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Manuscript Title

Preventive therapy for child contacts of multidrug-resistant tuberculosis: a prospective cohort study

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Summary

A three drug preventive regimen for the treatment of children exposed to multidrug-resistant tuberculosis was well tolerated with limited toxicity. Few children developed tuberculosis or died. This regimen should be seen as a safe and effective option.

ABSTRACT

Background

Evidence is limited to guide the management of children exposed to multidrug-resistant (MDR) tuberculosis (TB). We aimed to study the tolerability and toxicity of a standard preventive therapy regimen, given to children exposed to infectious MDR-TB, and explore risk factors for poor outcome.

Methods

Prospective cohort study: Western Cape, South Africa. Children <5 years old, or HIV-positive children <15, were recruited from May 2010 through April 2011 if exposed to an ofloxacin-susceptible, MDR-TB source case. Children were started on preventive therapy as per local guidance: ofloxacin, ethambutol and high-dose isoniazid for six months. Standardized measures of adherence and adverse events were recorded; poor outcome was defined as incident TB or death from any cause.

Results

186 children were included, median age 34 months (inter-quartile range: 14-47). Of 179 children tested for HIV, 9 (5.0%) were positive. Adherence was good in 141 (75.8%) children. Only 7 (3.7%) children developed Grade 3 adverse events. One child (0.5%) died and six (3.2%) developed incident TB during 219 patient years of observation time. Factors associated with poor outcome were: age <1 year (rate ratio: 10.1; 95%CI: 1.65-105.8; p=0.009), HIV-positive status (rate ratio: 10.6; 95%CI: 1.01-64.9; p=0.049), exposure to

multiple source cases (rate ratio: 6.75; 95%CI: 1.11-70.9; p=0.036) and poor adherence (rate ratio: 7.50; 95%CI: 1.23-78.7; p=0.026).

Conclusions

This three-drug preventive therapy regimen was well tolerated and few children developed TB or died if adherent to therapy. The provision of preventive therapy to vulnerable children following exposure to MDR-TB should be considered.

INTRODUCTION

For a child to develop tuberculosis (TB), they must first be exposed to an infectious TB source case, then become infected and finally progress to disease.[1] Children at the highest risk of progressing from infection to disease are young (<5 years)[2] and HIV-positive children.[3] If children with *Mycobacterium tuberculosis* infection are given effective therapy to prevent the progression to disease, many children will be spared TB disease episodes. This has clinical implications for the individual, reducing morbidity, mortality and avoiding lengthy, unpleasant and potentially costly treatment with associated adverse events. It also has implications for the community as children provide a reservoir for future disease, with propagation of the epidemic by those children who develop infectious TB. The first trials of isoniazid as preventive therapy for TB were carried out over fifty years ago,[4] and isoniazid has been demonstrated to reduce the risk of progression from infection to disease in HIV-positive and HIV-negative children following exposure to drug-susceptible TB.[5-6] The majority of international agencies and National TB Programs therefore advise providing children less than five years and all HIV-positive children with isoniazid daily for six months following exposure to an infectious case of drug-susceptible TB.[7]

Multidrug-resistant (MDR) TB is caused by *M. tuberculosis* resistant to at least rifampin and isoniazid.[8] Following exposure to a source case with MDR-TB it is unclear how children should be managed.[9] Although concordance between putative source cases and child contacts is not complete, many clinicians are uncomfortable treating a child exposed to an MDR organism with isoniazid. Cases have been reported of children exposed to MDR-TB developing TB disease on isoniazid preventive therapy.[10-11] The Centers for Disease

Control identified the need for a preventive therapy trial for contacts of MDR-TB in 1992.[12] Since then numerous international agencies and experts have also recommended that the investigation of MDR-TB preventive therapy should be a global public health priority.[13-16] However, no trials have been conducted to date.

