Title: Treatment outcomes and safety in children with rifampicin-resistant tuberculosis: a prospective cohort study

Authors and affiliations: Elisa Lopez-Varela (1,2), Anthony J. Garcia-Prats (1,3), James A. Seddon (1,4), Heather R. Draper (1), Jana Winckler (1), Louvina van der Laan (1), Megan Palmer (1), W. Andre Burger (5), H. Simon Schaaf* (1), Anneke C. Hesseling* (1)

*Contributed equally to this manuscript

1. Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

2. ISGlobal, Barcelona Centre for International Health Research (CRESIB), Hospital Clínic - Universidad de Barcelona, Barcelona, Spain

3. Department of Paediatrics, University of Wisconsin School of Medicine & Public Health, Madison, Wisconsin, USA

4. Department of Infectious Diseases, Imperial College London, London, United Kingdom

5. Brewelskloof Hospital, Worcester, South Africa

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§ Corresponding author:

Elisa López-Varela, MD, PhD
ISGlobal, Hospital Clínic - Universitat de Barcelona, C/ Rosselló, 132, 5th 2nd. 08036. Barcelona, Spain.

Phone: (+34) 627136952.

Email: elisa.lopez@isglobal.com

ABSTRACT

Background. The treatment of rifampicin-resistant (RR) tuberculosis (TB) in children is evolving rapidly. As newer regimens are introduced into routine care, it is vital to compare their outcome and safety to well-characterized clinical cohorts treated with historical regimens.

Methods. A prospective observational cohort of children on routine RR-TB treatment, enrolled from 2011 to 2015 in Cape Town, South Africa. Children were followed for safety, treatment response and outcome.

Results. Of 136 children included, 27(19.9%) were living with HIV and 48 (37.8%) had severe TB. The median time-to-culture conversion in children with bacteriological confirmation (n=44), was 28.5 days (IQR 14.5-45). Overall, 118/129 (91.5%) had favourable TB treatment outcomes. Of 106 (77.9%) children who received an injectable drug, 9 (8.5%) developed hearing loss and 7/136 (5.1%) developed other grade 3 or higher adverse events likely related to treatment.

Conclusions. In this cohort with a substantial proportion of children with severe manifestations of TB and with HIV, TB treatment outcomes were excellent. Apart from hearing loss, few children developed severe adverse events related to treatment. This study provides robust reference data for future evaluation of shorter, injectable-sparing regimens.

Key words: multidrug-resistant, paediatric, mycobacteria

INTRODUCTION

Approximately 30,000 children develop rifampicin–resistant (RR) tuberculosis (TB) globally each year.[1,2] RR-TB includes rifampicin-mono-resistant (RMR), multidrug-resistant (MDR)-TB (i.e., *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin), and cases where resistance to rifampicin has been established but isoniazid susceptibility has not been tested. RR-TB is challenging to confirm and is complex to treat in children, yet children on treatment typically have excellent outcomes, considerably better than in adults.[3]

Until recently, RR-TB treatment regimens remained long (up to 18-20 months), toxic (resulting in hearing loss in up to 25% of children on injectable drugs),[4] poorly tolerated, and frequently required long-term hospitalization.[5] Regimens have changed dramatically recently with the addition of new and repurposed drugs, the introduction of shorter regimens, and a move towards all-oral MDR-TB treatment regimens and community-based treatment.[6] However, the implementation and scale-up of these regimens in most high-burden settings is slow, and critical evidence gaps remain for the use of bedaquiline and delamanid in children under 6 and 3 years, respectively. Efficacy trials for drug-resistant (DR)-TB regimens are unlikely to be implemented in children given that efficacy can reasonably be extrapolated from adults to children for most forms of TB. Novel and repurposed TB drugs will therefore be evaluated mainly for their dosing, pharmacokinetics and safety, and novel regimens in children will be compared to data from historical paediatric cohorts.[7] Thus, rigorously characterized cohorts prior to the introduction of new, injectable-sparing regimens provide important reference data on RR-TB treatment and toxicity in children.

Microbiological treatment response during therapy is a useful measure of response to antituberculosis treatment.[8] Monitoring treatment response in children allows for earlier identification of failing therapy due to additional undetected resistance at baseline, co-morbidities, poor adherence or acquisition of resistance.[9] Microbiological response is also a useful surrogate marker of treatment efficacy in TB trials.[10] Given the paucibacillary nature of most TB in children and challenges in sampling, few studies have systematically evaluated the microbiological response to therapy in children with RR-TB. The aim of this study was to describe the safety, microbiological

response and overall treatment outcome in children routinely treated for RR-TB prior to the use of injectable-sparing regimens in children.

