes.

STUDY POPULATION AND METHODS

Study Design

Retrospective hospital-based cohort study.

Setting and patient management

This study was undertaken at three hospitals in the Western Cape Province, South Africa, where the TB notification rate was 954.1 cases per 100,000 population in 2010.[20] Tygerberg Children's Hospital (TCH) is a large provincial referral centre for children, where, as part of ongoing surveillance, a database of all routine culture-confirmed TB in children is maintained. Brooklyn Hospital for Chest Diseases (BHCD) is a specialized TB hospital which cares for children with drug-resistant-TB, TB meningitis (TBM) and children who need social support. Brewelskloof Hospital (BKH) is a regional TB hospital managing the long-term treatment of drug-resistant TB patients, including children.

Mycobacterial cultures were routinely performed at the South Africa National Health Laboratory Service (NHLS) laboratories, according to a standardized protocol using Middlebrook 7H9 broth base (Mycobacteria Growth Indicator Tubes [MGIT]; Becton Dickinson, Sparks, MD, USA). Before August 2008, drug susceptibility testing (DST) was done with the Bactec 460TB System (Becton-Dickinson, Sparks, MD, USA) according to international norms. INH was tested at a concentration of 0.1 µg/ml and

RIF at 2.0 µg/mL, with resistance defined as ≥1% bacterial growth in drug-containing compared to non-drug-containing media. After August 2008, DST was done using the line-probe assay (LPA; GenoType® MTBDR*plus*, Hain Lifescience, Nehren, Germany).

Children with uncomplicated HRRS-TB were generally managed in the community, with 6-9 months of all four drugs RHZE (RIF, INH, PZA, EMB, with number before the abbreviation indicating months) for the full duration of treatment, per national South African guidelines.[10] Children with severe disease or poor response to treatment were typically referred for specialist consultation and prescription of more complex regimens, which in addition to RHZE could include a fluoroquinolone, ethionamide, and/or terizidone. As most children were treated with fixed-dose combination tablets of the first-line TB drugs, INH was most often included in the regimen, usually at a higher dose (15-20mg/kg, up to 400mg). Repeat respiratory cultures were recommended but were variably done based on clinical practice and ability to collect respiratory samples in children in different clinical settings. Local guidelines recommend 6-9 months of INH, RIF, PZA and ethionamide for all cases of TB meningitis (TBM).

Study population

Children were included if they were <13 years of age, routinely diagnosed or managed at any of the three study hospitals, and had a culture from any clinical specimen positive for *M. tuberculosis*, with DST demonstrating INH-resistance and RIF-susceptibility, between January 1, 2006 through December 31, 2011.

Data collection

Potentially eligible patients were identified from the ongoing routine surveillance at the 3 hospitals. For identified patients, medical records were reviewed and relevant data extracted using a standard form. Mantoux tuberculin skin test (TST) results were considered positive if ≥5mm in HIV-infected children and ≥10mm in HIV-uninfected children. Previous treatment was considered receipt of TB medications for disease or preventive therapy. TB was classified according to site of disease as pulmonary, extrapulmonary, or both, and the severity of disease was categorized according to consensus classification of TB disease severity in children.[21] Weight-

for-age Z-scores (WAZ) were calculated using the 1990 British growth reference, as WHO growth references only include children up to 10 years of age.[22] TB treatment outcomes were classified as either “Favourable”, which included cure, probable cure, and treatment completion,[23] or “Unfavourable”.[23] Children with positive cultures at month 5 of treatment were considered to have treatment failure, even if they ultimately completed treatment successfully.

Analysis

Demographic, clinical and treatment characteristics and outcomes were summarized using descriptive statistics. Associations between clinically relevant characteristics with unfavourable outcome and with a positive culture at ≥2 months, were assessed with chi-square or Fisher’s exact tests for categorical variables, and t-test or Wilcoxon rank sum test for continuous variables. Assessed characteristics included age, gender, previous treatment, WAZ, TB type, HIV-infection, disease severity, acid-fast bacilli (AFB) smear positivity (respiratory specimens), INH resistance mutation, and treatment with >1 month of RHZ. Analyses were performed using Stata version 12.0 (Stata Corp, College Station, TX, USA).

Ethics

Approval for the study was provided by the Stellenbosch University Faculty of Medicine and Health Sciences Health Research Ethics Committee (S12/06/184).