One of the major concerns regarding the provision of preventive therapy in children using drugs other than isoniazid is potential toxicity in healthy children. In the treatment of MDR-TB disease, the risk-benefit ratio of potentially toxic therapy is relatively clear. In contrast, this risk-benefit ratio is altered when using potentially toxic preventive therapy in children who are currently well, but are at risk of developing future disease. Particular caution has been exercised regarding the use of the fluoroquinolones in children, based on early animal model data showing damaging effects to the cartilage growth of young beagles.[17] There are limited published data regarding the efficacy, tolerability and toxicity of preventive therapy regimens given to children exposed to MDR-TB.

The World Health Organization (WHO) estimates that there were 650,000 prevalent cases of MDR-TB in 2010.[18] A previous MDR-TB contact study suggested that in a setting with a high burden of TB there are nearly two child contacts for each adult TB source case.[19] As many as a million children could therefore be exposed to MDR-TB globally each year, many of whom, in the absence of effective preventive therapy, will go on to develop MDR-TB disease. While treatment outcomes for MDR-TB disease are good with tailored individualized therapy in children, the treatment in children is complex, long and associated with significant adverse events.[20] Appropriate drugs and child-friendly formulations are limited and interactions between antiretroviral and anti-TB drugs are common.[21-22] MDR-

TB is expensive to treat and often requires prolonged hospitalization.[23] We therefore aimed to study the tolerability and toxicity of a standard MDR-TB preventive therapy regimen, given to children following documented exposure to adults with MDR-TB, and determine how many children develop poor outcomes.

METHODS

Setting

The Western Cape province of South Africa had a TB notification rate of 976 per 100,000 in 2009.[24] Among children with culture-confirmed TB at the regional referral hospital for pediatric drug-resistant TB, Tygerberg Children's Hospital (TCH), 8.9% had MDR-TB during 2007-2009.[25] Children exposed to an infectious case of MDR-TB are routinely referred to a specialist pediatric drug-resistant TB clinic at TCH, or to community outreach clinics served by a specialist from this hospital.

Standard of Care

Following exclusion of TB disease through history, clinical examination, plain film chest radiology (with mycobacterial culture in the presence of symptoms or abnormal chest radiography), children who were less than five years of age or HIV-positive, with significant exposure to an infectious (sputum smear or culture positive) pulmonary MDR-TB source case, were routinely given a regimen of MDR-TB preventive therapy, irrespective of tuberculin skin test (TST) result, as advised by provincial guidelines. Significant exposure was defined as living with or having regular daily interaction with the MDR-TB source case. If the source case had MDR-TB with susceptibility to the fluoroquinolones, the child was given

ofloxacin (15-20mg/kg daily; the only fluoroquinolone available for children at the time), ethambutol (20-25mg/kg daily) and isoniazid (15-20mg/kg daily) for 6 months. Children were routinely evaluated at two, four, six and twelve months, at TCH or the community outreach sites, through clinical evaluation and chest radiography. Drugs were dispensed at local community TB clinics, on either a daily, weekly or monthly basis, depending on clinic and patient preference. HIV testing was offered to all child TB contacts following informed consent from the parent or legal guardian, with assent from the child where appropriate. An ELISA was used in children older than 18 months or DNA PCR if younger or breast-fed. Combination antiretroviral therapy (cART) was routinely initiated in all HIV-positive children following appropriate evaluation. TST was completed by TB clinic personnel by injecting two tuberculin units intradermally (purified protein derivative RT23, Statens Serum Institute) with results read at 48-72 hours; an induration of ≥10mm (or ≥5mm if HIV-positive) was regarded as positive.

Study population and eligibility

All children evaluated at TCH or community outreach clinics were eligible if they had been in significant contact with an infectious case of pulmonary MDR-TB ('the source case'), within the preceding six months and if the drug susceptibility test (DST) of the isolate from the source case showed susceptibility to ofloxacin. Children were enrolled if they had started preventive therapy from May 2010 through April 2011. Children were recruited following written, informed consent from their caregivers with assent from the child where appropriate. The study was approved by the Stellenbosch University and London School of Hygiene and Tropical Medicine Ethics Committees.