METHODS

Study design

We conducted a prospective observational cohort study in children routinely treated for RR-TB in Cape Town, South Africa. Data on the pharmacokinetics of TB drugs from this cohort was previously reported.[11–15] From November 2011 to October 2015, we enrolled children under 15 years of age, who had been on RR-TB treatment for at least 2 weeks, from Tygerberg Hospital (a regional referral hospital for pediatric services), Brooklyn Chest Hospital (a provincial specialist TB hospital) and Brewelskloof Hospital (a regional specialist TB hospital). Children below 5 kg or with a haemoglobin value under 8 g/dL were excluded or deferred, given requirements for intensive pharmacokinetic sampling. In this analysis, we excluded children who were initially started on RR-TB treatment but who were subsequently confirmed to have drug-susceptible (DS)-TB, and children who were on TB treatment for 8 weeks or longer.

Clinical Care

Treatment for RR-TB was provided according to routine guidance at the time and based on the drug susceptibility test (DST) pattern of the child's isolate or the isolate of their most likely source case identified. Treatment included a minimum of four confirmed or likely effective drugs, generally given for 12-18 months, provided as directly observed therapy at community-based TB clinics or in hospital (See supplementary data).

Microbiology

Children had specimens sent for mycobacterial culture at diagnosis and monthly (respiratory specimens) thereafter, until after culture-conversion, with at least two consecutive negative cultures required to consider culture-negativity. Time to culture

positivity (TTP) was defined as the number of days between sample inoculation and detection of mycobacterial growth. Time to culture conversion was defined as the time from start of RR-TB treatment to the sampling of the first negative culture, if no further positive cultures.

Study measures

Socio-demographic and clinical data, including anthropometrics (weight, height, and mid-upper arm circumference) were collected at enrolment. Weight-for-age, height-for-age and weight-for-height z-scores were calculated based on the British 1990 growth reference centiles.[16] Malnutrition was defined as weight-for-age z-score of < -2. Chest radiographs (CR) at baseline were systematically reviewed by an expert reader using a standard approach.[17] The severity of TB disease was classified based on standard criteria considering clinical, bacteriological, and imaging data.[18]

Children had monthly visits for the first 6 months and two-monthly thereafter, or as clinically indicated, until treatment completion, including anthropometric, symptom and clinical evaluation, CR and laboratory monitoring (full blood count, potassium, creatinine, alanine aminotransferase [ALT], total bilirubin, thyroid function) and microbiology. Adverse events (AEs) were graded according to the Division of AIDS (DAIDS) criteria.[19] In case of hypothyroidism as drug AE, levothyroxine was added to the end of treatment with the responsible drug(s). Hepatotoxic drugs were discontinued or interrupted if ALT was more or equal to Grade 3 AE.

Hearing in children who received injectable agents was assessed at baseline and monthly, using pure-tone audiometry or oto-acoustic emissions, depending on the child's age. The severity of hearing loss was classified according to the International Society of Pediatric Oncology (SIOP), Boston ototoxicity scale, highly sensitive to capture high-frequency loss, specifically developed for reporting paediatric hearing outcomes in research.[20] If hearing loss was found, the injectable agent was discontinued, and if clinically indicated, replaced with para-aminosalicylic acid if response to treatment was good.

RR-TB treatment outcomes were classified as cure, probable cure, treatment completed, treatment failure, death, lost to follow-up and transferred out.[21]

Statistical analysis

Baseline characteristics were presented with descriptive analysis. Bivariate logistic regressions were performed to evaluate factors potentially associated with failure to culture convert (binary outcome) at one month in the subset of children with pulmonary TB who were culture-confirmed from a respiratory sample at baseline, using logistic regression. Variables with significance levels ≤0.20 in the univariate analysis were included in multivariate logistic regression models. Odds ratio (OR) and 95% confidence intervals (CI) were calculated.

AEs were considered related if they were possibly, probably or definitely antituberculosis drug related. Incidence rates for AEs were calculated per person-time of observation. Person-time was calculated from baseline assessment until treatment completion, or the last available study visit for patients who did not complete study follow-up.

Data was analysed with STATA V.15 (StataCorp Inc., USA); missing data were excluded from analysis. Further methods are described in the online supplement.

Ethical considerations

Written informed consent was provided by the parent or legal guardian, and written informed assent was given by participants 7 years and older. This study was approved by the Human Research Ethics Committee, Stellenbosch University (N11/03/059) and provincial department of health and relevant hospitals.

