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TUBERCULOSIS

Tuberculosis prevention in children: a prospective community-based study in South Africa

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In high TB burden communities, preventive therapy substantially reduces risk of TB among child contacts, especially those who are <5 years of age, living with HIV, recently TB exposed or have a positive *M. tuberculosis*-specific immune response https://bit.ly/3dKHpUc

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ABSTRACT Tuberculosis (TB) preventive therapy reduces TB risk in children. However, the effectiveness of TB preventive therapy in children living in high TB burden settings is unclear.

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

Among 966 children (median (interquartile range) age 5.07 (2.52–8.72) years), 676 (70%) reported exposure to an adult with TB in the past 3 months and 240 out of 326 (74%) eligible children initiated isoniazid preventive therapy under programmatic guidelines. Prevalent (n=73) and incident (n=27) TB were diagnosed among 100 out of 966 (10%) children. Children who initiated isoniazid preventive therapy were 82% less likely to develop incident TB than children who did not (adjusted OR 0.18, 95% CI 0.06–0.52; p=0.0014). Risk of incident TB increased if children were <5 years of age, living with HIV, had a positive *Mycobacterium tuberculosis*-specific immune response or recent TB exposure. The risk of incident TB was not associated with sex or *Mycobacterium bovis* bacille Calmette–Guérin vaccination status. Number needed to treat (NNT) was lowest in children living with HIV (NNT=15) and children <5 years of age (NNT=19) compared with children of all ages (NNT=82).

In communities with high TB prevalence, TB preventive therapy substantially reduces the risk of TB among children who are <5 years of age or living with HIV, especially those with recent TB exposure or a positive *M. tuberculosis*-specific immune response in the absence of disease.

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Introduction

The End TB Strategy calls for a 90% reduction in tuberculosis (TB) mortality and an 80% reduction in TB incidence by 2030 [1]. TB remains among the top 10 causes of mortality in children <5 years of age [2]. Without additional efforts for prevention in children, these goals are unlikely to be met [3]. In recent years, the World Health Organization (WHO) has increasingly emphasised TB preventive therapy (TPT) with multiple guidelines promoting household contact investigation and management to identify children at risk of TB [4, 5]. WHO surveillance has also demonstrated increased use of isoniazid preventive therapy (IPT), the most commonly used preventive treatment regimen in high TB burden settings. In 2018, 27% of eligible children reported initiating IPT following TB exposure compared with 7% in 2015 [6, 7]. At the 2018 UN high-level meeting on TB, 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 randomised controlled trials dating back to the 1940s 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 TB/HIV syndemic has amplified the force of *Mycobacterium tuberculosis* infection in Southern Africa, and may alter the effectiveness and durability of IPT, with limited post-antibiotic effect found in some trials [12]. Furthermore, there is limited recent evidence assessing the efficacy of TPT targeting children *via* household contact investigation outside of clinical trials, which have limited generalisability to TB programmes in high TB burden settings due to ethical limitations precluding randomisation to a placebo arm. Hence, observational cohorts present a unique opportunity to measure the impact of TPT compared with 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 <5 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, which 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 TB who were consecutively recruited throughout the accrual period lasting from December 11, 2007 to December 2, 2011, and follow-up ended on June 29, 2012. In the study setting, TB incidence was 741 per 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 TB, 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 tuberculin skin tests (TSTs) in children living with HIV.

Following informed consent of guardians and assent of children, participants were recruited from three communities where neonatal *Mycobacterium 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 as an adult with pulmonary or extrapulmonary TB were recruited within 3 months of index case identification in the public community TB clinic [19]. To measure background community TB transmission, children were recruited in a standardised fashion from community paediatric HIV clinics and neighbouring households, irrespective of TB 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 approached in a clockwise fashion until one neighbouring home agreed to participate. Among all children, exposure to an adult with TB 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 0–10 was assigned.

