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Tuberculosis prevention in children: A prospective community based study in South Africa

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ABSTRACT (250/250)

Tuberculosis preventive therapy reduces tuberculosis risk in children. However, the effectiveness of tuberculosis preventive therapy in children living in high burden settings is unclear.

In a prospective observational community-based cohort study in Cape Town, South Africa, we assessed the effectiveness of routine tuberculosis preventive therapy in children ≤15 years of age in a tuberculosis and HIV high-prevalence setting.

Among 966 children (median age 5.07 years; inter-quartile range [IQR] 2.52,8.72), 676 (70%) reported exposure to an adult with tuberculosis in the past 3 months and 240/326 (74%) of eligible children initiated isoniazid preventive therapy (IPT) under programmatic guidelines. Prevalent (n=73) and incident (n=27) tuberculosis were diagnosed among 100/966 (10%) of children. Children who initiated IPT were 82% less likely to develop incident tuberculosis than children who did not (aOR=0.18; 95% confidence-interval [CI] 0.06,0.52; p=0.0014). Children's risk of incident tuberculosis increased if they were younger than five years, living with HIV, had a positive *M.tuberculosis* specific immune response, or recent tuberculosis exposure. The risk of incident tuberculosis was not associated with gender or *M. bovis*-BCG vaccination status. Number needed to treat (NNT) was lowest in children living with HIV (NNT=15) and children less than five years of age (NNT=19) compared to children of all ages (NNT=82).

In communities with high tuberculosis prevalence, tuberculosis preventive therapy substantially reduces the risk of tuberculosis among children who are younger than five years or living with HIV, especially those with recent tuberculosis exposure or a positive *M.tuberculosis* specific immune response in the absence of disease (Mtb-sir-nodis).

Take home message:

In TB high-burden communities, preventive therapy substantially reduces risk of TB among child contacts, especially those who are younger than five years, living with HIV, recently TB exposed, or have a positive *M.tuberculosis* specific immune response.

Plain language summary:

Although preventive therapy can prevent tuberculosis in children, its' effectiveness in children living in settings with high burdens of tuberculosis is unclear. We assessed the risk of developing tuberculosis and the effectiveness of routine tuberculosis preventive therapy in South African children 15 years of age or younger living in a tuberculosis and HIV high prevalence setting in Cape Town. Among nearly 1000 children, we found that children who initiated preventive therapy were 82% less likely to develop tuberculosis than children who did not. The risk of tuberculosis was highest among children younger than 5 years of age, children living with HIV, those who had a positive *M. tuberculosis* specific immune response, and those who reported recent exposure to an adult with infectious pulmonary tuberculosis. Less than 20 children needed to initiate preventive therapy in order to prevent one case of tuberculosis

among children living with HIV and children less than five years of age. In communities with high tuberculosis prevalence, tuberculosis preventive therapy substantially reduces the risk of tuberculosis and should target children at highest risk of disease; children who are younger than 5 years of age or living with HIV, especially those with recent tuberculosis exposure or a positive *M.tuberculosis* specific immune response.

INTRODUCTION

The End TB Strategy calls for a 90% reduction in tuberculosis mortality and 80% reduction in tuberculosis incidence by 2030 [1]. Tuberculosis remains among the top ten causes of mortality in children under five years of age [2]. Without additional efforts for prevention in children, these goals are unlikely to be met [3]. In the last five years, the WHO increasingly emphasized tuberculosis preventive therapy (TPT) with multiple guidelines promoting household contact investigation and management to identify children at risk of tuberculosis [4, 5]. WHO surveillance has also demonstrated increased use of isoniazid preventive therapy (IPT), the most commonly used preventive treatment regimen in high-tuberculosis burden settings. In 2018, 27% of eligible children reported initiating IPT following tuberculosis exposure [6] compared to 7% in 2015 [7]. At the 2018 UN high-level meeting on tuberculosis, Heads of States endorsed a global target of providing TPT to at least 30 million people during 2018-2022. These global targets are more feasible as rifamycin-based preventive therapy regimens of shorter treatment duration and comparable efficacy, tolerability, and safety are now recommended for all ages and increasingly available [8, 9].

A systematic review of evidence from randomized control trials dating back to the 1940's found a nearly 60% risk reduction in children who receive TPT during 6 month to 10 year follow-up periods [10]. Some observational studies, most outside of Africa, have found that preventive therapy was similarly effective [11] . Nevertheless, the tuberculosis/HIV syndemic has amplified

the force of *M. tuberculosis* infection in Southern Africa, and may alter the effectiveness and durability of IPT, with limited post-antibiotic effect found in some trials [12]. Further, there is limited recent evidence assessing the efficacy of TPT targeting children via household contact investigation outside of clinical trials, which have limited generalizability to tuberculosis programmes in high-burden tuberculosis settings due to ethical limitations precluding randomization to a placebo arm. Hence, observational cohorts present a unique opportunity to measure the impact of TPT compared to no treatment, under routine conditions, which reflects the current reality for >70% of children following *M. tuberculosis* exposure.