RESULTS

Clinical presentation

Of the 174 children with RR-TB overall, 136 were included in this analysis; 129 had TB treatment outcomes assessed (**Figure 1**). The median age at the time of treatment initiation was 3.3 years (interquartile range [IQR] 1.5- 5.6) (**Table 1 and supplemental Table S1**). Of the 136 children, 103 (75.7%) had pulmonary TB (PTB) and 48 (37.8%) had severe forms of TB. Twenty-seven (19.9%) children were living with HIV of whom 15 (55.6%) were on antiretroviral therapy (ART) prior to initiation of RR-TB treatment. The most frequent basis for TB treatment initiation was clinical manifestations of TB disease combined with exposure to a RR-TB source case (n=75, 55.1%) followed by bacteriologically confirmed RR-TB with clinical manifestations (n=48, 35.3%). Of the 132 (97.1%) children with CR at enrolment, the most common features were lymph node enlargement (n=67, 50.8%), alveolar consolidation (n=60, 45.5%), and interstitial infiltrates (n=26, 19.7%) with cavities in 14 (10.6%). In total, 85/132 (64.4%) had CR typical of intrathoracic TB (**Supplemental table S2**).

Bacteriology

TB was confirmed in 62 (45.6%) children; 61 had positive cultures with a median TTP of 22 days (IQR 14.0-28.0) and one child was diagnosed based on positive Xpert MTB/RIF only **(Table 2)**. Eighteen of 58 (31.0%) children with smear microscopy for acid-fast bacilli (AFB) available were sputum smear positive. DST was completed in 59/61 (96.7) children's isolates; 39 (66.1%) had MDR-TB, 10 (16.9%) RMR, and 10 (16.9%) had MDR-TB with additional resistance.

Culture conversion data (respiratory specimens) was evaluable in 44 children: 26.8% (11/41) and 7.5% (3/40) failed to convert their culture at one and two months, respectively. The median time to culture conversion was 28.5 days (IQR 14.5-45). In univariate analysis, smear positivity and cavities on CR were associated with failure to culture convert at one month. No factors remained significant in multivariable analysis (**Table 3).**

Treatment and safety

Figure 2 shows the drugs used as part of the RR-TB treatment regimens. The median treatment duration was 15.5 months (IQR: 13.5-18.3), while 106 (77.9%) received some treatment with an injectable drug, for a median of 5.98 months (IQR: 4.04-5.98). The commonest reported AEs were gastrointestinal (nausea and/or vomiting, anorexia), skin related, and hypothyroidism (Table 4). Nine children treated with injectables (8.5%) developed hearing loss, of which 4 were SIOP grade 1, and 5 were SIOP grade 3 or 4. An additional 31/136 (22.8%) children experienced grade 3 or higher AEs, of which 7/136 (5.1%) were at least possibly related to TB treatment. Nineteen children had a total of 20 serious AEs, with two at least possibly related to TB medication - both grade 4 ALT elevations.

TB treatment outcome (Table 5)

At the end of TB treatment, 118/129 (91.5%) children had a favourable outcome; 24 were cured, 90 were probably cured and 4 successfully completed treatment. There were no deaths. At TB treatment completion, the proportion of children who were underweight had halved, from 21.6% to 10.1%.

DISCUSSION

We describe the clinical presentation, disease spectrum, treatment safety and outcomes in a well-characterized cohort of children with RR-TB, prior to the more widespread uptake of repurposed (linezolid, clofazimine) and novel drugs (bedaquiline, delamanid). We also characterize the microbiological treatment response in children with confirmed pulmonary RR-TB. We found that, despite the high proportion of children with severe TB and bacteriological confirmation, and minimal access to new or repurposed drugs, TB treatment outcomes were excellent. Apart from the concerning occurrence of hearing loss, typically irreversible, few clinically significant AEs related to TB medications were reported. Most children with confirmed pulmonary TB had culture conversion by 1 month, but those with smear-positive respiratory samples or cavities at baseline were at risk of delayed culture conversion.

Children in this cohort were largely treated with a regimen consisting of a backbone of ethambutol, pyrazinamide, a fluoroquinolone (mostly levofloxacin or moxifloxacin,

depending on age), terizidone, ethionamide, and/or high-dose isoniazid, with a second-line injectable drug. The median overall treatment duration was 15 months. Treatment success remained very high. This is even better than previously reported individual patient (IPD) data meta-analyses on global paediatric RR-TB cohorts of more than 900 children treated, where 78% had a favourable treatment outcome,[3] and substantially higher than the 60% reported in adults prior to the introduction of new drugs,[22] likely reflecting differences in paediatric vs. adult disease spectrum. In the IPD, nearly 40% of children were living with HIV; ART access was not uniform, and HIV status and severe TB predicted mortality. In the present study, where ART availability was good, almost half of the children living with HIV were not on ART at the time of RR-TB treatment initiation, highlighting the importance of HIV testing with early ART initiation (or re-initiation in the case of treatment interruption) in children investigated for RR-TB.