At enrolment, children simultaneously completed the TST (2 tuberculin units RT-23; Statens Serum Institute, Copenhagen, Denmark) and interferon-γ release assays (IGRAs), including QuantiFERON-TB Gold In-Tube (Qiagen, Venlo, The Netherlands) and T-Spot.*TB* (Oxford Immunotec, Oxford, UK); a subset of children ⩾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 ⩾10 mm in children without HIV and ⩾5 mm in

children living with HIV. IGRAs were interpreted following the manufacturers' guidelines. 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 TSTs or IGRAs were considered to have a positive Mtb-sir. The study team was blinded to the 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 TB, children completed evaluation for TB at baseline, 3, 6, 15 and 27 months after enrolment [21]. All children were screened for TB using standard symptom screening [22], chest radiography and mycobacterial culture of gastric aspirates or sputum at baseline, and again if clinically indicated during follow-up. Anteroposterior and lateral chest radiographs were read by two independent experts, blinded to clinical information, using a standard international paediatric TB radiological classification tool [23]. Prevalent TB was defined as a TB diagnosis made ⩽3 months from enrolment; incident TB was defined as TB diagnosed >3 months after enrolment. "A positive *M. tuberculosis*-specific immune response in the absence of active TB" was abbreviated as "Mtb-sir-nodis"; this classification is used to analyse baseline results of children who developed incident TB or remained disease free.

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

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

The effectiveness of IPT was estimated in children who developed incident TB compared with children who remained disease free while considering other recognised clinical and epidemiological risk factors, including age, sex, HIV status, BCG vaccination status, history of TB contact and Mtb-sir-nodis. To understand how the effectiveness of IPT may vary across subgroups, sensitivity analysis was completed in children <5 years of age, children with reported TB exposure and children with Mtb-sir-nodis. We also estimated the odds of TB with associated 95% confidence intervals and number needed to treat (NNT) for one person to avert TB. Children with prevalent TB were excluded from these analyses. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used 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 3 months of study follow-up (median (interquartile range) age at enrolment 5.07 (2.52–8.72) years), 62% (601 out of 966) were recruited from households of TB index cases, 22% (212 out of 966) from households neighbouring those of index cases and 16% (153 out of 966) from households affected by HIV (figure 1). 70% (676 out of 966) of children had been exposed to an adult with TB. Notably, 22% (81 out of 365) of children recruited from neighbouring households reported TB exposure compared with 11% (17 out of 153) of children recruited from households affected by HIV. Children with known exposure to an infectious TB index case were nearly two times more likely (OR 1.81, 95% CI 1.36–2.39; p<0.0001) to have Mtb-sir than children without known exposure (53.6% *versus* 39.0%; p<0.0001). Furthermore, Mtb-sir was common in children recruited not only from households of known index cases (54% (326 out of 601)) but also in children recruited from neighbouring households (45% (96 out of 212)) and households affected by HIV (35% (53 out of 153)). Prevalent and incident TB were identified in children recruited from all three groups.

Tuberculosis was diagnosed among 10% (100 out of 966) of children (table 1); most TB was prevalent (n=73) compared with incident (n=27). Bivariate analysis demonstrated strong associations between TB