We assessed the effectiveness of TPT in nearly 1000 children enrolled in a household contact study in South African communities where IPT is routinely offered to exposed children less than five years of age or living with HIV [13-15].

METHODS

Between December 2007 and June 2012, a prospective, community-based household contact diagnostic study was conducted in Cape Town, Western Cape Province, South Africa that provided the observational cohort examined in this study. The diagnostic study cohort included children (≤15 years of age) with and without known exposure to an adult with tuberculosis who were consecutively recruited throughout the accrual period lasting from 12/11/2007 to 12/02/2011, and follow-up ended on 6/29/2012. In the study setting, tuberculosis incidence was 741/100,000 while the prevalence of HIV infection was 19% among pregnant women in

2012 [16, 17]. In 2009, children represented 13% of notified cases in the Cape Town metropolitan area [18]. Children were observed until they developed tuberculosis, died, or completed the study period which was 27 months for children living with HIV and 15 months for children free of HIV-infection. The differential length of follow-up was required by the funder due to potential safety concerns regarding serial TST in children living with HIV.

Following informed consent of guardians and assent of children, participants were recruited from three communities where neonatal *M. bovis* bacille Calmette Guérin (BCG) vaccination is routinely given to all neonates; vaccination rates exceeded 90% in 2012 [16]. Children living in the same household [19] as an adult with pulmonary or extrapulmonary tuberculosis were recruited within three months of index case identification in the public community tuberculosis clinic. To measure background community tuberculosis transmission, children were recruited in a standardized fashion from community pediatric HIV clinic and neighbouring households, irrespective of tuberculosis exposure history. Research assistants knocked on the door of the home immediately to the right of the index case and offered study participation; homes were systematically approach in a clockwise fashion until one neighbouring home agreed to participate. Among all children, exposure to an adult with tuberculosis during the preceding 3 months was quantified using an established and validated scoring system consisting of 10 binary questions assessing proximity and duration of contact and infectivity of the index case [14, 20]. As 1 point is assigned for each question answered positively, a score of zero to ten was assigned.

At enrolment, children simultaneously completed the tuberculin skin test (TST; two Tuberculin Units RT-23, Statens Serum Institute, Copenhagen, Denmark) and Interferon-γ release assays (IGRA) including the Quantiferon TB-Gold In-Tube (Qiagen, Venlo, The Netherlands) and the T-Spot.*TB* (Oxford Immunotec, Oxford, UK); a sub-set of children greater than 5 years of age did not complete T-Spot.*TB* testing due to budget constraints. These tests do not directly measure infection, but measure host immune response to past or current infection. The TST was classified as positive if an induration was ≥10mm in children without HIV and ≥5mm in children living with HIV. IGRAs were interpreted following manufacturers' guidelines [21, 22]. Children with negative baseline TST and IGRA were considered to have no evidence of an *M. tuberculosis* specific immune response (Mtb-sir), while children with one or more positive baseline TST or IGRA were considered to have a positive Mtb-sir. The study team was blinded to children's IGRA results as testing was completed for research purposes and not recommended within the study setting.

Employing a standard case definition that captures microbiologically confirmed and clinically diagnosed tuberculosis, children completed evaluation for tuberculosis at baseline, 3, 6, 15, and 27 months after enrolment [23]. All children were screened for tuberculosis using standard symptom screening [24], chest radiography, and mycobacterial culture of gastric aspirates or sputum at baseline, and again if clinically indicated during follow-up. Antero-posterior and lateral chest radiographs were read by two independent experts, blinded to clinical information, using a standard international pediatric tuberculosis radiologic classification tool [25]. Prevalent tuberculosis was defined as a tuberculosis diagnosis made up to 3 months from

enrolment; incident tuberculosis was defined as tuberculosis diagnosed more than 3 months after enrolment. “A positive *M.tuberculosis*-specific immune response in the absence of active tuberculosis” was abbreviated as “Mtb-sir-nodis”; this classification is used to analyze baseline results of children who developed incident tuberculosis or remained disease free.

All children with unknown or negative HIV-infection status underwent HIV testing using a HIV-1/2 rapid test (Abbott Determine^{TM} HIV-1/2 rapid test, Abbott Diagnostic Division Hoofddorp, The Netherlands), followed by confirmatory ELISA (children $\geq$ 18 months) or DNA polymerase chain reaction (children <18 months) if positive or indeterminate. During the study period, local guidelines recommended TPT with 6 months’ daily isoniazid for children <5 years of age and all children living with HIV, after exposure to a patient with infectious tuberculosis or following a positive TST. Children were not offered TPT if they did not qualify per local guidelines. After excluding tuberculosis in the child and providing family education, the study team referred eligible children to community-based tuberculosis clinics for IPT. The study team documented IPT initiation at subsequent study visits and repeatedly referred uninitiated children to the tuberculosis clinic.

Comparisons between children who did and did not initiate IPT were performed using Pearson’s Chi-square and Wilcoxon rank sum tests. Comparisons were also performed between tuberculosis disease status using the same statistical tests. The association between co-variates and disease status (any disease, prevalent, or incident vs. no disease) was assessed using logistic regression while controlling for *M.tuberculosis* exposure.