Documentation of toxicity for RR-TB regimens is typically poor in programmatic settings.[23] Few published cohorts have systematically evaluated and prospectively reported AEs, and the limited paediatric studies have not used standard grading and reporting systems.[24,25] A previous study in Cape Town systematically reported toxicity, but used a different grading, making direct comparison of results challenging.[24] However, other than ototoxicity, more severe AEs were also relatively uncommon in that study.[4] Ascribing causality to a single drug or drug combination for RR-TB is challenging given the complexity of RR-TB regimens, concomitant treatment and comorbidities. Our finding of few grade 3 or higher AEs, apart from hearing loss, is reassuring and provides a benchmark to compare the safety of new regimens. Less serious AEs, however, were frequently reported. Gastrointestinal and skin problems could substantially impact on regimens' tolerability and hypothyroidism and asymptomatic transaminitis were also commonly observed. Ototoxicity, a serious and irreversible AE, was seen in 8.5% of children, most being mild cases. There is now general recognition that injectables should only be used in children with RR-TB if there are no other treatment options, and with careful monitoring of hearing.

A unique aspect of this study was the evaluation of microbiological treatment response. Because children are typically less likely to have bacteriologically confirmed disease than adults, culture results from serial respiratory samples are seldom reported. In adults with DS-TB, culture-conversion by 2 months is regarded as a

reasonable surrogate marker of ultimate treatment outcome.[26] We found that higher bacillary load was associated with longer time to culture conversion, in line with previous studies.[27] This group of children, typically with adult-type disease, may merit more aggressive treatment strategies.

The treatment landscape for RR-TB is changing rapidly. However, while guidelines for the treatment of adult RR-TB treatment are increasingly informed by data from trials, paediatric treatment guidelines are extrapolated from adult data with some evidence from observational paediatric clinical cohorts.[28] Most of the ongoing RR-TB clinical trials evaluating new and shorter regimens exclude young children.[6] Since the efficacy of new regimens will likely not be evaluated in children in controlled trials, there is a need for rigorous high-quality data in children receiving older regimens as a reference.[29] The high overall treatment success and relatively low overall toxicity in this cohort sets a high bar for new, short RR-TB treatment regimens in children. Regimens with higher toxicity or reduced efficacy will unlikely be attractive; however, other factors may be important including the duration of treatment, models of care, regimen tolerability, frequency of follow-up visits, pill burden and stigmatizing treatment effects. The skin pigmenting effect of clofazimine is particularly challenging, especially for adolescents. For health services, the costs of treatment and of monitoring of safety, the costs of managing AEs and the need for hospitalization need to be considered.

Our study has important limitations. Without post-treatment follow-up we did not evaluate TB recurrence. AEs were evaluated at each follow-up but reporting of drug AEs can be challenging in young children. The international scale used for ototoxicity was different from previously used classification and adequate and interpretable audiological assessments could only be completed in 86,8% of cases. However, the scale is sensitive and specific for paediatric amikacin toxicity. The recording of drug use, duration, dose and how drugs were combined was complex, as drugs were sometimes changed (temporarily paused, stopped or substituted due to additional information about resistance patterns (second-line drug resistance was done by phenotypic DST), adaptations due to treatment response, and toxicity (e.g., with raised ALT – hepatotoxic drugs paused, and with hearing loss, amikacin was

stopped or substituted with PAS). We therefore were unable to evaluate the contribution of any individual drug, combination of drugs, drug duration or dosages on AEs, culture conversion or treatment outcome. Finally, there were some missing microbiological data at follow-up.

Despite these limitations, this was a large cohort of relatively young children routinely treated for RR-TB, evaluated rigorously, and followed systematically and with high quality radiological and microbiological data. This cohort, which shows excellent treatment outcomes, predates the introduction of new drugs for RR-TB and provides a useful reference standard for the evaluation of safety and treatment outcome of novel regimens in children.