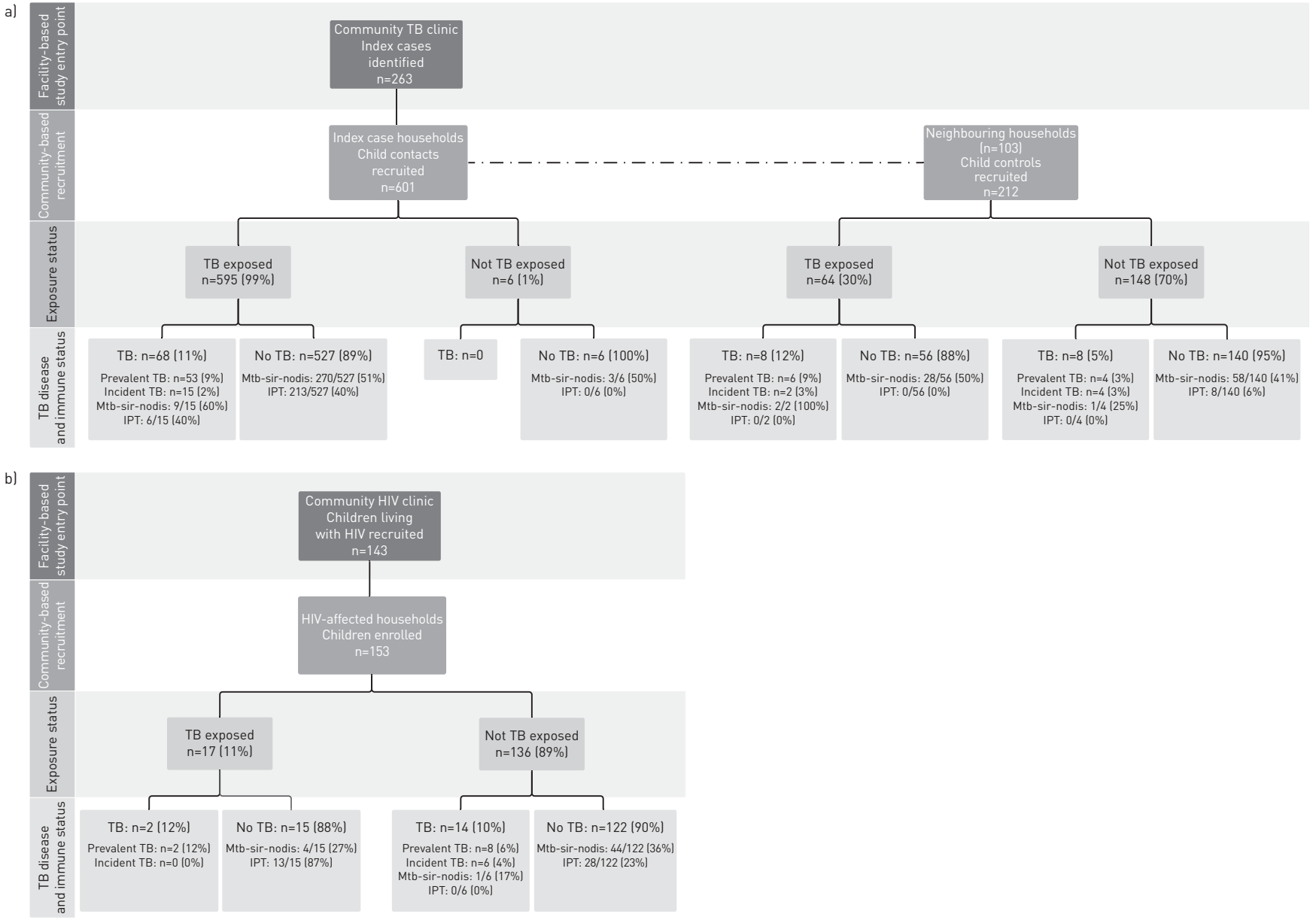

FIGURE 1 Prevalence of tuberculosis (TB) and a positive *Mycobacterium tuberculosis*-specific immune response in the absence of active TB (Mtb-sir-nodis) in participants according to the two healthcare facility-based entry points employed in the study: a) local TB clinics and b) HIV clinics. IPT: isoniazid preventive therapy. Children were recruited from the homes of TB index cases (n=601) and from neighbouring 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 TB exposure, Mtb-sir-nodis at baseline and TB were identified in all groups. Percentages may not total 100% due to rounding.