The effectiveness of IPT was estimated in children who developed incident tuberculosis compared to children who remained disease free while considering other recognized clinical and epidemiological risk factors including age, gender, HIV status, BCG vaccination status, history of tuberculosis contact, and Mtb-sir-nodis. To understand how the effectiveness of IPT may vary across subgroups, sensitivity analysis was completed in children less than five years of age, children with reported tuberculosis exposure, and children with Mtb-sir-nodis. We also estimated the odds of tuberculosis with associated 95% confidence intervals (CI) and number needed to treat (NNT) for one person to avert tuberculosis. Children with prevalent tuberculosis were excluded from these analyses. We used SAS 9.4 (SAS Institute, Inc, Cary, NC, USA) for all analyses.

Research was conducted according to the principles of the World Medical Association Declaration of Helsinki. The research ethics committees of Stellenbosch University, Baylor College of Medicine, Case Western Reserve University, and local health authorities approved the study. Confidentiality of data was maintained at all times; only de-identified data were used.

RESULTS

Among 966 children who completed at least three months of study follow-up (median age at enrolment 5.07 years; IQR: 2.52, 8.72), 62% (601/966) were recruited from households of tuberculosis index cases, 22% (212/966) from households neighboring those of index cases, and 16% (153/966) from households affected by HIV (**Figure 1**). Seventy percent (676/966) of children had been exposed to an adult with tuberculosis. Notably, 22% (81/365) of children recruited from neighboring households reported tuberculosis exposure compared to 11% (17/153) of children recruited from households affected by HIV. Children with known exposure to an infectious tuberculosis index cases were nearly 2 times more likely (odds ratio [OR] =1.81 (95% CI: 1.36, 2.39) p<0.0001 to have Mtb-sir than children without known exposure (53.6% vs 39.0%, p<0.0001). Further, Mtb-sir was common in children recruited not only from households of known index cases (54%; 326/601), but also in children recruited from neighboring households (45%; 96/212) and households affected by HIV (35%; 53/153). Prevalent and incident tuberculosis was identified in children recruited from all three groups.

Tuberculosis was diagnosed among 10% (100/966) of children (**Table 1)**; most tuberculosis was prevalent (n=73) compared to incident (n=27). Bivariate analysis demonstrated strong associations between tuberculosis and younger age, exposure to an adult with tuberculosis, and Mtb-sir (**Table 1)**. Of note, 71% of prevalent and 78% of incident tuberculosis was observed in children less than 5 years of age.

While considering other factors that influence a child's risk of tuberculosis, children reporting recent exposure to a tuberculosis patient were nearly 4 times more likely to have prevalent

tuberculosis than their unexposed community-based peers selected based on geographic proximity (**Table 2**). Similarly, children with Mtb-sir were nearly 5 times more likely to have prevalent tuberculosis than children without Mtb-sir. Children were also more likely to have prevalent tuberculosis if they were younger and living with HIV. Compared to children less than three years of age, the risk of prevalent TB was reduced by 73% (OR=0.27; 95% CI 0.14, 0.52) in children 5 to <10 years of age and 85% (OR=0.15; 95% CI 0.0, 0.45) in children 10 to 15 years of age **(Supplemental Table 1)**. The risk of tuberculosis was not associated with gender or BCG vaccination status.

Within the entire cohort, 34% (326/966) of children were eligible for IPT in accordance with local guidelines previously outlined; 74% (240/326) initiated routinely offered IPT. Aligned with IPT eligibility criteria, children were more likely to initiate IPT if they were younger, or reported contact to a patient with tuberculosis (**Table 3**). Initiation of IPT was not associated with gender, TST positivity, HIV status, or a history of prior tuberculosis treatment.

More than 92% of children completed a six month study visit, while 70% completed a 15 month visit. Multivariable regression analysis demonstrated that children who initiated IPT were less likely to develop incident tuberculosis than children who did not (**Table 4**). The protective effect of IPT was greatest when controlling for the degree of tuberculosis exposure in adjusted model 2, (OR=0.18; 95% CI 0.06, 0.52; p=0.0014). Children's risk of developing incident tuberculosis increased if at baseline they were younger, living with HIV, reported known recent tuberculosis exposure, or had Mtb-sir-nodis. Compared to children less than three years of age, the risk of

incident TB was reduced by 82% (OR=0.18; 95% CI 0.06, 0.52) in children 5 to <10 years of age and 99% (OR=0.01; 95%CI <0.01, 0.25) in children 10 to 15 years of age **(Supplemental Table 2)**. Risk of incident tuberculosis was not associated with gender or BCG vaccination status. Sensitivity analysis completed in children <5 year of age, children with reported tuberculosis exposure, and children with Mtb-sir-nodis found similar associations and estimation of the protective effect of IPT (**Table 5).** Among the 130 participants living with HIV, 93% were receiving ART and 32% initiated IPT. Incident TB was captured in 6 children living with HIV of whom 83% were receiving ART and 0% initiated IPT.

