Clinical Infectious Diseases

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Risk of Tuberculosis Infection in Young Children Exposed to Multidrug-resistant Tuberculosis in the TB-CHAMP Multi-site Randomized Controlled Trial

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Background. Young children have a high risk of developing tuberculosis (TB) disease following infection with *Mycobacterium tuberculosis* in the absence of preventive treatment. Infection prevalence and risk factors for infection impact delivery of prevention strategies. We aimed to determine the prevalence of infection in child household contacts aged <5 years exposed to adults with confirmed pulmonary multidrug-resistant (MDR)-TB and to determine risk factors for infection.

Methods. TB-CHAMP was a trial of MDR-TB prevention that recruited children younger than age 5 years, regardless of *M. tuberculosis* infection status. All children enrolled had an interferon-gamma release assay (IGRA) at baseline. We described *M. tuberculosis* infection prevalence, developed directed acyclic graphs to clarify causal relationships, and used modified Poisson regression models to assess the relationship between risk factors and IGRA positivity.

Results. Of 785 included children, 160 (20.4%) had a positive IGRA. Duration of cough and drug misuse in the index patient, age of the child, relationship between the child and the index patient, and study site were significantly associated with risk of infection.

Conclusions. The prevalence of infection was lower than observed in previous studies. This may be related to improved diagnosis and treatment of MDR-TB in the study setting and/or test limitations and has implications for TB preventive treatment. When considering TB preventive treatment for child contacts, healthcare providers should be especially concerned about any young child exposed to an adult index patient who is his/her parent/primary caregiver, has a chronic cough, and/or a history of drug misuse.

Keywords. levofloxacin; risk factors; interferon-gamma release assays; preventive treatment; directed acyclic graphs; Poisson regression.

Young children have a high risk of developing tuberculosis (TB) disease following infection with *Mycobacterium tuberculosis* in the absence of TB preventive treatment (TPT) [1]. Multidrug-resistant (MDR)-TB, caused by *M. tuberculosis* resistant to isoniazid and rifampicin, is threatening global TB control [2]. An estimated 2 million children younger than age 15 years are currently infected with MDR-*M. tuberculosis* and approximately 30 000 develop MDR-TB disease each year [3]. To design effective strategies to prevent MDR-TB, it is important to understand the risk of infection as measured by current diagnostic tools, and the factors that determine this risk.

There is currently no diagnostic gold standard to measure *M. tuberculosis* infection. Various commercially approved tests of infection are available, including tuberculin skin tests, interferon-gamma release assays (IGRAs) and tuberculosis antigen-based skin tests. Although children with a negative test of infection may have a higher risk of disease progression than previously appreciated [4], children with a positive test of *M. tuberculosis* infection have a substantially higher 2-year cumulative TB disease incidence than children with a negative result [1].

Estimates of the prevalence of *M. tuberculosis* infection in household contacts (HHCs) of adults with infectious TB disease vary greatly. Estimates of prevalence of infection for HHCs younger than age 5 years of drug-susceptible TB in

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low- and middle-income countries vary from 16% to 53% [5–7]. The prevalence of infection in HHCs younger than age 5 years of age exposed to drug-resistant TB seems comparable, with prevalence varying from 44% to 59% [8–11].

The risk of *M. tuberculosis* infection in close child contacts has been positively correlated with factors relating to the child, the index patient (IP) and the environment [10, 12–15]. However, much of the work on risk of *M. tuberculosis* infection was completed more than a decade ago, with subsequent changes in the diagnosis and treatment of rifampicin-resistant (RR)/MDR-TB [16, 17], scale-up of effective human immunodeficiency virus (HIV) test-and-treat strategies, and increased availability of more acceptable antiretroviral regimens; and, in South Africa, access to rapid molecular testing for TB. It is therefore important to understand the contemporary risk of having a positive test of infection [1] and the factors that modulate this risk in child household RR/MDR-TB contacts in settings with a high burden of TB and HIV.

TB-CHAMP was a trial of MDR-TB prevention conducted in South Africa that recruited children younger than age 5 years of age regardless of *M. tuberculosis* infection status, and children aged 5–17 years with a positive IGRA or living with HIV. The trial investigated the efficacy and safety of 24 weeks of daily levofloxacin versus placebo. We estimated the prevalence of *M. tuberculosis* infection in child HHCs to be 40%, based on previous observational South African studies. The observed underlying incidence of TB disease in the control arm in TB-CHAMP was less than half of that expected, emphasizing the importance of understanding infection dynamics in children exposed to MDR-TB.

We aimed to determine the prevalence of *M. tuberculosis* infection in child HHCs aged <5 years exposed to adults with infectious pulmonary MDR-TB in the household and to determine risk factors for infection in these child contacts, in this large prevention trial.