TABLE 1 Baseline characteristics of children with and without tuberculosis (TB)

	No disease	Prevalent TB	Incident TB	p-value
Subjects	866	73	27	
Age years	5.30 (2.69–9.03)	3.30 (1.61–5.25)	3.29 (1.19–4.62)	<0.0001
Age group years				
0–<3	246 (28.4)	34 (46.6)	13 (48.2)	<0.0001
3–<5	156 (18.0)	18 (24.7)	8 (29.6)	
5–<10	292 (33.7)	16 (21.9)	6 (22.2)	
10–15	172 (19.9)	5 (6.8)	0 (0)	
Male	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

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. BCG: bacille Calmette–Guérin; Mtb-sir: *Mycobacterium tuberculosis*-specific immune response (irrespective of TB disease status). [#]: any contact was defined as a contact score >0.

and younger age, exposure to an adult with TB and Mtb-sir (table 1). Of note, 71% of prevalent and 78% of incident TB was observed in children <5 years of age.

While considering other factors that influence a child's risk of TB, children reporting recent exposure to a TB patient were nearly four times more likely to have prevalent TB than their unexposed community-based peers selected based on geographic proximity (table 2). Similarly, children with Mtb-sir were nearly five times more likely to have prevalent TB than children without Mtb-sir. Children were also more likely to have prevalent TB if they were younger and living with HIV. Compared with children <3 years of age, the risk of prevalent TB was reduced by 73% (OR 0.27, 95% CI 0.14–0.52) in children 5–<10 years of age and 85% (OR 0.15, 95% CI 0.0–0.45) in children 10–15 years of age (supplementary table S1). The risk of TB was not associated with sex or BCG vaccination status.

Within the entire cohort, 34% (326 out of 966) of children were eligible for IPT in accordance with local guidelines previously outlined; 74% (240 out of 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 TB (table 3). Initiation of IPT was not associated with sex, TST positivity, HIV status or history of prior TB treatment.

More than 92% of children completed a 3-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 TB than children who did not (table 4). The protective effect of IPT was greatest when

TABLE 2 Risk factors for prevalent tuberculosis (TB) in children

	Unadjusted model		Adjusted model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age years	0.86 (0.80–0.92)	<0.0001	0.82 (0.75–0.90)	<0.0001
Sex (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
TB 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

BCG: bacille Calmette–Guérin; Mtb-sir: *Mycobacterium tuberculosis*-specific immune response (irrespective of TB disease status). [#]: results were similar in an adjusted model that considered a continuous measure of the degree of TB contact.

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

	IPT initiated	IPT not initiated	p-value
Subjects	276	617	
Age years	3.0 (1.8–4.3)	7.02 (4.0–10.3)	<0.0001
Age group years			
0–<3	138 (50.0)	121 (19.6)	<0.0001
3–<5	94 (34.1)	70 (11.4)	
5–<10	40 (14.5)	258 (41.8)	
10–15	4 (1.4)	168 (27.2)	
Male	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 TB	6 (2.2)	21 (3.4)	0.3214

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. TB: tuberculosis; TST: tuberculin skin test. [#]: any contact was defined as a contact score >0.

controlling for the degree of TB exposure in adjusted model 2 (OR 0.18, 95% CI 0.06–0.52; p=0.0014). Children's risk of developing incident TB increased if at baseline they were younger, living with HIV, reported known recent TB exposure or had Mtb-sir-nodis. Compared with children <3 years of age, the risk of incident TB was reduced by 82% (OR 0.18, 95% CI 0.06–0.52) in children 5–<10 years of age and 99% (OR 0.01, 95% CI <0.01–0.25) in children 10–15 years of age (supplementary table S2). Risk of incident TB was not associated with sex or BCG vaccination status. Sensitivity analysis completed in children <5 years of age, children with reported TB 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 antiretroviral therapy and 32% initiated IPT. Incident TB was captured in six children living with HIV, of whom 83% were receiving antiretroviral therapy and 0% initiated IPT.