RESULTS

Seventy-two children were included; sixty (83%) from TCH, 9 (13%) from BHCD, and 3 (4%) from BKH. Key characteristics at diagnosis are shown in table 1. Seventeen (24%) children had 19 previous TB treatment episodes (INH preventive therapy in four, standard drug-susceptible TB treatment for TB disease in ten, treatment for multidrug-resistant TB in one and unknown in four). Cases treated in the year prior to their HRRS-TB episode are described in table 2.

Seventy of 72 (97%) had treatment data recorded, with 63 (88%) having data on their entire treatment regimen. Regimens were highly variable in content and duration; key treatment characteristics are listed in table 3. Many children started

treatment with a three-drug intensive phase (RHZ), including 10 of 36 (28%) children with severe pulmonary TB (PTB) on their initial chest radiograph. Fifty-two children (74%) received fluoroquinolones with or without additional second-line TB medications; at least a proportion of these were started on MDR-TB treatment empirically because of a known MDR-TB source case or a concern for acquired drug resistance during inadequate treatment for HRRS-TB.

Eleven (15%) children were treated for TBM, four of whom had cerebrospinal fluid (CSF) culture positive for HRRS-TB, six with Stage 2 and four with Stage 3 TBM. All were started on a four-drug regimen of high-dose INH, RIF, PZA, and ethionamide; 10 of 11 had a fluoroquinolone with or without terizidone added to their regimen within two months of treatment initiation. One died (table 2), but all other TBM cases had favourable outcome.

Sixty-three (88%) children had data on final TB treatment clinical outcomes; 55 of 63 (88%) were favourable (table 3). The one death and three treatment failures are described in more detail in table 2. Of the 60 with PTB, 37 had follow-up cultures on respiratory specimens after initiating treatment; the percentage of positive cultures at each month is shown in figure 1. Ten children had a positive follow-up culture at ≥2 months after starting treatment, representing 17% of all those with PTB and 27% of those with a follow-up culture. Three children accounted for the five positive culture results three months or more after starting treatment.

In univariable analysis, no characteristics were associated with unfavourable outcome; older age (p=0.008), documented previous TB treatment (p=0.023) and severe PTB (p=0.018) were associated with positive follow-up cultures at ≥2 months after treatment initiation (table 4).

DISCUSSION

In this large cohort of children with culture-confirmed HRRS-TB, overall clinical outcomes were good. However a number of children had prolonged culture positivity and treatment failure, emphasizing the need for additional attention to clinical management of this subgroup of children with TB. To our knowledge, the largest

report to date is a single case series of 26 children treated for HRRS-TB in New York between 1961 and 1972.[16] One child died, but the remaining patients completed treatment with good outcomes. The relevance of that study to current practice is limited, as the majority were treated without RIF or PZA, and received variable three and four drug combinations of INH, para-aminosalicylic acid (PAS), streptomycin, RIF, EMB, ethionamide and cycloserine.[16] The cohort we report here provides data on the clinical presentation, treatment, and outcomes of a substantial number of children with HRRS-TB, which reflects currently available drug regimens in global settings.

In our study, just over 60% of children had a known potential TB source case, consistent with children with culture-confirmed TB in our context.[5] However, only 24% of the potential source cases had confirmed HRRS-TB. The potential MDR-TB source cases reported in eight patients may reflect infection of the child with HRRS *M.tuberculosis* prior to the source case's acquisition of additional RIF resistance. The majority of the adult source cases had unknown drug-susceptibility. Clinical records however frequently indicated that source cases were retreatment cases or were on an injectable (indicating a retreatment regimen or MDR-TB); this was difficult to quantify, but it is likely that a substantial portion of those source cases with unknown drug-susceptibility were in fact HRRS-TB. The high proportion of source cases with unknown drug-susceptibility may have contributed to delayed initiation of an appropriate treatment regimen in child contacts. In keeping with this concern, 36% of children in our cohort were initially started on a 3-drug intensive phase with RHZ. However, the presence of a known source case was not a risk factor for having an unfavourable outcome or prolonged culture positivity. With the roll-out of Xpert MTB/RIF test as the initial diagnostic test for TB, information regarding the INH resistance of source cases is likely to become less available. This has important implications for the prophylaxis and treatment of children exposed to adults with HRRS-TB.