METHODS

Setting

TB-CHAMP was conducted at 5 sites across 6 provinces in South Africa, all serving poorly resourced communities. The trial was conducted at the Desmond Tutu TB Centre (Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, Western Cape), the Perinatal HIV Research Unit (Matlosana Wits Health Consortium, Matlosana, North-West province), the Wits RHI Shandukani Research Centre (Johannesburg, Gauteng), and the Tuberculosis & HIV Investigative Network (Pietermaritzburg and Durban, KwaZulu-Natal). The fifth site that opened to accrual in the final year of the trial did not enroll children aged <5 years and is excluded from this analysis. South Africa has a high-burden country of TB, HIV-associated TB, and MDR-TB [2].

Trial Design

TB-CHAMP was a cluster-randomized, double-blind, placebo-controlled MDR-TB prevention trial, comparing levofloxacin (15–20 mg/kg) with placebo. Households were randomized 1:1 to either levofloxacin or placebo taken daily for 24 weeks. Follow-up was for 72 weeks in total [18]. The trial enrolled children between 27 September 2017 and 29 July 2022. Children <5 years were eligible regardless of their IGRA status at screening.

All children enrolled had an IGRA (QuantiFERON-Gold Plus: Qiagen) collected at baseline before study drug was initiated. IGRAs were collected and transported according to manufacturer's specifications, then analyzed at a single central certified trial laboratory (BARC Laboratories, South Africa). *M. tuberculosis* infection was defined as being QuantiFERON-Gold Plus positive, based on standard manufacturer guidelines.

Inclusion and Exclusion Criteria

Adult IPs were identified following a routine diagnosis of confirmed pulmonary MDR-TB and recruited if there was at least 1 child aged <5 years living in the same household in the previous 6 months. Children aged <5 years were recruited if exposure to the MDR-TB IP had been substantial in the preceding 6 months. Before enrollment, children were evaluated for prevalent TB disease with history, examination, and plain-film chest radiography, and respiratory sampling in the case of symptoms or abnormal chest radiographs. Only children in whom TB disease had been confidently excluded were enrolled. All randomized participants aged <5 years with documented IGRA status at baseline were included in this analysis.

Data Collection and Statistical Analysis

At screening, demographic, medical history, and substance use data were collected for all IPs, and demographic, medical history, TB exposure history, and clinical data were collected for all child participants. Socioeconomic data for each household were systematically collected.

The prevalence of IGRA positivity at baseline in child participants was described and compared between sites. Variables for analysis were identified based on biological plausibility and findings from prior studies [12, 14, 15]. These included factors relating to IPs (age, sex, duration of TB symptoms including cough, smoking, HIV status), child participants (age, sex, weight-for-age [WFA] *z*-score, duration of exposure to MDR-TB, relationship to the IP, HIV status, previous TPT or antibiotic use, recent hospitalization), household characteristics (number of household members, number of rooms, socioeconomic indicators) and study site. A per-household socioeconomic status (SES) score was developed by applying the published principle component analysis coefficients of questions in the South African Demographic and Health Survey 2016 [19], to applicable household characteristics of trial households. The TB-CHAMP household SES index was then

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translated to quintiles of Demographic and Health Survey households to enable a comparison of the SES of TB-CHAMP households to the general South African population, with the first quintile representing the lowest SES score (see Supplementary Appendix 2, Table 2). Directed acyclic graphs were drawn to help clarify causal relationships and identify a priori confounders and mediators [20], which were adjusted for in multivariable models (Supplementary Figure 1). The proportion of participants who were IGRA positive was described by each factor. Modified Poisson regression models were used to assess the relationship with IGRA positivity in univariable and multivariable analyses, with robust standard errors derived using a clustered sandwich estimator to allow for household clustering [21]. In the multivariable analysis of each potential risk factor, the model was adjusted for a priori confounders and study site (Supplementary Figure 1). Analyses were performed with Stata version 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX).

RESULTS

Description of Cohort

Of 839 children enrolled, 815 (97.1%) had an IGRA at baseline and 785 (93.6%) were included in analysis. Of children excluded, 24 had indeterminate IGRA results and 6 were late screen failures (initially enrolled but later found to have had TB at baseline) (Figure 1). Baseline characteristics of child HHCs (Table 1) were relatively uniform across the 4 sites. Overall, 50% were girls; median age was 2.5 years (interquartile range: 1.3–3.8); 42% of children were enrolled during and after the COVID-19 pandemic. One percent of children had HIV, 36% were HIV-exposed and uninfected, and 94% of children had received bacillus Calmette-Guérin (BCG) vaccine at birth (indicated by a scar or vaccination card). The median WFA z-score was −0.4 (interquartile range: −1.2 to 0.3). Overall, only 26% of households fell into the poorest 2 (1st, 2nd) SES score quintiles. For TB exposure history of child participants, see Supplementary Table 1.