The effectiveness of IPT was compared across subgroups of children with and without Mtb-sir-nodis, HIV infection and known TB contact (figure 2). IPT reduced the risk of incident TB by 82% in children with Mtb-sir-nodis (OR 0.17, 95% CI 0.05–0.66), 77% in children without HIV infection (OR 0.23, 95% CI 0.08–0.66) and 73% in children with known exposure to TB (OR 0.27, 95% CI 0.10–0.78). In our entire cohort including children up to 15 years of age, 82 children would need to initiate IPT in order for one

TABLE 4 Effectiveness of isoniazid preventive therapy (IPT) for the prevention of incident tuberculosis (TB)[#]

	Unadjusted model		Adjusted model	
	OR (95% CI)	p-value	OR (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
Sex (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
TB 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-sir-nodis (referent: Mtb-sir-nodis absent)	1.05 (0.49–2.25)	0.9061	2.22 (0.95–5.22)	0.0669

BCG: bacille Calmette–Guérin; Mtb-sir-nodis: *Mycobacterium tuberculosis*-specific immune response in the absence of active TB. [#]: includes only children with incident TB (n=27) of whom 48% (13 out of 27) had Mtb-sir-nodis at baseline; [¶]: results were similar in an adjusted model that considered a continuous measure of the degree of TB contact.

TABLE 5 Protective effect of isoniazid preventive therapy derived from sensitivity analysis

Risk factor	Analytic group	Sample size n	OR (95% CI)	p-value
Age	<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

TB: tuberculosis; Mtb-sir-nodis: *Mycobacterium tuberculosis*-specific immune response in the absence of active TB.

child to benefit by averting TB (NNT=82) (table 6). The NNT from initiating IPT was lowest in children living with HIV (NNT=15) and children <5 years of age (NNT=19).

Discussion

In an observational prospective cohort following nearly 1000 South African children, we demonstrate that children with known TB exposure who initiated TPT were up to 82% less likely to develop incident TB compared with 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 TB. Additionally, the protective effect of TPT was similar in children with Mtb-sir-nodis regardless of reported TB exposure. We introduce the term Mtb-sir-nodis in contrast to "latent *M. tuberculosis* infection" [24] 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 TB following household or other close exposure to TB, including children <5 years of age and those living with HIV infection [25]. 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 TB in both the household and community, and among children with Mtb-sir-nodis regardless of recent exposure.

Emerging evidence suggests that <20% of TB transmission among children and adults is due to household exposure in some settings [26, 27]. Furthermore, as the majority of childhood TB identified *via* household contact investigation is coprevalent with the index case [28], the value of preventive strategies dependent upon only household contact investigations is likely limited, particularly in settings with high rates of community transmission [29]. Our results lend credibility to these concerns as 73% of TB identified *via* household contact investigation was prevalent and 21% of children recruited from neighbouring control households reported recent TB exposure.

Within our cohort, over a quarter of eligible children did not initiate TPT and 45% of children who did not meet local TPT eligibility criteria had Mtb-sir-nodis. Utilising this observational comparison group, we demonstrate an 82% reduced risk of TB in children who initiated TPT compared with children who did