Data collection

Children were seen by the study team at their routine clinical appointments, as well as at any additional, unscheduled visits. At the initial interview, following screening for TB disease, data were collected regarding demographic and clinical details. At follow-up visits, after clinical assessment, parents/caregivers were interviewed concerning adherence and potential drug-related adverse events using a structured questionnaire. In addition, during the first half of 2012, children were traced and either recalled to clinic or visited at their local clinic or home by the study team. Where this was not possible, local clinics and families were contacted to confirm that the child was clinically well and was gaining weight. The date of this final interaction was recorded. Follow-up time for the children, therefore, was a minimum of 12 months and up to 24 months in some children.

Adherence was measured in two ways at each study visit. The first was a three-day recall and the second a 30-day visual analogue score. Each of these two measures was scaled to give a score out of thirty. Scores derived from both measures from each visit were added to determine a total 'score' for the whole period on treatment.[26-27] If this was above 80% of a possible maximum then adherence was recorded as good with scores less than 80% as poor.[28] Local clinics were also contacted to verify medication uptake. In cases of discrepancy, adherence was reported as being poor. Adverse events to medications were categorized using the Division of Microbiology and Infectious Diseases (DMID) system.[29] (Table 1). As arthralgia is not categorized in this classification we allocated five grades consistent with the DMID classification. If old enough to co-operate, visual toxicity was evaluated with Ishihara charts. Parental impression of visual function was used for children who could not be evaluated in this way. Study outcomes were: well at the end of the

observation period, death of any cause and incident TB disease. Standardized research definitions were applied to classify incident TB disease in children [30]; confirmed and probable disease were considered incident TB. Where patients were lost to follow-up their censoring date was recorded as the last interaction with the study team. A combined endpoint of incident TB and/or death was classified as poor outcome.

Data analysis

Data were double-entered and checked for entry errors. Data were analyzed using STATA software (version 11; Stata Corp, College Station, TX). Cohort analysis was undertaken to examine factors associated with poor outcome. Time of entry into the cohort was the date of recruitment and time exiting the cohort was the date of death, diagnosis of incident TB or date of last contact with the study team. Due to the small number of events, exact Poisson analysis was undertaken for a limited number of predetermined characteristics of the child and treatment, with rate ratios (RR), 95% confidence intervals (CI) and p-values calculated.

RESULTS

Of 245 children initially eligible, 186 were included as contacts of 164 MDR-TB source cases. Of the children excluded, 12 were brought by an adult who could not provide legal consent, for two children consent was not given, 29 were contacts of MDR-TB source cases with additional resistance to ofloxacin and in the remainder (n=16), although the source case was said to have MDR-TB at the initial assessment, and the child was initially given MDR-TB preventive therapy, the adult was subsequently confirmed to have resistance to only either isoniazid or rifampin. For the children included, the median age was 34 months (inter-

quartile range [IQR]: 14-47), and 102 (55%) were boys (Table 2). The mean weight-for-age z-score was 0.59 standard deviations below the reference population. Of 179 children tested for HIV, 9 (5.0%) were positive. Adherence was good in 141 (75.8%) children and only two children were lost to follow-up before twelve months.

Adverse events are demonstrated in Table 3, with all Grade 3 adverse events shown in Table 4. Of the six children (3.2%) who experienced a Grade 3 adverse event, three were associated with inadvertent overdosing of ofloxacin. No adverse events necessitated the discontinuation of preventive therapy and all resolved without intervention. The most common Grade 2 or higher adverse events were loss of appetite and nausea (12 children; 6.2%), itchy skin (9 children; 4.7%), disturbance of sleep or mood (7 children; 3.6%) and skin rash (7 children; 3.6%).