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Conflicts of interest

None declared

Authors' contributions:

Conceptualization: ELV, ACH, AJGP, JAS, HSS; Data curation: AJGP, JW, LVDL, MP, AB, HSS; Data analysis: HRD, ELV; Supervision: HSS, ACH; Writing – original draft: ELV; Writing – review & editing: all

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TABLES AND FIGURES

Table 1. Demographic and clinical characteristics of children on treatment for rifampicin-resistant tuberculosis (N = 136)

Days on TB treatment at enrolment (IQR)	21.5 (12.0-37.5)
Median age (years) at TB treatment initiation (IQR)	3.3 (1.5-5.6)
Male gender (%)	68 (50.0)
Previous TB episode or treatment (%) [n=135]	34 (25.2)
Known TB source case (%) [n=135]	99 (73.3)
Basis on which RR-TB treatment initiated [n=131]	
Bacteriological confirmation (%)	48 (36.6)
RR-TB exposure (%)	75 (57.3)
Failing first-line TB treatment (%)	7 (5.3)
Failing DR-TB treatment (%)	1 (0.8)
TB disease type	
PTB only (%)	103 (75.7)
EPTB only (%)	12 (8.8)
PTB and EPTB (%)	21 (15.4)
Severe TB disease (%) [N=127]	48 (37.8)
Weight-for-age Z-score <-2.0 (%) [n=134]	29 (21.6)
Height-for-age Z-score <-2.0 (%) [n=133]	39 (29.3)
MUAC <12.5cm (%) [n=97]	7 (7.2)
HIV-positive (%)	27 (19.9)
HIV treatment history [n=27]	
Never on ART	1(3.7)
Receiving ART for ≥1 month at start RR-TB treatment	11 (40.7)
Receiving ART for <1 month at start RR-TB treatment	4 (14.8)
Initiated ART after starting RR-TB treatment	11 (40.7)

Abbreviations: IQR, interquartile range; TB, tuberculosis; PTB, pulmonary TB; EPTB, extrapulmonary TB; RR, rifampicin-resistant; MUAC, mid upper-arm circumference; ART, antiretroviral therapy

Table 2: Characteristics of children with bacteriologically confirmed, culture-positive RR-TB at diagnosis; n=61[#]

Characteristic	**Number (%) ***
Spectrum of disease	
PTB only	37 (35.9)
EPTB only	9 (75.0)
PTB and EPTB	15 (71.4)
Median TTP at baseline (IQR) [n=55]	22.0 (16.0, 28.0)
DST pattern	[n=59]
Rifampicin mono-resistant	10 (16.9)
MDR-TB	39 (66.1)
MDR-TB plus resistance to ofloxacin	5 (8.5)
MDR-TB plus resistance to amikacin	2 (3.4)
MDR-TB plus resistance to ofloxacin and amikacin	3 (5.1)

* Unless indicated otherwise

[#] A total of 62 children had confirmed TB, 61 on culture and an additional case confirmed through Xpert.

Abbreviations: DST, drug susceptibility testing; IQR, interquartile range; PTB, pulmonary TB; EPTB, extrapulmonary TB; MDR-TB, multidrug-resistant TB; TTP, time to culture positivity

422 **Table 3. Predictors of culture conversion at 1 months**

	Failure to culture convert by 1 month (out of N=41 cases)						
		Univariable analysis			Multivariable		
	Proportion of failure (n/N)	OR	95% CI	*P value*	aOR	95% CI	*P value*
Total	11/41						
Age at TB treatment initiation							
<5 years	3/21	Ref					
≥5 years	8/20	4.00	0.88-18.19	0.073	1.19	0.15-9.52	0.869
Gender							
Male	6/19	Ref					
Female	5/22	0.64	0.16-2.55	0.525			
HIV status							
negative	7/26	Ref					
positive	4/15	0.99	0.23-4.15	0.986			
Previous TB episode or treatment							
No	8/30	Ref					
Yes	3/11	1.03	0.22-4.89	0.969			
TB contact							
No	5/15	Ref					
Yes	6/26	0.60	0.15-2.45	0.477			
Weight-for-age-Z-score <-2							
No	7/24	Ref					
Yes	4/17	0.75	0.18- 3.17	0.689			
Height-for-age-Z-score <-2							
No	7/25	Ref					
Yes	4/16	0.86	0.21- -3.58	0.833			
TB disease type							
Pulmonary only	10/31	Ref					
Pulmonary + EPTB	1/10	0.48	0.16- 1.45	0.195	0.31	0.03- 3.34	0.331
TB disease severity							
No	3/14	Ref					
Yes	8/27	1.54	0.34-7.06	0.576			
Time to positivity at baseline (1 week)		0.62	0.34-1.13	0.117	0.88	0.41-1.88	0.739
Cavities on CR							
No	5/29	Ref					
Yes	6/12	4.80	1.09-21.22	0.039	1.73	0.22-13.42	0.599
AFB smear-positive at baseline							
No	4/25	Ref					

