

1 Supplementary appendix

2 **Content**

3 **1. Supplementary Online Methods**

4 **2. Supplementary Tables**

5

6 **1. Supplementary Online Methods**

7 **Clinical procedures**

8 Treatment regimens included mainly combinations of a fluoroquinolone (ofloxacin
9 before 2013 and levofloxacin thereafter in children <8 years, and moxifloxacin in
10 those ≥8 years of age), a second-line injectable drug (SLID mainly amikacin, with
11 the duration and inclusion of SLID dependent on disease severity or extended
12 resistance), ethionamide, high-dose INH, terizidone, pyrazinamide, and
13 ethambutol, with para-aminosalicylic acid (PAS), linezolid and clofazimine reserved
14 for MDR-TB cases with additional drug resistance. Treatment supervision was
15 provided by the caregiver (ambulatory care, with bi-weekly or monthly dispensing
16 and visits to the local health facility) or by nursing staff if in hospital

17 All children with unknown HIV status had routine testing with HIV-ELISA in
18 children more than 18 months of age and HIV DNA PCR testing in children less
19 than 18 months. All children living with HIV and not on antiretroviral therapy
20 (ART) were started on ART after RR-TB treatment initiation, typically within 2
21 weeks. ART was provided by routine care services.

22 **Laboratory procedures**

23 Microbiological sampling included expectorated or induced sputum, gastric
24 aspirates, fine needle aspirates, biopsy or other clinically relevant samples. Xpert
25 MTB/RIF (Cepheid) was introduced from August 2013. Mycobacterial culture was
26 completed at the accredited regional National Health Laboratory Service referral
27 laboratories following standard protocols. Samples were decontaminated and then
28 cultured using the Mycobacterial Growth Indicator Tube (MGIT) 960 system
29 (Becton Dickinson, Sparks, Maryland, USA). The presence of *M. tuberculosis* was
30 confirmed by PCR. Line-probe assays (GenoType MTBDR*plus*; Hain Lifescience,
31 Nehren, Germany) were carried out for genotypic drug susceptibility testing (DST)
32 to isoniazid and rifampicin. DST to second-line drugs was completed by the

33 phenotypic indirect proportional method on Middlebrook 7H10 agar using critical
34 concentrations of amikacin 40 µg/mL, ofloxacin 2 µg/mL and ethionamide 10
35 µg/mL. In cases of discrepancy in drug susceptibility testing results between adult
36 source case and child contact, both results were followed up with the reference
37 laboratory to confirm that this was not a lab error.

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39 **Safety**

40 Adverse events were assessed for attribution to each of the drugs used in the
41 regimen based on the judgement of the investigators. Serious adverse events (SAE)
42 were defined as any untoward medical occurrence that at any dose, either resulted
43 in death, was life-threatening, required inpatient hospitalization or caused
44 prolongation of existing hospitalization, resulted in persistent or significant
45 disability/incapacity, may have caused a congenital anomaly/birth defect, or
46 required intervention to prevent permanent impairment or damage.

47 **Data management and analysis**

48 All data were recorded in case report forms and double entered into an electronic
49 database. All identifier details were dissociated from clinical data by unique study
50 numbers.

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52 **2. Supplementary Tables**

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Table S1. Additional demographic and clinical characteristics of children on treatment for rifampicin-resistant tuberculosis (N = 136)

Age at TB treatment initiation	
0-1 years (%)	52 (38.2)
2-4 years (%)	47 (34.6)
5-9 years (%)	19 (14.0)
10-14 years (%)	18 (13.2)
Number of previous TB episodes [n=34]	
One previous episode (%)	31 (91.2)
Two previous episodes (%)	3 (8.8)
Outcome of most recent previous TB episode [n=31]	
Cured (%)	6 (19.4)
Treatment completed (%)	12 (38.7)
Lost to follow-up (%)	3 (9.7)
Treatment failure (%)	10 (32.3)
Known TB source case (%) [n=135]	99 (73.3)
Relationship to the primary TB source case [n=92]	
Mother (%)	42 (45.7)
Father (%)	11 (12.0)
Other (%)	39 (42.3)
Extrapulmonary TB site (%) [n=32]	
Miliary (without TB meningitis)	4 (12.5)
Central nervous system disease	10 (31.2)
Abdominal TB (%)	6 (18.8)
Peripheral lymph node disease (%)	7 (21.9)
Pleural effusion (%)	5 (15.6)
Pericardial effusion (%)	1 (3.1)
Bone/Joint/Spine TB (%)	1 (3.1)
Weight-for-age Z-score <-2.0 (%) [n=134]	29 (21.6)
Height-for-age Z-score <-2.0 (%) [n=133]	39 (29.3)
Median MUAC in cm (IQR) [n=97]	15.3 (14.2, 16.2)

HIV status	
HIV-positive (%)	27 (19.9)
HIV-exposed negative (%)	22 (16.2)
HIV-negative (%)	80 (58.8)
HIV-negative unknown HIV exposure	7 (5.2)
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)
Median number of days on ART at TB treatment initiation (IQR) [n=11]	15 (12,19)
Regimen (%) [n=26]	
ABC-3TC-LPV/r (%)	16 (61.5)
ABC-3TC-EFV (%)	7 (26.9)
d4T-3TC-EFV (%)	1 (3.8)
d4T-3TC-LPV/r (%)	1 (3.8)
Unknown regimen	1 (3.8)
Median CD4 absolute count in cells/mm ³ (IQR) [n=26]	579 (155, 1087)
WHO immunodeficiency stage [n=26]	
None or not significant (%)	8 (30.8)
Mild (%)	1 (3.8)
Advanced (%)	2 (7.7)
Severe (%)	15 (57.7)

54 Abbreviations: IQR, interquartile range; TB, tuberculosis; MUAC, mid upper-
55 arm circumference; ART, antiretroviral therapy; ABC, abacavir; 3TC,
56 lamivudine; LPV/r, Lopinavir/ritonavir; EFV, efavirenz; d4T, stavudine
57

58 **Table S2: Chest radiograph characteristics in children with RR-TB at**
 59 **diagnosis (N = 132)**

CR feature	n (%)
Alveolar consolidation/opacification	60 (45.5)
Bronchopneumonic opacification	10 (7.6)
Miliary opacification	4 (3.0)
Expansile pneumonia	3 (2.3)
Ghon focus	2 (1.5)
Cavities	14 (10.6)
Interstitial/perihilar streakiness	26 (19.7)
Volume loss/collapse	9 (6.8)
Mediastinal lymphadenopathy	67 (50.8)
Perihilar LN	60 (45.5)
Paratracheal LN	17 (12.9)
Tracheal or bronchial compression due to LN	9 (6.8)
Pleural effusion	2 (1.5)
Calcification (parenchymal or nodes)	2 (1.5)
Fibrosis	2 (1.5)
Normal CR ¹	16 (12.1)

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Abbreviations: CR=chest radiographs; LN=lymph nodes.

61 More than one of the abnormalities described were present in the majority of
 62 cases

63 ¹Five had extrapulmonary TB (EPTB) and 3 were EPTB plus pulmonary TB

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