As would be expected for hospital-based cohorts, children in this study had significant clinical disease with 50% being underweight (WAZ<-2), 60% of those with PTB having severe disease, and 45% of those tested being AFB sputum smear-positive. The proportion with severe PTB in our cohort is comparable to children with

culture-confirmed MDR-TB from the same setting (45.9% with severe chest radiograph findings),[24] although the case definitions differed slightly between the two studies. The high proportion of severe disease in our study may reflect delays in presentation and initiation of appropriate treatment.

Treatment regimens were highly variable and difficult to classify. The long treatment duration was likely related to the observed severity of disease, as well as a conservative approach taken given concern about potentially acquired resistance during periods of inadequate treatment. However, the duration of treatment with a regimen appropriate to HRRS-TB was within the recommended range (6-12 months) for most patients.

A substantial risk of treatment failure and acquired drug resistance in adults with HRRS-TB has been reported in adults receiving standard short course chemotherapy and in those treated with RHZE.[25, 26] Conclusions about the most appropriate regimen or treatment duration for HRRS-TB in children should be drawn cautiously from our study, which was observational and had no control arm. Children treated with a fluoroquinolone may have done equally well with a less intensive regimen such as 6RHZE, and shorter treatment durations may have been as effective. However, given increasing concerns about low RIF exposures in children,[27, 28] and a growing body of evidence regarding fluoroquinolone safety in children,[29, 30] the addition of a fluoroquinolone may be reasonable. It is important to note that children in this cohort treated with the long durations and fluoroquinolone-containing regimens had good outcomes, despite having severe disease.

Microbiological outcomes in children treated for TB have not been well described. A substantial proportion of children in our cohort had positive cultures at one and two months after initiating TB treatment; of 37 patients with at least one follow-up culture, 10 (27%) had positive cultures at ≥2 months. In a cohort of children with MDR-TB in our setting, 9 of 41 (22%) with bacteriological confirmation remained culture-positive at 2 months.[29] The three patients with failed treatment and prolonged culture positivity (table 2) are particularly concerning. Poor adherence cannot be ruled out as a cause of the prolonged culture-positivity, however this delayed treatment response is unusual in cases with drug-susceptible TB in our experience. The child

with acquisition of rifampicin-resistance and progression of disease on inadequate treatment has been described in detail elsewhere,[31] and highlights the potential risk for children with HRRS-TB inadequately treated. Our cohort received highly individualized treatment; in settings where there is limited access to culture and DST and children with HRRS-TB may receive standard short-course regimens, outcomes may not be as good. We suspect the four patients treated with standard drug-susceptible TB treatment in the months prior to their HRRS-TB episode likely had HRRS-TB in their first episode, which then relapsed (table 2); this provides additional evidence of poor treatment response.

HRRS-TBM may be particularly problematic to treat, due to poor penetration of RIF and EMB into CSF, and some adult data suggest a worse outcome compared to drug-susceptible TBM.[32] The favourable outcomes in children with HRRS-TBM in our cohort may be related to the empiric regimen for TBM in use in our setting, which includes higher doses of INH and RIF, and ethionamide, which has excellent CSF penetration. The majority of children with TBM in this cohort also received a fluoroquinolone with or without terizidone, both of which have good CSF penetration. Fluoroquinolones are being investigated for their potential to improve TBM outcomes in adults.[33]

In univariable analysis there were no statistically significant associations with unfavourable treatment outcomes. However, older age, previous treatment, and severe PTB were associated with culture positivity at ≥2 months' treatment. We hypothesize that this is driven primarily by disease severity. Older age was associated with severe PTB, and older children have a well-described higher risk of developing adult-type disease.[34] Previous treatment was also associated with severe TB and may be a marker of failed previous treatments. We explored these associations using multivariable logistic regression; however this analysis was limited by the small sample size, associations between all the included variables, and numeric challenges including zero-cells.

A limitation of the study is the retrospective design. There was limited information on adherence, which may have impacted on clinical and microbiologic outcomes. The lack of a drug-susceptible TB control group prohibited us from concluding whether

outcomes in our cohort significantly differed from children with drug-susceptible TB. There may be limited generalizability of our findings to children treated in the community, where less severe TB would be expected and treatment responses may be more favourable given lower organism burden.