The effectiveness of IPT was compared across subgroups of children with and without Mtb-sir-nodis, HIV infection, and known tuberculosis contact (**Figure 2**). IPT reduced the risk of incident tuberculosis by 82% in children with Mtb-sir-nodis (OR = 0.17; 95%CI 0.047, 0.660), 77% in children without HIV-infection (OR=0.234, 95% CI 0.083, 0.661), and 73% in children with known exposure to tuberculosis (OR=0.27, 95% CI 0.099, 0.775). In our entire cohort including children up to 15 years of age, 82 children would need to initiate IPT in order for one child to benefit by averting tuberculosis (NNT=82) (**Table 6**). The NNT from initiating IPT was lowest in children living with HIV (NNT = 15) and children less than five years of age (NNT = 19).

DISCUSSION

In an observational prospective cohort following nearly one thousand South African children, we demonstrate that children with known tuberculosis exposure who initiated TPT were up to 82% less likely to develop incident tuberculosis compared to children who did not initiate TPT.

The protective effect of TPT was greatest in children living with HIV and children <5 years of age as evident in a NNT <20 to prevent one child from developing tuberculosis. Additionally, the protective effect of TPT was similar in children with Mtb-sir-nodis regardless of reported tuberculosis exposure. We introduce the term Mtb-sir-nodis in contrast to "latent *M.tuberculosis* infection" (LTBI)[26], as the new term is less speculative and *M.tuberculosis* infection is often progressive and not persistently latent in children who are at high risk for active disease. TPT has traditionally targeted groups at highest risk of progression to active tuberculosis following household or other close exposure to tuberculosis including children <5 years of age and those living with HIV-infection [27]. Our evidence supports these existing strategies but also highlights important opportunities to improve the potential impact of TPT by increasing initiation among children with exposure to tuberculosis in both the household and community, and among children with Mtb-sir-nodis regardless of recent exposure.

Emerging evidence suggests that less than 20% of tuberculosis transmission among children and adults is due to household exposure in some settings [28, 29]. Further, as the majority of childhood tuberculosis identified via household contact investigation is co-prevalent with the index case [30], the value of preventive strategies dependent upon only household contact investigations is likely limited, particularly in settings with high rates of community transmission [31]. Our results lend credibility to these concerns as 73% of tuberculosis identified via household contact investigation was prevalent and 21% of children recruited from neighboring control households reported recent tuberculosis exposure.

Within our cohort, over one quarter of eligible children did not initiate TPT and 45% of children who did not meet local TPT eligibility criteria had Mtb-sir-nodis. Utilizing this observational comparison group, we demonstrate an 82% reduced risk of tuberculosis in children who initiated TPT compared to children who did not initiate TPT. In addition, subgroup analysis demonstrated that the protective effect of TPT was similar among children with tuberculosis exposure and children with Mtb-sir-nodis. This well-described, observational cohort affords a unique opportunity to examine TPT strategies that prioritize children with known tuberculosis exposure both within their households and their broader communities. The results demonstrate the potential impact of these strategies and supports current guidelines targeting children with reported household tuberculosis exposure [4]. Nevertheless, the effectiveness of strategies dependent upon a household contact approach are blunted by delays in case finding as highlighted in this study despite enrolment limited to children reporting exposure within the past 3 months. A recent study found that a community-wide screening intervention reduced tuberculosis by 44% at the population level [32]. Such an intervention, partnered with household contact tracing of exposed children, may both increase case detection among adults and target exposed children at high-risk to develop tuberculosis. Our results further show high rates of tuberculosis (8%) and Mtb-sir (39%) in children screened within the community, and highlight the need for preventive strategies uniquely targeting children at risk of non-household exposure to tuberculosis.

The increased risk of tuberculosis in children living with HIV is well recognized. Guidelines recommend that children living with HIV complete assessment for tuberculosis exposure and

symptom screening at every clinical encounter [33]. Nevertheless, emerging data from children and adolescents living with HIV demonstrates sub-optimal performance of facility-based symptom screening [34, 35]. In contrast, evidence from household contact tracing studies conducted in communities with high burdens of tuberculosis and HIV-infection demonstrates a 1.5-fold increase in disease identification in HIV-affected households compared to unaffected households [35]. Similarly, this study identified high rates of prevalent and incident tuberculosis in HIV-affected households regardless of known TB exposure. This study further demonstrates that IPT is highly effective among children living with HIV as only 15 children need to initiate IPT in order for one child to avert tuberculosis. Integration of TPT and community case finding strategies that prioritizes HIV-affected households could significantly reduce tuberculosis among children and adolescent living with HIV.