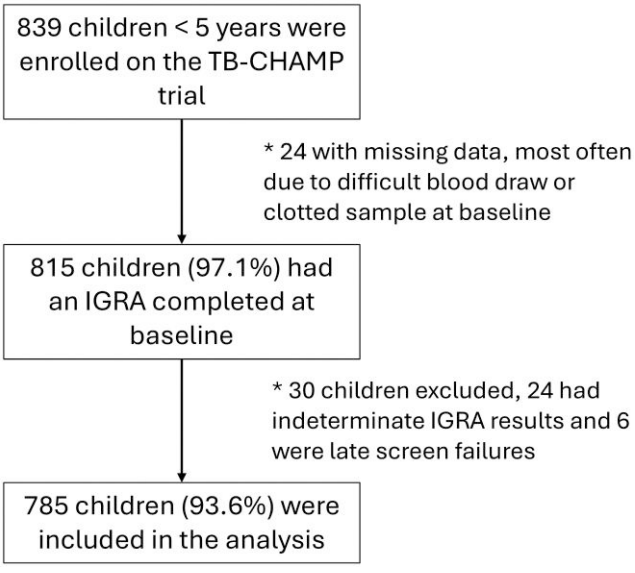

Figure 1. Flow of patients included in the analysis. Abbreviation: IGRA, interferon-gamma release assay.

IGRA Status at Baseline

Of 785 children included, 160 (20.4%) had a positive IGRA result (Table 1). IGRA results varied between sites, from 13% positivity (Matlosana, periurban) to 26% (Desmond Tutu TB Centre, urban, densely populated).

IGRA Status in Children Who Developed TB Disease

Of the 16 children younger than age 5 years who developed TB disease during follow-up, baseline IGRA status was positive in 6 and negative in 10; 6/160 (3.8%) of IGRA-positive children developed TB disease versus 10/625 (1.6%) of children with negative IGRA at baseline.

Directed Acyclical Graphs

Directed acyclic diagrams were drawn to identify a priori the confounding variables for estimating causal effects (Figure 2). Relationships between variables were found to be complex and interconnected. Some variables (infectiousness of the IP and the immune status of the child) could not be directly measured, but duration of cough in adults and presence of chronic illness/HIV/poor nutrition in child participants were used as proxies.

Risk Factors for Infection (Table 2, Figure 3)

IP Factors

In the univariable model, IPs' age and sex were associated with prevalence of infection (Table 2). In the multivariable models, only drug misuse in the past 6 months (risk ratio [RR], 1.49; 95% confidence interval [CI]: 1.01–2.21; $P = .047$) and longer duration of cough (>4 weeks; RR, 1.65; 95% CI: 1.20–2.26; <4 weeks; RR, 1.06; 95% CI: .73–1.56; $P = .006$, when compared with no cough) remained associated. No relationship was found between alcohol use, smoking, or HIV status of the IP and prevalence of infection in the child.

Child Factors

In univariable and multivariable analyses, only increasing age was linked to prevalence of infection in children (multivariable: 1 to <3 years; RR, 1.54; 95% CI: .99–2.40; to <5 years; RR, 1.80; CI: 1.16–2.77; $P = .030$, when compared with <1 year). Sex, WFA *z*-score, HIV status, previous TB treatment, and BCG immunization status showed no association.

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Table 1. Baseline Characteristics and IGRA Results of Child Participants Aged <5 y With Known Baseline IGRA Status, by Study Site

		DTTC	Shandukani	Matlosana	THINK	Total
N children randomized	N	377 (100%)	163 (100%)	232 (100%)	13 (100%)	785 (100%)
Sex	Male	191 (51%)	84 (52%)	112 (48%)	5 (38%)	392 (50%)
	Female	186 (49%)	79 (48%)	120 (52%)	8 (62%)	393 (50%)
Age (y)	Median (IQR[a])	2.5 (1.3, 3.9)	2.4 (1.1, 3.8)	2.8 (1.3, 3.8)	2.0 (1.2, 3.3)	2.5 (1.3, 3.8)
	range	0.1, 5.0	0.2, 5.0	0.1, 5.0	0.3, 4.3	0.1, 5.0
	<1	72 (19%)	34 (21%)	44 (19%)	3 (23%)	153 (19%)
	1 to <3	152 (40%)	62 (38%)	81 (35%)	4 (31%)	299 (38%)
	3 to <5	153 (41%)	67 (41%)	107 (46%)	6 (46%)	333 (42%)
HIV status	Positive	4 (1%)	5 (3%)	2 (1%)	0 (0%)	11 (1%)
	HIV-exposed but uninfected	114 (30%)	63 (39%)	93 (40%)	8 (62%)	278 (36%)
	HIV-negative	259 (69%)	95 (58%)	135 (59%)	5 (38%)	494 (63%)
	N missing	0	0	2	0	2
Bacillus Calmette-Guérin vaccination	No	24 (6%)	3 (2%)	19 (8%)	0 (0%)	46 (6%)
	Yes	350 (94%)	160 (98%)	212 (92%)	13 (100%)	735 (94%)
	N missing	3	0	1	0	4
Previously received TB treatment[a]	No	371 (98%)	162 (99%)	228 (98%)	13 (100%)	774 (99%)
	Yes	6 (2%)	1 (1%)	4 (2%)	0 (0%)	11 (1%)
Weight-for-age *Z* score[b]	N	377	163	232	13	785
	median (IQR[a])	−0.3 (−1.0, 0.5)	−0.3 (−1.0, 0.3)	−0.7 (−1.6, −0.1)	0.1 (−0.7, 0.8)	−0.4 (−1.2, 0.3)
SES score[c]	N	377	163	232	13	785
	median (IQR)	0.2 (−0.2, 0.5)	0.3 (−0.1, 0.5)	0.0 (−0.3, 0.3)	0.1 (−0.2, 0.1)	0.2 (−0.2, 0.4)
SES quintile[c]	1st	23 (6%)	1 (1%)	22 (9%)	0 (0%)	46 (6%)
	2nd	70 (19%)	24 (15%)	59 (25%)	4 (31%)	157 (20%)
	3rd	168 (45%)	90 (55%)	123 (53%)	8 (62%)	389 (50%)
	4th	116 (31%)	48 (29%)	28 (12%)	1 (8%)	193 (25%)
	5th	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Y of enrollment	Pre-2020	197 (52%)	84 (52%)	176 (76%)	0 (0%)	457 (58%)
	Post-2020	180 (48%)	79 (48%)	56 (24%)	13 (100%)	328 (42%)
IGRA test result[d]	Negative	279 (74%)	134 (82%)	201 (87%)	11 (85%)	625 (80%)
	Positive	98 (26%)	29 (18%)	31 (13%)	2 (15%)	160 (20%)