CONCLUSIONS

Although the impact of treatment regimens and treatment outcomes in this cohort should be interpreted with caution, our data has begun to fill an important gap in knowledge on the treatment of HRRS-TB in children. This is the largest study describing treatment and outcomes of HRRS-TB in children. As there are implications for preventive therapy and treatment in children exposed to and diseased due to HRRS-TB, the relevance of knowing the INH resistance pattern of the child and source case needs to be considered with the broad roll-out of Xpert MTB/RIF. Our data raises sufficient concern to warrant further evaluation of the most appropriate treatment of HRRS-TB in children.

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Table 1. Demographic and clinical characteristics of children with culture-confirmed isoniazid-resistant rifampicin-susceptible tuberculosis at diagnosis (n=72)

	n (%)
Median age in months (IQR)	50.1 (21.5 – 102.5)
Male sex	30 (42%)
Identified potential TB source case	
None	28 (39%)
One potential source case	34 (47%)
Two potential source cases	10 (14%)
Potential source case's drug-susceptibility results (n=54)*	
Drug-susceptible (INH-susc, RIF-susc)	1 (2%)
INH-monoresistant (INH-Res, RIF-susc)	13 (24%)
Multidrug-resistant (INH-Res, RIF-Res)	8 (15%)
RIF-monoresistant (INH-susc, RIF-Res)	1 (2%)
Unknown	31 (57%)
Previous TB treatment episode	
None	55 (76%)
One episode	15 (21%)
Two episodes	2 (3%)
Positive Mantoux tuberculin skin test (n = 53 tested)*	43 (81%)
Median weight-for-age Z-score (IQR)	-2.01 (-3.25 to -0.99)
Weight-for-age Z-score <-2	36 (50%)
HIV-infected (n = 66 tested)*	12 (17%)
Severe WHO immunologic stage at TB diagnosis	5 (42%)
On ART before TB diagnosis	3 (25%)
TB type	
PTB only	36 (50%)
Both PTB and EPTB	24 (33%)
EPTB only	12 (17%)
Site of EPTB (n=37, more than one site is possible)*	
Miliary (no TB meningitis)	1 (3%)
TB meningitis	11 (30%)
Abdominal	6 (16%)
Peripheral lymph node disease	11 (30%)
Pleural effusion	3 (8%)
Pericardial effusion	2 (5%)
Bone/joint/spine	8 (22%)
Other	2 (5%)
Severe PTB (n=60 with PTB)*	36 (60%)
AFB sputum smear-positive (n=56 tested)*	25 (45%)
INH resistance mutation (n=38 tested)*	
inhA mutation	26 (68%)
katG mutation	10 (26%)
Both *inhA* and *katG* mutations	2 (5%)

*indicates less than 72 had results

IQR = interquartile range, INH = isoniazid, RIF = rifampicin, susc = susceptible, Res = resistant, WHO = World Health Organization, TB = tuberculosis, ART = antiretroviral therapy, PTB = pulmonary TB, EPTB = extrapulmonary TB, AFB = acid-fast bacilli

Table 2. Description of children with isoniazid-resistant rifampicin-susceptible tuberculosis with recent previous TB treatment (<1 year prior) and those with death/treatment failure