Reflecting the high annual risk of infection in this study setting, half of the cohort had Mtb-sir. Independent of reported tuberculosis exposure, children with Mtb-sir-nodis were nearly four times more likely to develop incident tuberculosis than peers without Mtb-sir-nodis. In contrast, recent evidence from a primarily adult cohort found no association between Mtb-sir-nodis and incident tuberculosis [36] likely reflecting the increased risk of recent infection in children. Although not required for initiation of TPT, WHO guidelines support the use of TST and IGRA in children living in low- and middle-income countries [37]. Coupled with evidence demonstrating that TPT is more effective in people with Mtb-sir-nodis compared to those without [38-41], our study results suggests that expansion of testing in high tuberculosis prevalence settings could improve the delivery of TPT targeting children at greatest risk of

progression to tuberculosis. However, when evaluated in our entire cohort including children up to 15 years of age, children free of HIV-infection, and children with no known tuberculosis contact living in a tuberculosis high-burden community, the NNT was higher in children with Mtb-sir-nodis compared to children without Mtb-sir-nodis; this observation highlights the need to consider children's Mtb-sir in the context of other risk factors including age and HIV status. Nevertheless, similar to adults[42], many children with incident TB had no detectable Mtb-sir at baseline illustrating the heterogeneous nature of immune responses which are poorly understood but possibly contribute to TB disease progression and response to therapy. Finally, the high costs of current tests of *M.tuberculosis* specific immunity limit the potential role of control strategies incorporating these tools in most high burden settings [43].

Despite our robust sample size and longitudinal study design, the data analysis has limitations. High rates of BCG vaccination in our study population may have contributed to positive TST results due to BCG vaccination rather than *M.tuberculosis* infection among younger study participants [44]; nevertheless, assessment of the *M.tuberculosis*-specific immune response using two IGRAs in combination with the TST limited this source of bias. We were unable to assess the influence of TPT adherence as data was incomplete and TPT was provided by community tuberculosis clinics as part of routine care. Based on past reports in the study communities [45], adherence to TPT was likely poor in this observational cohort and result in underestimation of the potential protective effect of TPT with improved adherence. Nevertheless, our results provide a realistic estimate of protective effectiveness outside of

clinical trials. Targeted recruitment of children from households of known tuberculosis index cases resulted in a cohort with 70% known tuberculosis exposure. As the majority of cases identified in this cohort were prevalent, estimates of TPT effectiveness to prevent incident tuberculosis was characterized by broad confidence intervals and the small number of incident cases in children >5 years of age precluded sensitivity analysis in this sub-group. Although several shorter and at least equally effective TPT regimens are now recommended that are associated with improved completion rates [8], IPT is still the most common regimen offered to eligible children in tuberculosis/HIV high-burden settings [6].

In conclusion, in communities with high tuberculosis prevalence, TPT substantially reduces the risk of tuberculosis among children who are young or living with HIV, especially those who have recent tuberculosis exposure or Mtb-sir-nodis regardless of known exposure to tuberculosis.

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Table 1: Baseline characteristics of children with and without tuberculosis

Variable	No Disease (n=866)	Prevalent tuberculosis (n=73)	Incident tuberculosis (n=27)	P-Value
Median Age years (IQR)	5.30 (2.69, 9.03)	3.30 (1.61, 5.25)	3.29 (1.19, 4.62)	<0.0001
Age				
0 to < 3 years	246 (28.4%)	34 (46.6%)	13 (48.2%)	<0.0001
3 to < 5 years	156 (18.0%)	18 (24.7%)	8 (29.6%)	
5 to < 10 years	292 (33.7%)	16 (21.9%)	6 (22.2%)	
10 to <= 15 years	172 (19.9%)	5 (6.8%)	0 (0%)	
Male Sex	401 (46.3%)	33 (45.2%)	12 (44.4%)	0.9675
HIV Infected	124 (14.3%)	13 (17.8%)	6 (22.2%)	0.3941
Prior TB Treatment	87 (10.1%)	7 (9.6%)	3 (11.1%)	0.9749
BCG Scar/History	739 (85.3%)	69 (94.5%)	25 (92.6%)	0.0569
TB Contact				
Any Contact*	598 (69.0%)	61 (83.6%)	17 (63.0%)	0.0248
Contact Score	4.0 (0.0, 6.0)	5.0 (2.0, 7.0)	4.0 (0.0, 5.0)	0.0025
Mtb-sir	407 (47.0%)	55 (75.3%)	13 (48.2%)	<0.0001

Abbreviations: IQR=Interquartile Ratio; HIV= Human Immunodeficiency Virus; IGRA = Interferon-γ release assay; TST = tuberculin skin test; Mtb-sir = *M. tuberculosis*-specific immune response (irrespective of tuberculosis disease status)

*Any contact was defined as a contact score > 0.