Over a total of 219 patient years of observation time one child died (0.5%; most likely of sudden infant death syndrome) and six developed incident TB (3.2%). All had probable disease. (Table 5) The rate for poor outcome was 31.9 outcomes (95%CI: 12.8-65.9) per 1000 years of patient follow up. Factors associated with increased risk of poor patient outcome (Table 6) were: age less than one year (rate ratio [RR]: 10.1; 95%CI: 1.65-105.8; p=0.009), HIV positivity (RR: 10.6; 95%CI: 1.01-64.9; p=0.049), exposure to multiple source cases (RR: 6.75; 95%CI: 1.11-70.9; p=0.036) and poor adherence (RR: 7.50; 95%CI: 1.23-78.7; p=0.026).

DISCUSSION

We demonstrate that the provision of MDR-TB preventive therapy in child MDR contacts is well tolerated, associated with few clinically significant adverse events, and results in a low rate of incident TB or death. The three cases of Grade 3 toxicity, associated with inadvertent overdosing of ofloxacin, is concerning. In South Africa, at the time our study was conducted, ofloxacin was available in two formulations: 200mg and 400mg. Medications are frequently dispensed as loose tablets within a re-sealable packet with the number of tablets to be taken written on the outside. If the packet is refilled with a different strength of tablet, confusion can occur. We noted only one Grade 2 or higher episode of joint, muscle or bone pain. Given the historical concerns regarding fluoroquinolone use in children, these findings are reassuring. We also observed no hepatotoxicity or visual problems.

During over 200 patient years of follow-up, only one child died and six developed incident TB. It is likely that the child that died did not develop TB but died of some other illness. Of the six children who developed incident TB, four were not given the prescribed medications conscientiously and no children given medications under daily observed therapy developed TB. Risk factors for poor outcome included young age (<12 months) and HIV infection. These risk factors are well described in the drug-susceptible pediatric TB literature[2-3] and should prompt enhanced vigilance in these especially vulnerable populations. That children exposed to multiple source cases had higher rates of poor outcome is interesting. It may be that having multiple source cases increases the risk of mycobacterial transmission or it may be that highly virulent strains circulate in some households. It may be that genetic factors

render certain families more susceptible to TB or it may be that social factors such as crowding, alcohol, drugs, nutrition or adherence influence both the adults and the children.

Few studies have previously assessed preventive therapy for child contacts of MDR-TB and no randomized controlled trials have been conducted.[31] One study in Cape Town examined 105 children; 41 were given a multidrug preventive regimen tailored to the drug susceptibility test pattern of the source case isolate.[19] Only two of the 41 treated patients (5%) developed TB disease compared to 13 (20%) observed without treatment. A study in Rio de Janeiro followed 218 adult and child contacts of MDR-TB; 45 had been given isoniazid.[32] There was no protective effect of the isoniazid. A final study in Chuuk, Federated States of Micronesia, examined 110 infected adult and child MDR-TB contacts, given a twelve-month individually tailored multi-drug preventive regimen under directly observed therapy. No patients given preventive therapy developed TB.[33] Guidelines vary[34-36] as do expert opinion[37-38] and published practice.[11, 39-42] Some agencies advise careful follow-up alone,[7, 43] some recommend isoniazid,[44] some suggest two drugs to which the index case's TB strain is susceptible,[12] and some advocate specialist referral.[45] A Delphi survey of experts was unable to reach consensus,[46] and two systematic reviews concluded that there was not enough evidence to inform policy development regarding MDR-TB preventive treatment.[47] A report from the European Centre for Disease Prevention and Control suggest that either tailored preventive therapy with close follow-up or close follow-up alone are acceptable options in the absence of better data.[13]