Abbreviations: HIV, human immunodeficiency virus; IGRA, interferon gamma release assay; IQR, interquartile range; SES, socioeconomic status.

[a]All treated for drug-sensitive tuberculosis, apart from 1 child with unknown relevant information.

[b]Standardized to the World Health Organization reference.

[c]SES status score derived from South Africa Demographic and Health Survey figures. SES quintiles range from the poorest (1st) to the wealthiest (5th). There were no households in the 5th quintile.

[d]For a small number of children aged <5 y without a test result at screening, test result up to wk 4 postrandomization was used.

Level of Exposure to M. tuberculosis

Univariable analysis showed a strong association between the prevalence of infection and sleeping in the same room/bed as the IP as well as the number of hours of daily exposure. This was not maintained in the multivariable model.

Relationship Between the IP and Child

The relationship of the IP to the child and whether the IP was the primary caregiver were strongly associated in univariable analysis, with the effect for relationship remaining significant in multivariable analysis. The highest risk in multivariable analysis was seen when the IP was the father of the child (father: RR, 1.58; 95% CI: .82–3.05; $P = .001$—IP is the mother is used as reference group). There was substantially higher risk of infection if the IP was either the mother or father, when compared with other family/nonfamily members.

Geographic and Household Factors

Study site was significantly related to the prevalence of infection in univariable and multivariable analysis, with child contacts from the Cape Town site having the highest prevalence of infection, and Matlosana the lowest (Matlosana: RR, 0.52; 95% CI: .35–.79; $P = .012$ when compared with Desmond Tutu TB Centre). Overcrowding and household SES score did not influence prevalence of infection in these child contacts.

DISCUSSION

We characterized the prevalence of *M. tuberculosis* infection in young children with MDR-TB exposure across diverse settings in South Africa. The observed prevalence of *M. tuberculosis* infection of 20% was lower than that observed in previous studies [8–11]. Factors that had a significant impact on prevalence of infection included duration of cough and drug misuse in the