Table 2: Risk factors for prevalent tuberculosis in children

Variable	**Unadjusted Model** Odds ratio (95% CI) P-value	**Adjusted Model** Odds ratio (95% CI) P-value
Age (years)	0.86 (0.80, 0.92) <0.0001	0.82 (0.75, 0.90) <0.0001
Gender *Referent: female*	0.96 (0.59, 1.55) 0.8564	0.93 (0.56, 1.54) 0.7864
HIV status *Referent: not infected*	1.30 (0.69, 2.43) 0.4181	3.07 (1.21, 7.80.) 0.0183
BCG Scar/History *Referent: not vaccinated*	2.96 (1.06, 8.27) 0.0378	1.31 (0.42, 4.10) 0.6444
Tuberculosis contact *Referent: no contact*	2.28 (1.21, 4.30) 0.0111	3.79 (1.51, 9.49) 0.0045
Contact Score**	1.16 (1.07, 1.26) 0.0005	
Mtb-sir *Referent: absence of Mtb-sir*	3.44 (1.99, 5.96) <0.0001	4.88 (2.74, 8.68) <0.0001

Abbreviations: IPT = Isoniazid Preventive Therapy

** Results were similar in an adjusted model that considered a continuous measure of the degree of tuberculosis contact.

Table 3: Characteristics of children initiating and not initiating routine isoniazid preventive treatment (IPT)

Variable	IPT Initiated (n=276)	IPT not Initiated (n=617)	P-Value
Age (years)	3.0 (21.3, 51.8)	7.02 (4.0, 10.3)	<0.0001
Age			
0 - < 3 years	138 (50.0%)	121 (19.6%)	<0.0001
3 - < 5 years	94 (34.1%)	70 (11.4%)	
5 - < 10 years	40 (14.5%)	258 (41.8%)	
10 - <= 15 years	4 (1.4%)	168 (27.2%)	
Male Sex	129 (46.7%)	284 (46.0%)	0.8441
Living with HIV	41 (14.9%)	89 (14.4%)	0.8662
Prior TB Treatment	27 (9.8%)	63 (10.2%)	0.8516
TST positive	103 (37.7%)	241 (39.4%)	0.6290
TB Contact			
Any contact*	240 (87.0%)	375 (60.8%)	<0.0001
Contact score	5.0 (3.0, 6.0)	3.0 (0.0, 5.0)	<0.0001
Incident tuberculosis	6 (2.2%)	21 (3.4%)	0.3214
* Any Contact = Contact Score > 0			

Table 4: Effectiveness of isoniazid preventive therapy for the prevention of incident tuberculosis*

Variable	**Unadjusted Model** Odds ratio (95% CI) P-value	**Adjusted Model** Odds ratio (95% CI) P-value
IPT Initiated *Referent: not initiated*	0.63 (0.25, 1.58) 0.3254	0.22 (0.08, 0.60) 0.0033
Age (years)	0.78 (0.67, 0.90) 0.0007	0.68 (0.58, 0.81) <0.0001
Gender *Referent: female*	0.93 (0.43, 2.00) 0.8486	0.88 (0.40, 1.95) 0.7599
HIV status *Referent: not infected*	1.71 (0.68, 4.32) 0.2568	1.44 (0.43, 4.81) 0.5510
BCG Scar/History *Referent: not vaccinated*	2.15 (0.50, 9.18) 0.3022	0.51 (0.10, 2.52) 0.4080
Tuberculosis contact *Referent: no contact*	0.76 (0.34, 1.69) 0.5019	1.54 (0.51, 4.65) 0.4486
Contact Score**	1.01 (0.88, 1.15) 0.8919	
Mtb-siri-nodis *Referent: Mtb-sir-nodis absent*	1.05(0.49, 2.25) 0.9061	2.22 (0.95, 5.22) 0.0669

Abbreviations: Mtb-sir-nodis= *M. tuberculosis*- specific immune response- no disease

*Includes only children with incident tuberculosis (n=27) of whom 48% (13/27) had Mtb-sir-nodis at baseline