This is the largest study to date documenting the effect of a standard preventive therapy regimen for children exposed to MDR-TB. Follow-up was good and both adherence and adverse events were carefully documented. However, our study had several limitations. As this was an observational study without a control group, it is not possible to conclude with certainty that this regimen is effective. It is possible that the number of children developing TB could have been similar had they been given isoniazid alone or even no medications at all. However, the pre-chemotherapy data do not support this argument. In the absence of preventive therapy, it has been shown that up to 50% of *M. tuberculosis*-infected children less than twelve months of age developed TB disease.[2] The figure is 20-30% for children aged between one and two years and 5% for children aged between two and five years. Although only 40% of our cohort was TST positive, we would still expect to see far higher numbers of children developing TB if the regimen was not effective. In addition, the evidence that poor adherence to preventive therapy was strongly associated with poor outcome adds support to the argument that this regimen is effective in reducing the risk of progression from infection to disease. We included children irrespective of TST status, consistent with national and provincial guidelines. The rationale for this is that TST is not a highly sensitive test for *M. tuberculosis* infection, especially in the young infant, HIV-positive children and malnourished children nor is it highly specific in settings where BCG is routinely given at birth such as ours. By only including TST positive children a number of infected children would therefore have been excluded. Also, if a TST is negative at the time of initial assessment, there is a chance that the child may have been infected but may only convert their test later. Rather than use a two stage protocol with all children started on preventive therapy, which is then stopped if a second TST at follow-up is negative, the local policy is for all exposed children to be treated. We employed these operational entry criteria in our

study. It could, therefore, be argued that some of the children in the study did not require treatment. As mycobacteria were not isolated from any of the children that developed TB, we were unable to determine if this preventive therapy regimen resulted in increased rates of fluoroquinolone resistance. This is a potential concern and should be evaluated in future studies. A final limitation of the study is the duration of follow-up. All children were followed for a minimum of twelve months with some followed for 24 months. Although the vast majority (>90%) of children who develop disease do so within twelve months of infection,[4, 19] it is accepted that some children might progress to disease after the period of observation.

To conclusively determine the utility of preventive therapy for child contacts of MDR-TB, a clinical trial is warranted, one in which children are randomly and blindly assigned to either a fluoroquinolone-containing multi-drug regimen or to isoniazid alone. However, until that time, clinicians will continue to be confronted by children exposed to MDR-TB. We have demonstrated this regimen to be well tolerated and associated with limited toxicity. Also, clinicians should be confident when managing a child exposed to MDR-TB that providing this preventive therapy regimen results in reassuringly low rates of TB or death.

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CONFLICTS OF INTEREST

No conflicts of interest exist.

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Table 1. Classification of adverse events used in children receiving multidrug-resistant tuberculosis preventive therapy

Adverse event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Joint, muscle or bone pain	No adverse event	Pain but no interference with function or movement	Moderate pain, affecting function but able to carry out normal activities	Severe pain limiting activities	Disabling pain – unable to carry out activities
Skin Rashes	No adverse event	Small areas of redness /rash	Dry peeling or widespread rash	Wet peeling, ulcers or urticaria	Severe, widespread rash, necrosis needing hospitalization
Itchy skin	No adverse event	Slight itching in localized areas	Severe itching in localized areas	Widespread itching over entire body	Uncontrollable scratching needing hospitalization
Headache	No adverse event	Mild – does not need treatment	Transient/moderate – needs non-narcotic treatment	Severe –responds to narcotics	Intractable pain
Sleeping/mood	No adverse event	Mild anxiety	Moderate anxiety or problems getting to sleep	Severe anxiety, problems getting to sleep or repeated waking	Psychosis, unable to sleep for more than an hour
Lethargy	No adverse event	Activity Reduced but for <48 hours	Slightly irritable or slightly subdued	Very irritable or lethargic	Inconsolable or obtunded
Visual problems	No adverse event	None	Blurred vision or minor visual disturbance lasting less than 1 hour	Repeated episodes of blurring or visual disturbances which resolve	Permanent decrease in visual acuity or field defect
Vomiting	No adverse event	1 episode in 24 hours	2-3 episodes in 24 hours	4-6 episodes in 24 hours	>6 episodes in 24 hours or needing hospitalization
Diarrhea	No adverse event	Slight change in consistency or frequency of stool	Liquid stool	Liquid stool >4x normal frequency for child	Liquid stool >8x normal frequency for child
Jaundice	No adverse event	Jaundice detectable clinically – bilirubin 1.1 - 1.5 x ULN	Obvious clinical jaundice – bilirubin 1.6 – 2.5 x ULN	Severe jaundice – bilirubin 2.6 – 5 x ULN	Hospitalization – bilirubin >5x ULN
Loss of appetite/nausea	No adverse event	Mild – still eating/drinking well	Moderate - decreased appetite	Severe – little food taken	No solid or liquid food taken