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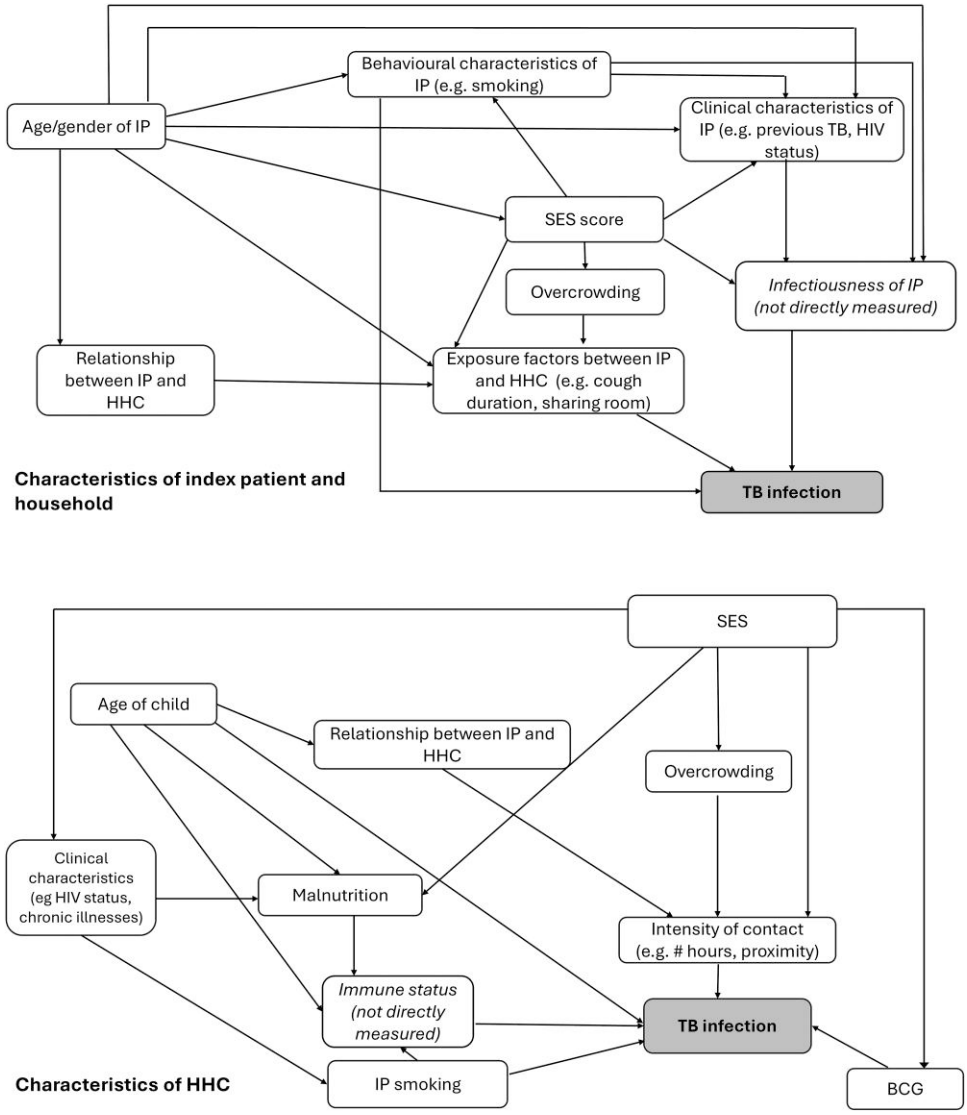

Figure 2. Directed acyclic graphs of the characteristics of the index patient (IP), the household and child household contact (HHC). Abbreviations: HHC, household contact; IP, index patient; SES, socioeconomic status; TB, tuberculosis.

IP, the age of the child, the relationship between the child and the IP, and the trial site where the child was enrolled.

There are several possible reasons to explain the lower-than-expected *M. tuberculosis* infection prevalence observed. South Africa was the first country to roll out Xpert MTB/RIF in 2011 and Xpert MTB/RIF Ultra in 2017 [22]. As these tools became increasingly available, it is likely that patients with RR/MDR-TB were diagnosed more rapidly, reducing duration of infectiousness. Since 2018, there has been widespread roll out of more effective MDR-TB treatment regimens (including bedaquiline and linezolid) in South Africa [16], which rapidly render IPs noninfectious [23, 24]. Contact management strategies for HHCs of adults with TB disease have also improved in South Africa over the past decade [25]. These changes would reduce the duration of exposure for HHCs and thus their risk of infection. All children screened for the trial were rigorously investigated for TB disease at baseline, and those considered to have TB disease excluded. Thus, the prevalence of *M. tuberculosis* infection reported here is for well children only. Several of the studies reporting higher prevalence of *M. tuberculosis* sensitization in child MDR-TB contacts included children with infection and disease [10, 11, 14], although this is unlikely to account for the markedly lower infection prevalence we observed.

Factors relating to the IP (age, chest radiograph disease severity, acid-fast bacilli smear-positive status, alcohol use, smoking), the child (age, sex, immune status, BCG vaccination status, and presence of other medical conditions), the level of *M. tuberculosis* exposure (being the parent or sleeping in the same room, duration of exposure), and environment (SES, presence of overcrowding) [7, 12, 26, 27] have all been

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Table 2. Univariate and Multivariate Analysis of Factors Affecting Risk of TB Infection for Participants Aged <5 y With Known Baseline IGRA Status