Yes	7/15	4.59	1.05-20.05	0.043	2.31	0.28-18.96	0.434

Abbreviations: AFB, acid-fast bacilli; aOR, adjusted odds ratio; CI, confidence interval; CR, chest radiograph; TB, tuberculosis; EPTB, extrapulmonary TB; OR, odds ratio

Table 4: Adverse events in children treated for rifampicin-resistant tuberculosis (N=136)

Adverse Event	Adverse event by grade							Adverse effects possibly, probably, or definitely attributed to RR-TB treatment by grade						
	# of patients with event	Grade 1	Grade 2	Grade 3	Grade 4	total # of events	Event Rate (per 100 person-years)	# of patients with event	Grade 1	Grade 2	Grade 3	Grade 4	total # of events	Event Rate (per 100 person-years)
Arthralgia	11	12	1	0	0	13	7.70	6	6	1	0	0	7	4.15
Arthritis	1	0	1	0	0	1	0.59	1	0	1	0	0	1	0.59
Pain other than traumatic injury	33	36	4	0	0	40	23.70	6	6	0	0	0	6	3.56
Headache	19	21	4	2	0	27	16.00	10	8	1	1	0	10	5.93
Neurosensory alteration	3	3	0	0	0	3	1.78	1	1	0	0	0	1	0.59
Visual changes (from baseline)	5	4	1	0	0	5	2.96	3	3	0	0	0	3	1.78
Neuromuscular weakness	6	5	1	2	1	9	5.33	0	0	0	0	0	0	---
Insomnia	8	0	8	0	0	8	4.74	6	0	6	0	0	6	3.56
Behavioural disturbance	1	0	1	0	0	1	0.59	1	0	1	0	0	1	0.59
Fatigue/malaise	8	6	3	1	0	10	5.93	3	2	1	0	0	3	1.78
Nausea	41	60	3	0	0	63	37.33	39	59	2	0	0	61	36.15
Vomiting	62	82	4	0	0	86	50.96	54	69	3	0	0	72	42.67
Anorexia	27	23	7	1	0	31	18.37	15	10	5	0	0	15	8.89
Vertigo	6	9	0	0	0	9	5.33	6	8	0	0	0	8	4.74
Ataxia	1	1	0	0	0	1	0.59	0	0	0	0	0	0	---
Gynecomastia	2	2	0	0	0	2	1.19	2	2	0	0	0	2	1.19
Pruritus	42	56	3	0	0	59	34.96	18	20	3	0	0	23	13.63

Skin hyperpigmentation	6	6	0	0	0	6	3.56	5	5	0	0	0	5	2.96
Skin hypopigmentation	1	1	0	0	0	1	0.59	1	1	0	0	0	1	0.59
Malar rash	3	3	0	0	0	3	1.78	3	3	0	0	0	3	1.78
Rash	37	40	12	0	0	52	30.81	14	12	5	0	0	17	10.07
Hair loss	1	1	0	0	0	1	0.59	1	1	0	0	0	1	0.59
Laboratory events														
Haemoglobin	59	44	17	15	1	77	45.63	8	6	1	3	0	10	5.93
WBC, decreased	1	0	1	0	0	1	0.59	0	0	0	0	0	0	---
Platelets, decreased	1	0	1	0	0	1	0.59	0	0	0	0	0	0	---
Hypothyroidism	82	21	61	0	0	82	48.59	81	21	60	0	0	81	48.00
Hyperthyroidism	2	1	1	0	0	1	0.59	2	1	1	0	0	2	1.19
Bilirubin	1	1	1	0	0	2	1.19	1	0	1	0	0	1	0.59
ALT	44	34	12	5	7	58	34.37	32	28	11	2	2	43	25.48
Creatinine	28	21	10	0	0	31	18.37	11	6	6	0	0	12	7.11
Potassium, serum high	13	10	3	0	0	13	7.70	2	0	2	0	0	2	1.19
Potassium, serum low	2	2	0	0	0	2	1.19	1	1	0	0	0	1	0.59

Abbreviations: ALT, alanine aminotransferase; WBC, white blood cells,
136 patients followed for a median time of 14.9 months (IQR: 12.5 - 17.9 months); Total person years = 168.75
An additional 9 children developed hearing loss, of which 4 were SIOP grade 1, 3 were SIOP grade 3 and 2 were SIOP grade 4.
Nighty-two of 106 (86,8%) children on injectables had adequate and interpretable hearing assessments up to 6 months after stopping their injectable.