Age, gender	HIV-status	Case description	Outcome
Patients previously receiving any TB treatment 1 year prior to HRRS-TB episode (n=8)			
12 year F	HIV-uninfected	Completed 18 months of treatment for confirmed MDR-PTB just prior to diagnosis of HRRS-TB episode; had new HRRS-TB exposure	Completed MDR-TB treatment
2 year F	HIV-uninfected	Diagnosed with PTB 9 months prior to HRRS-TB episode, interrupted treatment after only 3 months of standard TB treatment	Lost-to-follow-up, drug-susceptible TB treatment
1 year F	HIV-uninfected	Developed HRRS-TB 5 months into course of isoniazid preventive therapy	Failed isoniazid preventive therapy
7 year F	HIV-infected	Completed 6 months of standard TB treatment for drug-susceptible TB 4 months prior to HRRS-TB episode	Completed drug-susceptible TB treatment
4 month F	HIV-uninfected	Developed HRRS-TB meningitis roughly 1 month after starting isoniazid preventive therapy	Failed isoniazid-preventive therapy
11 year F	HIV-uninfected	Completed 6 months of standard drug-susceptible TB treatment 4 months prior to HRRS-TB episode; had poor radiological and clinical response to this treatment	Completed drug-susceptible TB treatment
14 year F	HIV-uninfected	Completed 6 months of standard drug-susceptible TB treatment 2 months prior to HRRS-TB episode; had poor clinical response to treatment	Completed drug-susceptible TB treatment
13 year F	HIV-uninfected	Completed >5 months of standard drug-susceptible TB treatment for extensive PTB just prior to confirmed HRRS-TB episode; was smear positive at month 5 of treatment	Failed drug-susceptible TB treatment
Patients with death or treatment failure from HRRS TB episode (n=4)			
4 year F	HIV-infected	Presented with severe PTB, Stage 2 TBM and severe immunosuppression (CD4 81, 19.6%); promptly started RHZ-ethionamide, but died in hospital 5 days after admission.	Death
12 year M	HIV-infected	After 5 months of community-based treatment with RHZE for confirmed HRRS-TB, remained sputum culture positive so started on empiric MDR-TB treatment, but DST continued to show HRRS-TB; treated successfully with a fluoroquinolone and other secondline.	Treatment failure
20 month M	HIV-uninfected	Treated with RHZ for extensive PTB and despite a poor treatment response, was switched to a 2-drug continuation phase (RH) after 2 months. Had worsening lung disease with persistent culture positivity; eventually was diagnosed with TBM and confirmed MDR-TB.	Treatment failure, acquired rifampicin resistance
6 year F	HIV-infected	Treated with RHZ at her community clinic for extensive PTB, but after confirmation of HRRS-TB and persistent culture positivity a fluoroquinolone and other secondline TB meds were added; she improved slowly and ultimately completed 20 months of treatment.	Treatment failure

M = male, F = female, TB = tuberculosis, HRRS = isoniazid-resistant rifampicin susceptible, PTB = pulmonary TB, R=rifampicin, H=isoniazid, Z = pyrazinamide, E = ethambutol, TBM = TB meningitis, MDR = multidrug-resistant

Table 3. Treatment regimens and clinical outcomes in children with culture-confirmed isoniazid-resistant rifampicin-susceptible tuberculosis (n = 70)

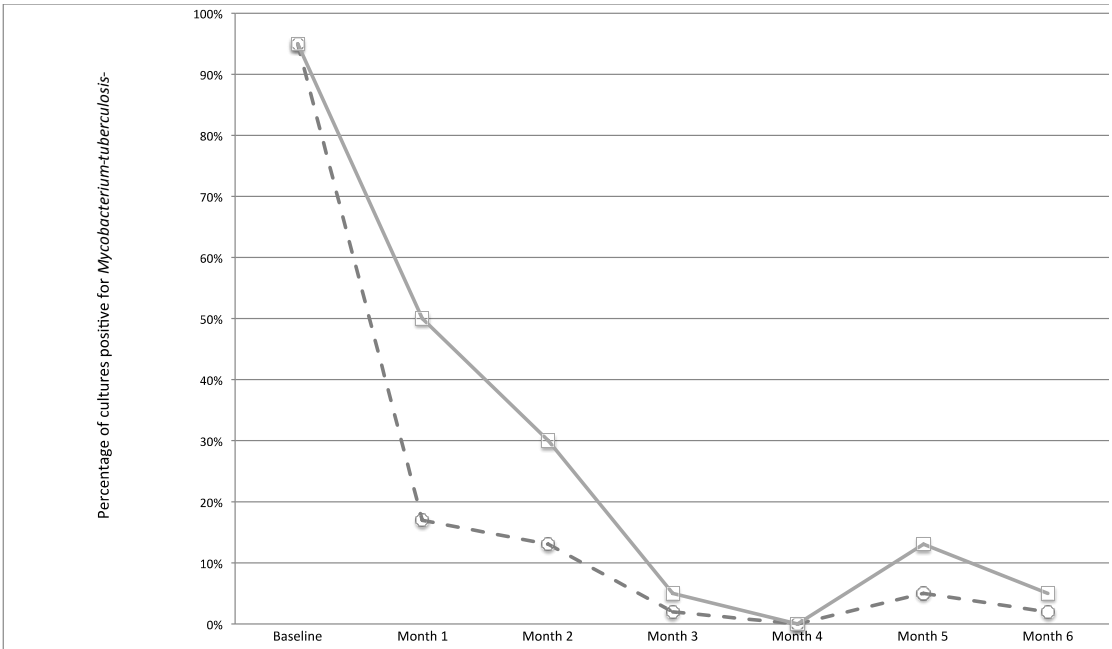
	n (%)
Treatment characteristics (n=70 with some data on treatment)	
Median total duration of treatment in months [(QR) [n=62]	11.3 (9 – 12.3)
Median duration of HRRS treatment in months (IQR) [n=58]	10.5 (8.7 – 12.2)
Initiated treatment with RHZ	25 (36%)
Treated with RHZ ≥ 1month	21 (30%)
Treated with RH in continuation phase (n=63)	6 (10%)
Treated with ≥6HRZE	6 (9%)
Treated with a fluoroquinolone, with or without other 2nd-lines	52 (74%)
Clinical outcomes (n = 63; 9 with unknown outcome)	
Favourable	55 (88%)
Cure	22 (31%)
Probable cure	7 (10%)
Treatment completed	26 (36%)
Unfavorable	8 (12%)
Lost-to-follow-up	3 (4%)
Death	1 (1%)
Treatment failure	3 (4%)
Transferred out	1 (1%)