		Univariate Model				Multivariate Model		
		N	Infected N (%)	Risk Ratio (95% CI)	*P*-value	N	Risk Ratio (95% CI)	*P*-value
Index patient factors								
IP age (y)	<30	239	60/239 (25%)	1	.005	783	1	.055
	30–39	247	45/247 (18%)	0.73 (0.50–1.05)			.79 (.55–1.13)	
	40–49	158	40/158 (25%)	1.01 (0.68–1.50)			1.31 (.90–1.91)	
	≥50	141	15/141 (11%)	0.42 (0.25–0.71)			.73 (.43–1.23)	
IP sex	Male	312	48/312 (15%)	1	.012	783	1	0.103
	Female	473	112/473 (24%)	1.54 (1.10–2.16)			1.52 (.92–2.51)	
IP current cough duration	No current cough	390	69/390 (18%)	1	.063	777	1	0.006
	Current cough <4 wks	171	33/171 (19%)	1.09 (0.72–1.65)			1.06 (.73–1.56)	
	Current cough ≥4 wks	218	58/218 (27%)	1.50 (1.06–2.13)			1.65 (1.20–2.26)	
IP previously treated for TB disease	No	341	66/341 (19%)	1	.572	780	1	0.140
	Yes	444	94/444 (21%)	1.09 (0.80–1.49)			1.25 (.93–1.67)	
IP smoked regularly in last 6 m	No	471	96/471 (20%)	1	.968	781	1	0.994
	Yes	312	64/312 (21%)	1.01 (0.73–1.38)			1.00 (.73–1.38)	
IP drug misuse in last 6 m	No	649	127/649 (20%)	1	.262	781	1	.047
	Yes	134	33/134 (25%)	1.26 (0.84–1.88)			1.49 (1.01–2.21)	
How often IP drinks alcohol	Never/rarely	557	127/557 (23%)	1	.056	781	1	.421
	Once per wk	120	18/120 (15%)	0.66 (0.41–1.06)			.84 (.53–1.35)	
	Many times per wk	106	15/106 (14%)	0.62 (0.38–1.02)			.75 (.47–1.20)	
IP HIV status	Positive	513	94/513 (18%)	1	.077	780	1	.283
	Negative	271	66/271 (24%)	1.33 (0.97–1.82)			1.18 (.87–1.61)	
Child factors								
Age (y)	<1	153	20/153 (13%)	1	.038	779	1	.030
	1–<3	299	63/299 (21%)	1.61 (1.03–2.53)			1.54 (.99–2.40)	
	3–<5	333	77/333 (23%)	1.77 (1.14–2.74)			1.80 (1.16–2.77)	
Sex	Male	392	83/392 (21%)	1	.571	779	1	.672
	Female	393	77/393 (20%)	0.93 (0.71–1.21)			.94 (.72–1.23)	
Weight for age *z*-score	<−2	80	19/80 (24%)	1	.407	775	1	.717
	−2 to < −1	152	29/152 (19%)	0.80 (0.47–1.37)			.99 (.61–1.60)	
	−1 to 0	276	50/276 (18%)	0.76 (0.45–1.29)			1.04 (.66–1.65)	
	0 to <1	191	47/191 (25%)	1.04 (0.61–1.76)			1.25 (0.79–1.98)	
	≥1	86	15/86 (17%)	0.73 (0.38–1.44)			1.10 (.59–2.04)	
HIV status	HIV-negative	494	102/494 (21%)	1	.325	775	1	.150
	HIV-exposed but uninfected	278	54/278 (19%)	0.94 (0.69–1.29)			.75 (.56–1.00)	
	HIV-positive	11	4/11 (36%)	1.76 (0.79–3.94)			.94 (.41–2.13)	
Previously received TB disease treatment	No	774	156/774 (20%)	1	.144	775	1	.421
	Yes	11	4/11 (36%)	1.80 (0.82–3.99)			1.34 (.66–2.74)	
BCG immunization	No	46	13/46 (28%)	1	.154	773	1	.505
	Yes	735	144/735 (20%)	0.69 (0.42–1.15)			.86 (.56–1.34)	
Level of exposure								
Slept in same room/bed as IP	Not same room	485	63/485 (13%)	1	<.001	777	1	.386
	Same room, not same bed	76	20/76 (26%)	2.03 (1.30–3.17)			1.35 (.84–2.19)	
	Slept same bed	224	77/224 (34%)	2.65 (1.97–3.56)			1.04 (.69–1.58)	
Average number of h per day spent with IP	0–4 h	125	15/125 (12%)	1	<.001	777	1	.678
	5–8 h	205	25/205 (12%)	1.02 (0.56–1.85)			.96 (.52–1.77)	
	9–12 h	141	24/141 (17%)	1.42 (.79–2.54)			1.09 (.59–2.02)	
	More than 12 h	314	96/314 (31%)	2.55 (1.56–4.16)			1.28 (.70–2.34)	
Relationship between index patient and contact								
Relationship of index patient	Mother	129	60/129 (47%)	1	<.001	777	1	.001
	Father	74	25/74 (34%)	.73 (.50–1.06)			1.58 (.82–3.05)	
	Other family member	491	65/491 (13%)	.28 (.21–.38)			.53 (.33–.86)	
	Other nonfamily member	91	10/91 (11%)	.24 (.13–.42)			.45 (.22–.93)	