** Results were similar in an adjusted model that considered a continuous measure of the degree of tuberculosis contact.

Table 5: Protective effect of IPT derived from sensitivity analysis

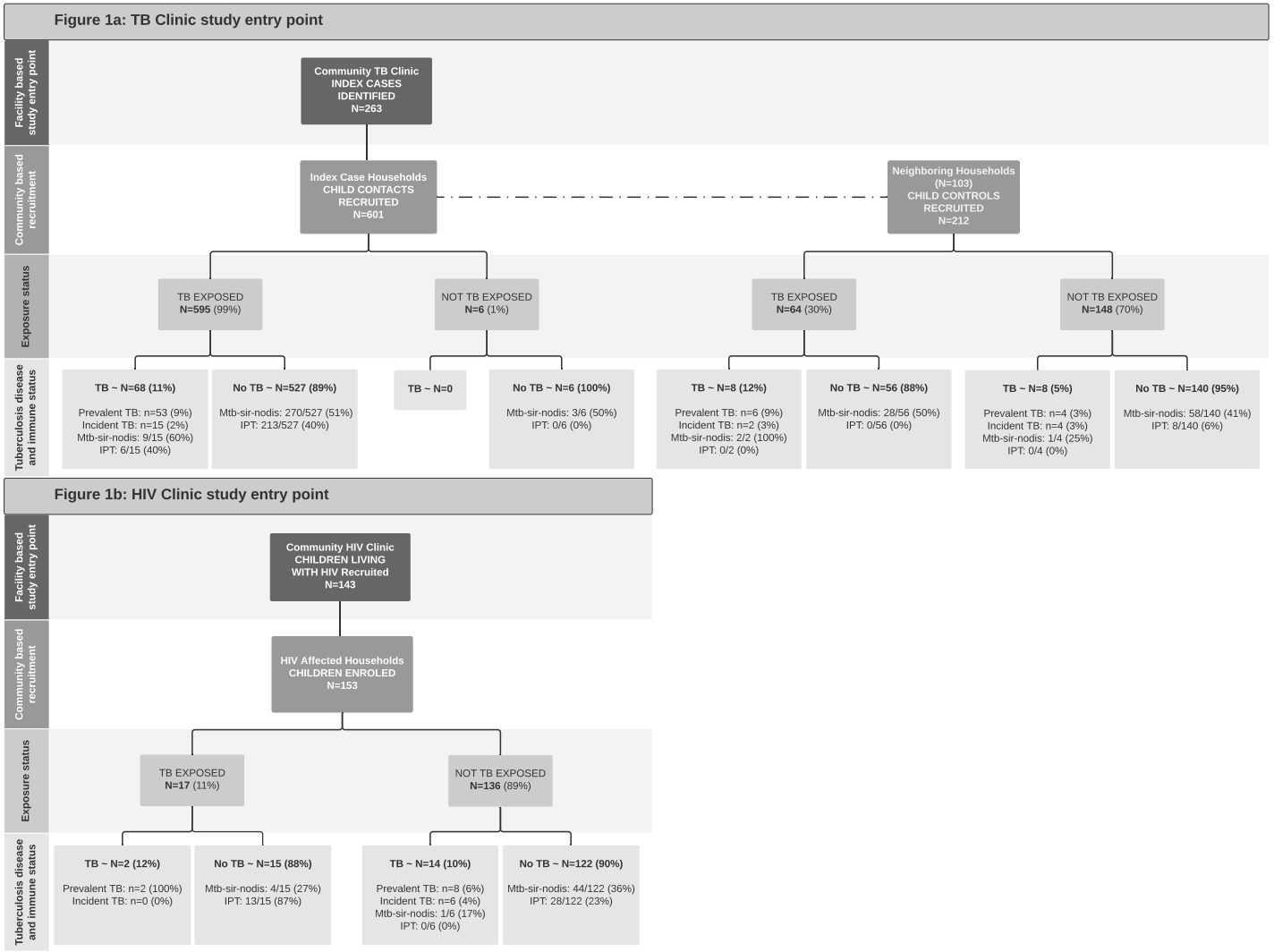
Risk factor	Analytic Group	Sample size	Odd Ratio (95% CI)	P-value
Age	Less than 5 years	423	0.19 (0.07,0.54)	<0.0019
TB exposure	Reported	615	0.23 (0.08,0.66)	<0.0067
Mtb-sir-nodis	Present	420	0.18 (0.05,0.66)	<0.0099

Table 6: Number needed to treat in order for one child to avert incident tuberculosis

Risk factor	Analytic Group	Sample size	Number needed to treat
AGE	All ages	893	82
	Less than 5 years	423	19
HIV	Living with HIV	130	15
	Free of HIV	763	348
TB CONTACT	Known contact	615	231
	NO known contact*	278	---
Mtb-sir-nodis	present	420	130
	absent	473	63

*unable to estimate due to limited sub-group sample size and incident tuberculosis cases.

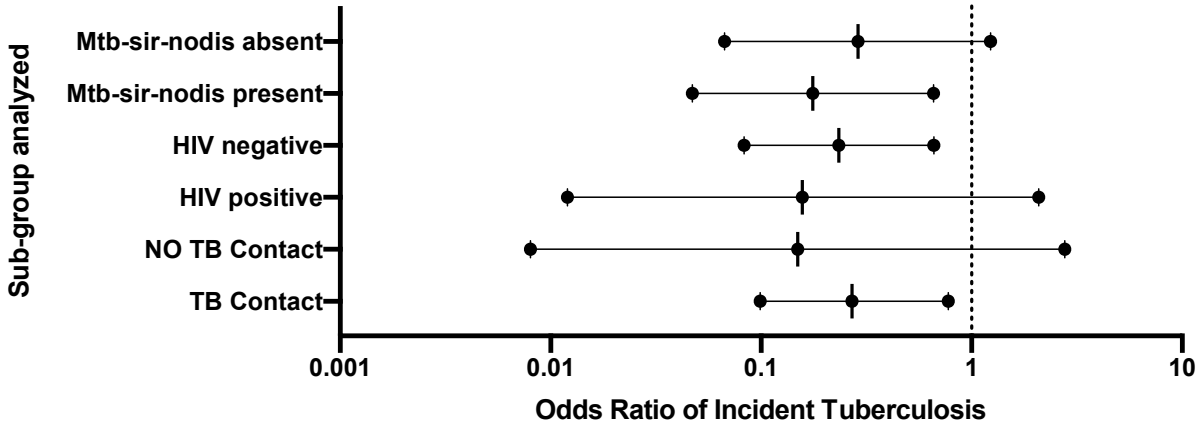
Figure 1: Prevalence of tuberculosis and a positive *M. tuberculosis*-specific immune response – no disease (Mtb-sir-nodis) in participants according to study entry point