ULN: Upper limit of normal (as determined by reference range for age of child and assay used)

Table 2. Baseline characteristics of children exposed to a multidrug-resistant tuberculosis source case and placed on preventive therapy (n=186)

Characteristic	Description	Result
Median age in months (IQR)		34 (14-47)
Male gender (%)		102 (54.8)
Ethnicity (%)	South African Colored	100 (53.8)
	Xhosa	84 (45.2)
	White	1 (0.5)
	Other	1 (0.5)
Mean weight-for-age z-score (SD; n=182)		-0.59 (1.51)
Mean height-for-age z-score (SD; n=142)		-1.00 (1.35)
TST positive (%; n=183)		73 (40.0)
Evidence of BCG scar (%; n=181)		145 (80.1)
Multiple MDR-TB source cases (%; n=176)		49 (27.8)
HIV-positive (%; n=179)		9 (5.0)
On cART at start of preventive therapy (%; n=9)		8 (88.9)
Type of medication delivery (%)	DOT at clinic	20 (10.8)
	DOT by treatment support worker	3 (1.6)
	Weekly supply for parents to administer	141 (75.8)
	Monthly supply for parents to administer	16 (8.6)
	Other	6 (3.2)

IQR= Interquartile range; SD = standard deviation; TST = tuberculin skin test; BCG = Bacillus Calmette–Guérin; MDR-TB = multidrug-resistant tuberculosis; HIV = human immunodeficiency virus; cART = combination antiretroviral therapy; DOT = directly observed therapy

Table 3. Summary of cumulative most severe adverse event in children receiving six months of multidrug-resistant tuberculosis preventive therapy (n=186)

Adverse event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Joint, muscle or bone pain*	178	5	1	0	0	184
Skin Rashes	140	40	6	0	0	186
Itchy skin	147	33	6	0	0	186
Headache*	153	3	2	0	0	158
Sleeping/mood	170	8	4	4	0	186
Lethargy	183	3	0	0	0	186
Visual problems	186	0	0	0	0	186
Vomiting	155	30	1	0	0	186
Diarrhea	170	15	1	0	0	186
Jaundice	186	0	0	0	0	186
Loss of appetite/nausea	150	15	19	2	0	186

*Total not 186 as some parents stated that they could not determine if the child had experienced the adverse event

Table 4. Characteristics of children developing Grade 3 adverse events (n=6) on MDR-TB preventive therapy