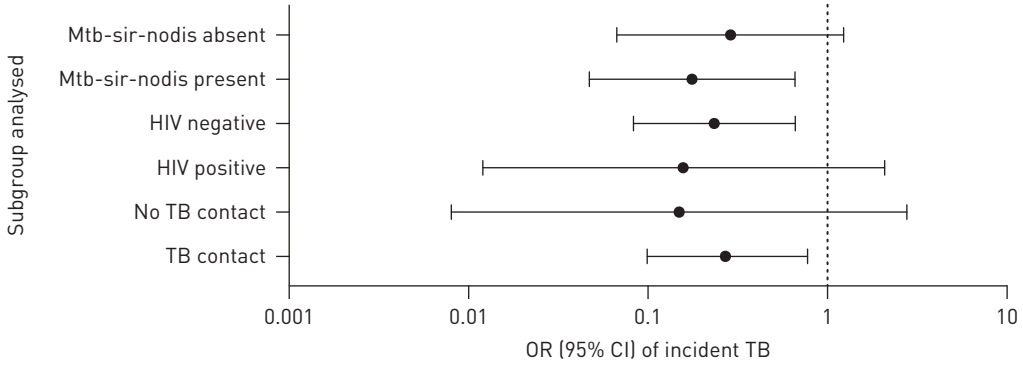

FIGURE 2 Comparative effectiveness of isoniazid preventive therapy (IPT). Within each subgroup included in this analysis, the effectiveness of IPT was estimated *via* calculation of an odds ratio. The odds ratio of incident TB represents the odds that a child will develop incident TB after initiating IPT compared with the odds that a child will develop incident TB when IPT was not initiated. Data are presented as point estimates with 95% confidence intervals; the *x*-axis utilises a logarithmic scale to provide a symmetrical display of OR >1.0 and <1.0. TB: tuberculosis; Mtb-sir-nodis: *Mycobacterium tuberculosis*-specific immune response in the absence of active TB.

TABLE 6 Number needed to treat (NNT) in order for one child to avert incident tuberculosis (TB)

Risk factor	Analytic group	Sample size n	NNT
Age	All ages	893	82
	<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

Mtb-sir-nodis: *Mycobacterium tuberculosis*-specific immune response in the absence of active TB. [#]: unable to estimate NNT due to limited subgroup sample size and incident TB cases.

not initiate TPT. In addition, subgroup analysis demonstrated that the protective effect of TPT was similar among children with TB exposure and children with Mtb-sir-nodis. This well-described, observational cohort affords a unique opportunity to examine TPT strategies that prioritise children with known TB 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 TB 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 TB by 44% at the population level [30]. 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 TB. Our results further show high rates of TB (8%) and Mtb-sir (39%) in children screened within the community, and highlight the need for preventive strategies uniquely targeting children at risk of nonhousehold exposure to TB.

The increased risk of TB in children living with HIV is well recognised. Guidelines recommend that children living with HIV complete assessment for TB exposure and symptom screening at every clinical encounter [31]. Nevertheless, emerging data from children and adolescents living with HIV demonstrates suboptimal performance of facility-based symptom screening [32, 33]. In contrast, evidence from household contact tracing studies conducted in communities with high burdens of TB and HIV infection demonstrates a 1.5-fold increase in disease identification in HIV-affected households compared with unaffected households [33]. Similarly, this study identified high rates of prevalent and incident TB 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 TB. Integration of TPT and community case-finding strategies that prioritises HIV-affected households could significantly reduce TB 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 TB exposure, children with Mtb-sir-nodis were nearly four times more likely to develop incident TB than peers without Mtb-sir-nodis. In contrast, recent evidence from a primarily adult cohort found no association between Mtb-sir-nodis and incident TB [34], likely reflecting the increased risk of recent infection in children. Although not required for initiation of TPT, the WHO guidelines support the use of the TST and IGRA in children living in low- and middle-income countries [35]. Coupled with evidence demonstrating that TPT is more effective in people with Mtb-sir-nodis compared with those without [36–39], our study results suggest that expansion of testing in high TB prevalence settings could improve the delivery of TPT, targeting children at greatest risk of progression to TB. 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 TB contact living in a high TB burden community, the NNT was higher in children with Mtb-sir-nodis compared with 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 [40], 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 TB burden settings [41].

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 [42]; 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 TB clinics as part of routine care. Based on past reports in the study communities [43], adherence to TPT was likely poor in this observational cohort and results 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 TB index cases resulted in a cohort with 70% known TB exposure. As the majority of cases identified in this cohort were prevalent, estimates of TPT effectiveness to prevent incident TB were characterised by broad confidence intervals and the small number of incident cases in children $\geqslant$5 years of age precluded sensitivity analysis in this subgroup. 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 high TB/HIV burden settings [6].

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

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