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Table 5: Treatment outcomes in children with rifampicin-resistant tuberculosis (N=129) *

Classification of RR-TB treatment outcome (%)	
Cured (%)	24 (18.6)
Probable Cure (%)	90 (69.8)
Treatment Completed (%)	4 (3.1)
Treatment Interrupted (%)	4 (3.1)
Lost-to-Follow-up (%)	7 (5.4)
Anthropometry	
Weight-for-age-Z-score <-2.0 (%)	13 (10.1)
Height-for-age-Z-score <-2.0 (%) [n=127]	25 (19.7)
Culture conversion (N=44)	
Median time culture conversion in days (IQR)	28.5 (14.5, 45)
Cumulative proportion of culture conversion	
30 days	30 /41 (73.2)
60 days	37 /40 (92.5)

428 * Of the 136 children 5 children withdrew from study and 2 transferred care

429 Abbreviations: RR-TB, rifampicin-resistant tuberculosis

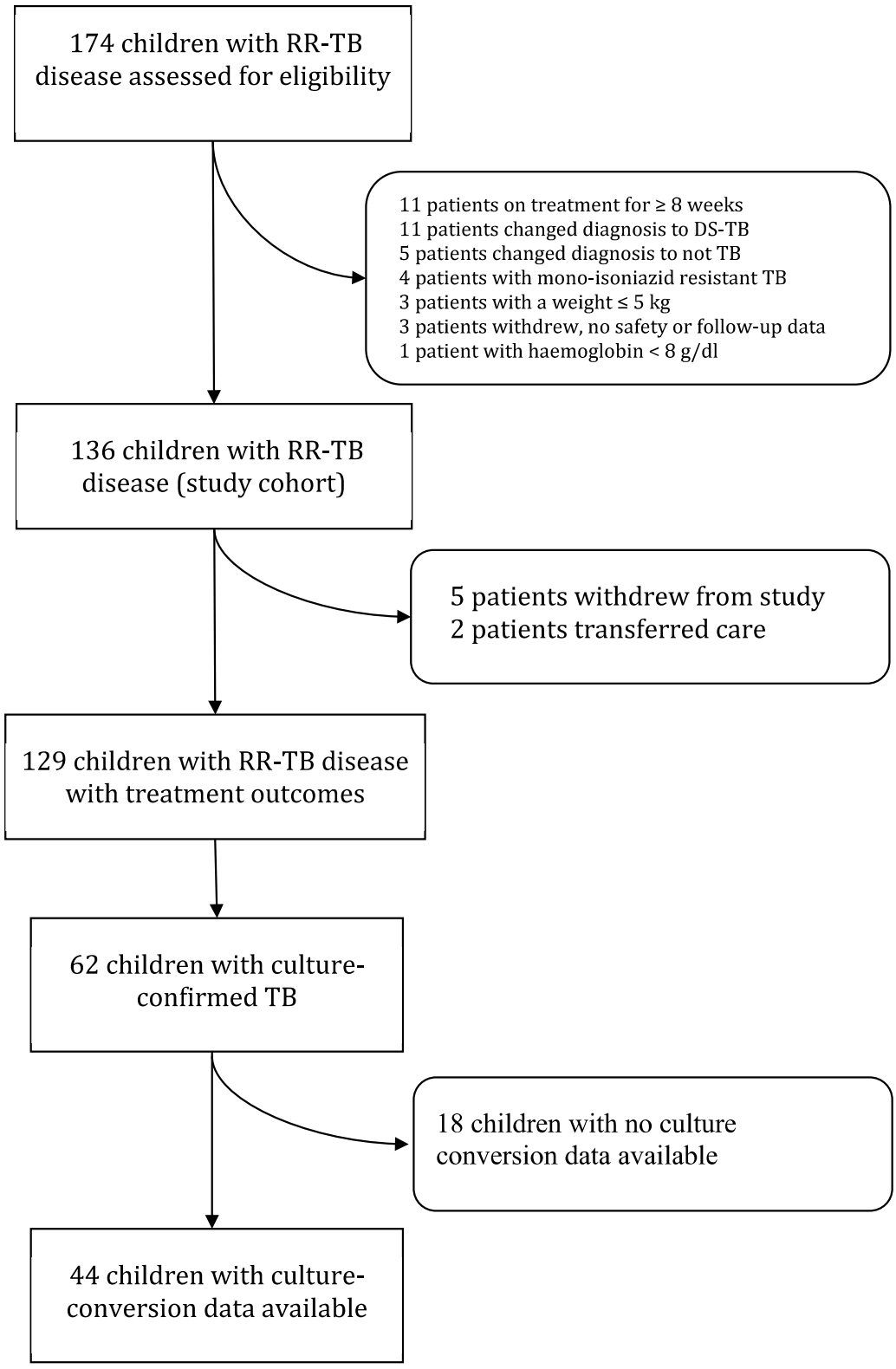

Figure 1. Study Schematic

Abbreviations: DS-TB, drug-susceptible tuberculosis; RR-TB, rifampicin-resistant tuberculosis