LEGEND: The study employed two healthcare facility based entry points including local tuberculosis (TB) clinics (Figure 1a) and Human immunodeficiency virus (HIV) clinics (Figure 1b). Children were recruited from the homes of tuberculosis index cases (n=601) and from neighboring households (n=212). As homes often house several families in our study setting and residence can be transient, not all children in the home reported exposure to the index at the time of household contact investigation. HIV-infected children were recruited from HIV treatment clinics (n=153). Children with tuberculosis exposure, a positive *M.tuberculosis*-specific immune response in the absence of disease (Mtb-sir-nodis) at baseline, and tuberculosis were identified in all groups.

Abbreviations: IPT = isoniazid preventive therapy

Figure 2: Comparative Effectiveness of Isoniazid Preventive Therapy



LEGEND: Within each sub-group included in this analysis, the effectiveness of isoniazid preventive therapy (IPT) was estimated via calculation of an odds ratio. The odds ratio of incident tuberculosis (TB) represents the odds that a child will develop incident tuberculosis after initiating IPT, compared to the odds that a child will develop incident tuberculosis when IPT was not initiated. Along each horizontal line, the point estimate of the odds ratio is indicated by the central marker (●) and the 95% confidence interval surrounding the estimate is indicated by the outer markers (●- and -●). The x-axis utilizes a logarithmic scale with log spaced minor ticks to provide a symmetrical display of odd ratios greater than 1.0 and less than 1.0.

Abbreviations: HIV= Human Immunodeficiency Virus; Mtb-sir-nodis = *M. tuberculosis* - specific immune response – no disease

Supplemental Table 1: Risk factors for prevalent tuberculosis in children

Variable	**Adjusted Model 1**** Odds ratio (95% CI) P-value	**Adjusted Model 2**** Odds ratio (95% CI) P-value
Age		
0 to < 3 years	Ref	Ref
3 to < 5 years	0.71 (0.38, 1.34)	0.71 (0.39, 1.34)
5 to < 10 years	0.27 (0.14, 0.52)	0.27 (0.14, 0.52)
10 to <=15 years	0.15 (0.05, 0.45)	0.16 (0.05, 0.49)
	<0.0001*	0.0001*
Gender *Referent: female*	0.92 (0.56, 1.52) 0.7392	0.96 (0.58, 1.58) 0.8479
HIV status *Referent: not infected*	3.18 (1.25, 8.08) 0.0152	2.33 (1.04, 5.21) 0.0394
BCG Scar/History *Referent: not vaccinated*	1.54 (0.48, 4.95) 0.4735	1.65 (0.51, 5.31) 0.4018
Tuberculosis contact *Referent: no contact*	3.97 (1.58, 9.97) 0.0033	
Contact Score		1.17 (1.06, 1.30) 0.0020
Mtb-sir *Referent: absence of Mtb-sir*	5.08 (2.85, 9.08) <0.0001	4.61 (2.56, 8.29) <0.0001

* joint test of the age group variables; all groups were significantly different ($p<0.05$) except for 0 to < 3 years vs. 3 to < 5 years and 5 to < 10 years vs. 10 to <= 15 years

Supplemental Table 2: Effectiveness of isoniazid preventive therapy for the prevention of incident tuberculosis*

Variable	**Adjusted Model 1**** Odds ratio (95% CI) P-value	**Adjusted Model 2**** Odds ratio (95% CI) P-value
IPT Initiated *Referent: not initiated*	0.24 (0.09, 0.63) 0.0035	0.20 (0.08, 0.54) 0.0014
Age 0 to < 3 years 3 to < 5 years 5 to < 10 years 10 to <=15 years	 Ref 0.90 (0.37, 2.15) 0.18 (0.06, 0.52) 0.01 (<0.01, 0.25) 0.0011*	 Ref 0.87 (0.36, 2.09) 0.16 (0.42, 1.81) 0.01 (<0.01, 0.24) 0.0007*
Gender *Referent: female*	0.86 (0.42, 1.79) 0.6969	0.67 (0.42, 1.81) 0.7081
HIV status *Referent: not infected*	1.33 (0.43, 4.10) 0.6217	1.62 (0.56, 4.70) 0.3748
BCG Scar/History *Referent: not vaccinated*	0.45 (0.12, 1.72) 0.2421	0.48 (0.12, 1.87) 0.2903
Tuberculosis contact *Referent: no contact*	1.40 (0.51, 3.87) 0.5114	
Contact Score		1.14 (0.98, 1.34) 0.0983
Mtb-sir-nodis *Referent: Mtb-sir-nodis absent*	2.11 (0.96, 4.62) 0.0623	1.90 (0.86, 4.24) 0.1139

* joint test of the age group variables; all groups were significantly different ($p<0.05$) except for 0 to < 3 years vs. 3 to < 5 years and 5 to < 10 years vs. 10 to <= 15 years