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Table 2. Continued

		Univariate Model				Multivariate Model		
		N	Infected N (%)	Risk Ratio (95% CI)	*P*-value	N	Risk Ratio (95% CI)	*P*-value
Whether IP is primary caregiver	Primary carer	160	72/160 (45%)	1	<.001	777	1	.081
	Not primary carer, regularly cares	372	56/372 (15%)	.33 (.25–.45)			.64 (.41–.98)	
	Neither	251	32/251 (13%)	.28 (.19–.42)			.58 (.34–1.00)	
Environmental factors								
Site	DTTC	377	98/377 (26%)	1	.006	782	1	.012
	Shandukani	163	29/163 (18%)	.68 (.47–1.00)			.75 (.51–1.12)	
	Matlosana	232	31/232 (13%)	.51 (.34–.77)			.52 (.35–.79)	
	THINK	13	2/13 (15%)	.59 (.22–1.61)			.57 (.22–1.45)	
Overcrowding	No	313	70/313 (22%)	1	.305	777	1	.708
	Yes	472	90/472 (19%)	.85 (.63–1.16)			.94 (.70–1.28)	
SES status								
SES quintile	1st	46	11/46 (24%)	1	.099	783	1	.151
	2nd	157	41/157 (26%)	1.09 (.63–1.91)			1.12 (.65–1.93)	
	3rd	389	64/389 (16%)	.69 (.40–1.18)			.75 (.43–1.31)	
	4th	193	44/193 (23%)	.95 (.55–1.66)			.93 (.52–1.66)	

Abbreviations: ART, antiretroviral therapy; BCG, bacillus Calmette–Guérin; CI, confidence interval; HIV, human immunodeficiency virus; IP, index patient; SES, socioeconomic status; TB, tuberculosis.

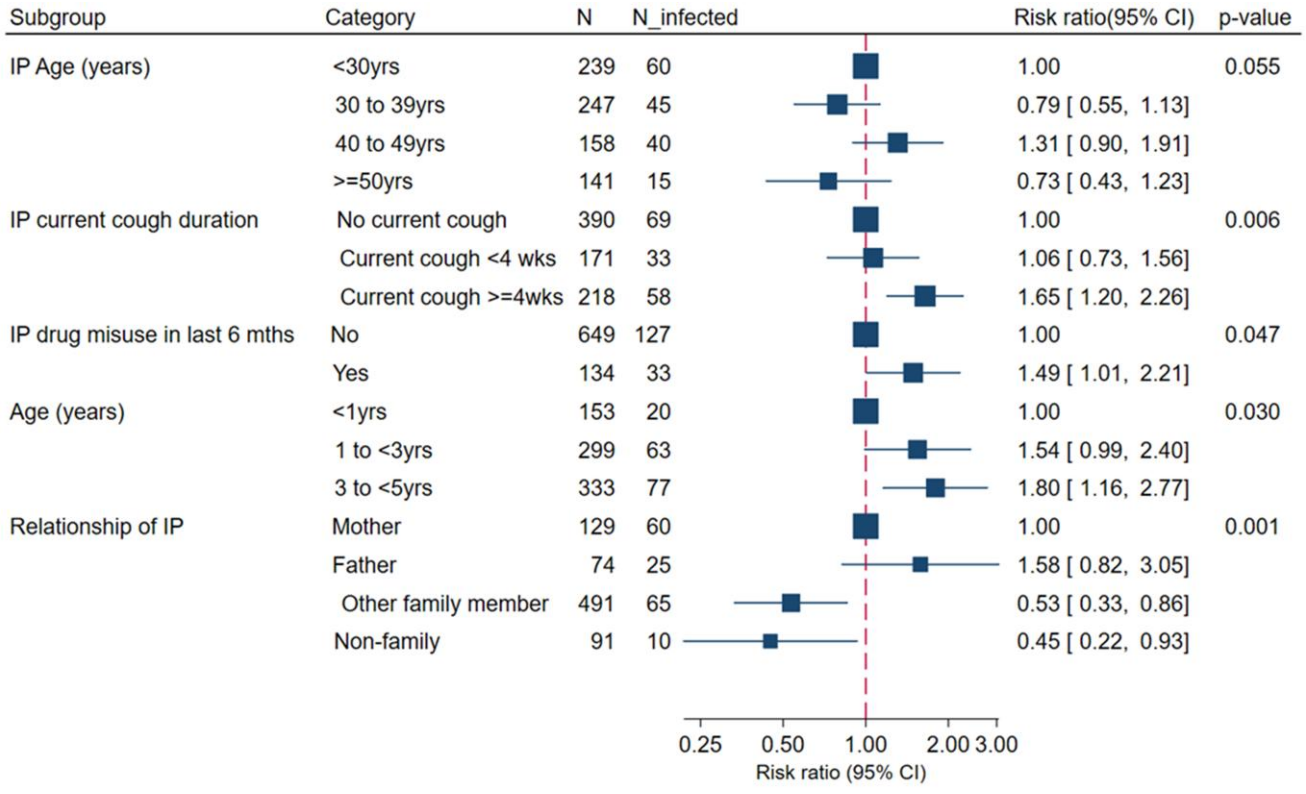

Figure 3. Forest plot showing variables associated with risk of infection on multivariate analysis. Abbreviations: CI, confidence interval; IP, index patient.