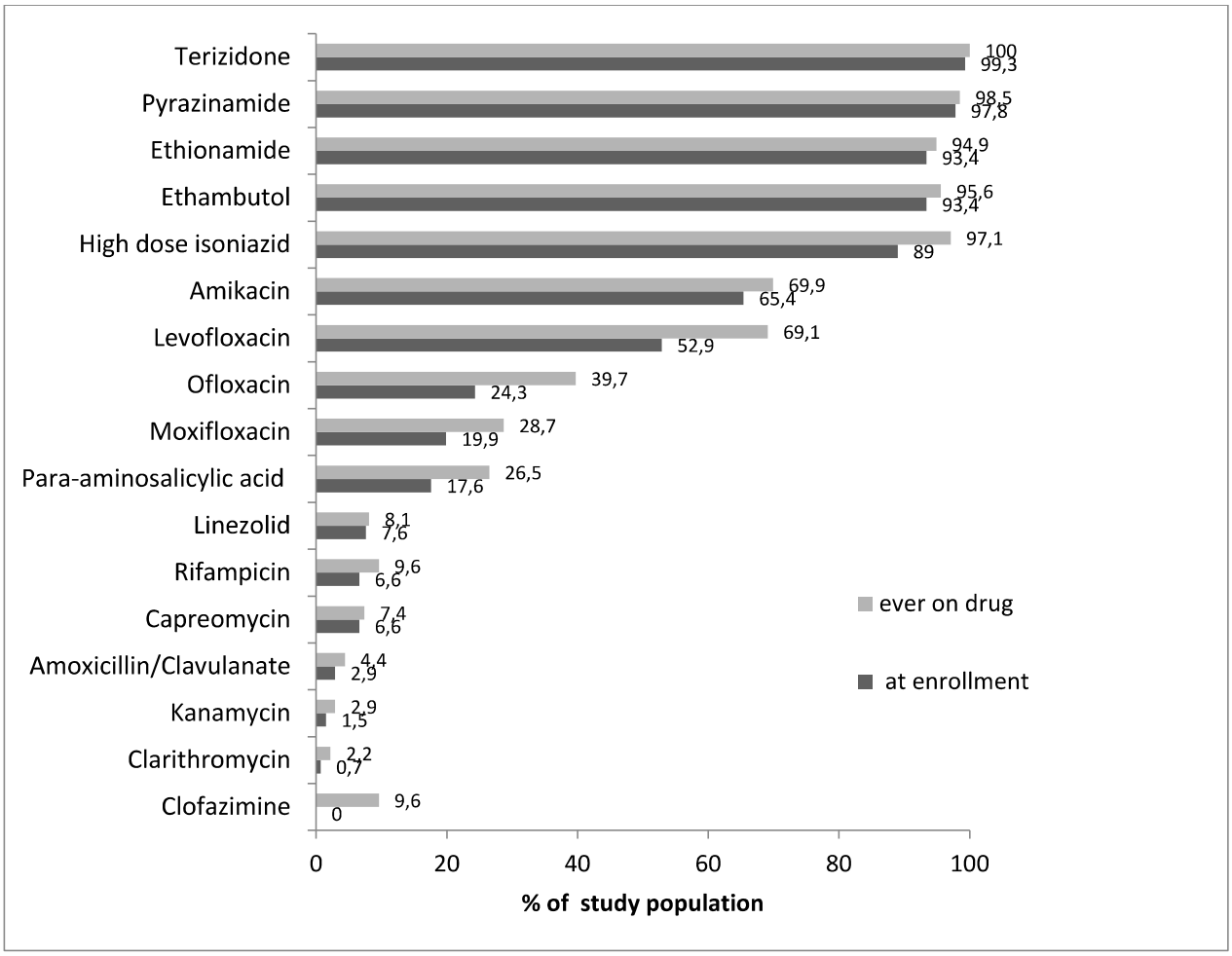

Figure 2: Proportion of children on each drug ever received during rifampicin-resistant tuberculosis treatment (N=136)