Age	Gender	HIV status	Adverse event(s)	Details
6 months	Girl	Negative	Loss of appetite	Appetite reported as normal at the two month appointment, Grade 2 at the four month appointment and Grade 3 at the six month appointment Mother reported that some of the loss of appetite might have been due to teething Preventive therapy continued throughout
14 months	Boy	Negative	Loss of appetite	Child reported to have Grade 3 appetite loss at two months, then none at 4 months but Grade 1 at six months Preventive therapy continued throughout
25 months	Boy	Negative	Insomnia and hallucinations	At the two month appointment child reported not sleeping due to hallucinations Child had been prescribed 300mg ofloxacin but inadvertently given 600mg by clinic staff Preventive therapy continued at correct dose and symptoms resolved
38 months	Girl	Negative	Insomnia	Mother reported severe insomnia at the two month appointment but stated that the problem had been evident prior to starting the preventive therapy Preventive therapy continued and sleeping improved
38 months	Girl	Negative	Insomnia and hallucinations	At the two month appointment the mother reported the child to be having hallucinations and sleep problems Child had been prescribed 300mg ofloxacin but inadvertently given 600mg by clinic staff Symptoms resolved on correct dosage
45 months	Boy	Negative	Insomnia	At the two month appointment the mother reported that the child did not sleep at all Child had been prescribed 300mg ofloxacin but inadvertently given 600mg by clinic staff Symptoms resolved on correct dosage

Table 5. Mortality and incident tuberculosis in children given preventive therapy for multidrug-resistant tuberculosis (n=7)

Age at cohort entry	Gender	TST result	HIV status	Source case	Outcome	Time to outcome	Adherence	Details
12 days	Boy	No result	Negative	Mother's cousin	Died	3 weeks	Poor	Baby died after three weeks in what appeared to be sudden infant death syndrome. No doses of preventive therapy given
2 months	Boy	0mm	Negative	Mother	TB	10 months	Poor	Developed TB ten months after initially being seen having received only intermittent preventive therapy
3 months	Boy	0mm	Positive	Mother	TB	9 months	Poor	Child not given preventive therapy after the point at which his mother was admitted to hospital (after 3 months of therapy)
9 months	Girl	0mm	Positive	Mother	TB	6 months	Poor	Poor adherence following the death of the mother which happened soon after the child was initially evaluated
10 months	Girl	0mm	Negative	Mother	TB	2 months	Good	Developed TB after two months on preventive therapy, with adherence reported to be good
34 months	Girl	10mm	Negative	Mother	TB	2 months	Poor	Preventive therapy prescribed but no doses given by parents
51 months	Boy	15mm	Negative	Aunt	TB	10 months	Good	Developed TB four months after stopping preventive therapy, reported to have been given with good adherence

TST: tuberculin skin test; HIV: human immunodeficiency virus; TB: tuberculosis

Table 6. Assessment of risk factors for poor outcome (death or incident tuberculosis disease) in children exposed to multidrug-resistant tuberculosis and treated with a preventive therapy regimen (n=186)

		Number of events	Years of observation	Incidence rate with 95% CI (events per 1000 person years)	Rate Ratio (95% CI)	p-value
Age	>12 months	2	175.5	11.4 (1.4-41.1)	1	
	0-12 months	5	43.5	114.9 (37.3-268.2)	10.1 (1.65-105.8)	0.009
Gender	Female	3	95.6	31.4 (6.5-91.7)	1	-
	Male	4	123.4	32.4 (8.8-83.0)	1.03 (0.17-7.05)	1.00
TST	Negative	4	132.1	30.3 (8.3-77.5)	1.0	-
	Positive	2	84.8	23.6 (2.9-85.2)	0.78 (0.07-5.43)	1.00
Source cases	Single	2	152.4	13.1 (3.28-52.5)	1.0	-
	Multiple	5	56.4	88.6 (36.9-213.0)	6.75 (1.11-70.9)	0.036
HIV status	Negative	5	201.5	24.8 (8.1-579.1)	1.0	-
	Positive	2	7.6	263.8 (31.9-950.6)	10.6 (1.01-64.9)	0.049
Adherence	Good	2	164.3	12.2 (1.5-44.0)	1.0	-
	Poor	5	54.8	91.3 (29.6-212.9)	7.50 (1.23-78.7)	0.026
Type of delivery	Daily observed therapy	0	31.5	0 (0-117.1)	-	-
	Other	7	187.6	37.3 (15.0-76.8)	-	0.68

CI = confidence interval; TST = tuberculin skin test; HIV = human immunodeficiency virus