IQR = interquartile range, HRRS = isoniazid-resistant rifampicin susceptible, RHZ = rifampicin-isoniazid-pyrazinamide, E = ethambutol

Table 4. Characteristics associated with unfavourable treatment outcome and prolonged culture positivity among children with culture-confirmed isoniazid-resistant rifampicin-susceptible tuberculosis

	Clinical outcomes				Microbiological outcomes			
	n	Favourable Outcome (n=55)	Unfavourable Outcome (n=8)	p-value	n	Follow-up culture not positive at ≥2 months (n=27)	Follow-up culture positive at ≥2 months (n=10)	p-value
Median age in months (IQR)	63	49.7 (24.9-91.3)	38.8 (20.7-66.5)	p=0.53	37	46.3 (18.9-107)	131.2 (82.1-146)	p=0.008
Male sex	63	22 (40%)	4 (50%)	p=0.43	37	11 (41%)	3 (30%)	p=0.71
Known previous treatment	63	12 (22%)	3 (38%)	p=0.29	37	7 (26%)	7 (70%)	p=0.023
WAZ <-2	63	26 (55%)	6 (75%)	p=0.26	37	15 (56%)	8 (80%)	p=0.26
Any EPTB	63	31 (57%)	4 (50%)	p=0.51	37	12 (24%)	2 (20%)	p=0.26
HIV-infected	58	9 (18%)	3 (43%)	p=0.15	36	3 (12%)	3 (30%)	p=0.32
Identified potential source case	63	31 (56%)	7 (88%)	p=0.13	37	16 (59%)	7 (70%)	p=0.71
Severe PTB	53	26 (58%)	5 (71%)	p=0.38	37	16 (59%)	10 (100%)	p=0.018
Sputum smear positive	48	18 (43%)	3 (43%)	p=1.00	34	10 (42%)	7 (70%)	p=0.26
Any *katG* gene mutation (vs *inhA* only)	38	9 (28%)	3 (50%)	p=0.36	21	3 (19%)	2 (40%)	p=0.55
RHZ>1m in intensive phase	63	16 (29%)	3 (38%)	p=0.46	37	3 (11%)	3 (30%)	p=0.31
Received FQN-containing regimen	63	41 (75%)	6 (75%)	p=1.00	37	24 (89%)	7 (70%)	p=0.31

IQR = interquartile range, WAZ = weight-for-age z-score, EPTB = extrapulmonary tuberculosis, PTB = pulmonary tuberculosis, RHZ = rifampicin-isoniazid-pyrazinamide, FQN = fluoroquinolone



Figure'1.'Posi- ve'respiratory'cultures'for'*Mycobacterium-tuberculosis*-as'percentages'of'all'pulmonary' tuberculosis'(PTB)'cases'and'of'follow?up'(F/U)'respiratory'cultures'among'children'with'culture'confirmed' isoniazid?resistant'rifampicin?suscep- ble'TB'