correlated with increased prevalence of *M. tuberculosis* infection in children in previous studies. In our study, increased duration of cough and drug misuse in the IP, older age of the child and a close relationship between the child and the IP showed significant association on multivariable analysis, after controlling for potential confounders. Although univariable analysis

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showed a strong association between prevalence of infection and sleeping in the same room/bed as the IP and the hours of daily exposure, this was not maintained in multivariable analysis, likely due to the strong influence of relationship between the IP and child contact on the level of exposure. Univariable analysis also identified mothers who were IPs as posing the highest risk to child contacts, but the risk was higher for fathers in multivariable analysis. There is likely to be collinearity between some of the factors relating to exposure of the child to the IP, making it challenging to assess their associations with TB infection status individually.

Infection rates varied considerably between sites, likely due to differences in risk factors (such as TB and HIV epidemiology, socioeconomic factors, healthcare practices, recruiting strategies, climate and genetic differences) that were not accounted for in our models. There appears to be an association between sites and the household SES score, which varied substantially between sites. In multivariable analysis, however, the standard errors of the estimates for the SES quintiles (as well as the corresponding global *P*-value) were similar in the models with and without adjustment for sites, suggesting collinearity was not an issue here. Our finding that relative SES was not associated with young children's TB infection status is surprising. It is possible that there is threshold level of deprivation below which further deprivation does not incur a greater risk for infection. Additionally, the single numerical SES score derived from the national South African population may not be sufficiently sensitive to reflect specific SES factors associated with increased infection risk. Importantly, this finding does not indicate that SES has no impact on the risk of *M. tuberculosis* infection, but that further work is required to better reflect the complexities of SES in relation to clinical outcomes of exposure of a young child to a household IP with TB.

Of note, of children who developed TB disease, more than half were IGRA negative at baseline. IGRAs are limited by reduced sensitivity in children younger than age 5 years, low predictive value for progression to TB disease, and multiple sources of variability if repeated [4, 20, 21]. IGRA results may have been negative due to very recent infection. There are several new tests of *M. tuberculosis* infection in the pipeline, but none are yet able to distinguish the continuum of *M. tuberculosis* infection or predict TB disease [22]. Biomarker-guided TPT is showing promise, with some signatures able to predict risk of disease progression [23]. More sensitive tools including novel biomarkers are needed to identify prevalence of infection and future disease progression to better guide prevention strategies.

Despite the robust sample size and collection of detailed data, our analysis was cross-sectional and limited to children younger than age 5 years. Repeating IGRAs may have yielded test conversion. Given the modest number of incident TB end points, stratified analysis by IGRA status was limited, and we could not assess the predictive utility of IGRA for incident TB disease. We used routine microbiological data reported from the national TB program to determine eligibility of IPs, but these results were not captured, and we did not complete additional microbiological testing or chest radiography in IPs. We were thus unable to assess additional measures of infectiousness of IPs beyond duration of cough. Child contacts who were screened out with likely TB disease were excluded from analysis. Thus, children included in this trial do not represent all children exposed to adults with MDR-TB in the household. Finally, the SES score we used summarized complex SES information into a single score and may not reflect the complex dynamic of different dimensions of SES on TB infection risk.

The World Health Organization now recommends levofloxacin as TPT in all close MDR-TB contacts once TB disease has been excluded, regardless of *M. tuberculosis* infection status [24]. Children younger than age 5 years remain a population of high priority given their risk of disease progression and severe forms of TB. The low prevalence of *M. tuberculosis* infection in child MDR-TB contacts seen in TB-CHAMP has implications. As infection is a prerequisite for disease, low infection prevalence implies less progression to TB disease. This also implies decreased absolute efficacy of TPT in a strategy where TPT is recommended for all contacts. That many IGRA-negative children developed TB disease in the trial suggests that the use of IGRA to predict disease progression is limited and better tests are needed to identify those at highest risk. Although TPT is now recommended for all MDR-TB contacts, children younger than age 5 years exposed to an infectious adult who is the parent/primary caregiver are at especially high risk of developing TB disease and should be prioritized in TB prevention programs.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. S. P. wrote the paper with support from J. A. S., A. C. H., H. S. S., T. D., and J. B. led the statistical analysis, with support and oversight from T. D. All authors reviewed the submitted and final version of the manuscript and approved of it.

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Data availability. Deidentified data set is available upon request, to researchers with approval for the proposed use of the data, and to policymakers.

Ethical considerations. The trial was approved by the Health Research Ethics Committee of Stellenbosch University (M16/02/009) and the University of the Witwatersrand (160409), the South African Health Products Regulatory Agency (20160128), and the South African Department of Health (DOH-27-0117-5309) and was registered in the ISRCTN registry (ISRCTN92634082). Informed consent was provided by

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all IPs and participants' parents or legal guardians. Data were stored using unique anonymized participant identifiers.

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