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Resistance to *Mycobacterium tuberculosis* Infection Among Household Contacts: A Multinational Study

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Background. Some contacts of patients with tuberculosis remain negative on tests for tuberculosis infection, despite prolonged exposure, suggesting they might be resistant to *Mycobacterium tuberculosis infection*. The objective of this multinational study was to estimate the proportion of household contacts resistant to *M. tuberculosis* (resisters).

Methods. We conducted a longitudinal study enrolling index patients enrolled in treatment for pulmonary multidrug- or rifampin-resistant tuberculosis and their household contacts. Contacts were tested for tuberculosis infection with a tuberculin skin test (TST) and interferon-gamma release assay (IGRA) at baseline and after 1 year. Exposure was quantified based on index patients' infectiousness, index patient and household contact interaction, and age. We explored multiple definitions of resistance to tuberculosis infection by varying TST negativity cutoffs (0 vs <5 mm), classification of missing test results, and exposure level.

Results. In total, 1016 contacts were evaluated from 284 households; 572 contacts aged ≥5 years had TST and longitudinal IGRA results available. And 77 (13%) or 71 (12%) contacts were classified as resisters with a <5 mm or 0 mm TST threshold, respectively. Among 263 highly exposed contacts, 29 (11%) or 26 (10%) were classified as resisters using TST cutoffs of <5 mm and 0 mm, respectively. The prevalence of resisters did not differ substantially by sex, age, human immunodeficiency virus (HIV) coinfection, or comorbid conditions.

Conclusions. At least 10% of household contacts can be classified as resistant to tuberculosis infection, depending on the definition used, including those with high exposure. Further studies to understand genetic or immunologic mechanisms underlying the resister phenotype may inform novel strategies for therapeutics and vaccines.

Keywords. tuberculosis; infection; exposure; resisters.

INTRODUCTION

Tuberculosis (TB) is a major public health problem and the leading cause of infectious disease-related mortality globally. In 2018, an estimated 10 million people fell ill with TB, and 1.2 million people with TB died worldwide [1]. An additional 23–32% of the world's population is infected with *Mycobacterium tuberculosis (Mtb)* and can remain asymptomatic for decades (ie, TB infection) [2]. Although risk factors for infection with *Mtb* and progression to active TB disease have been identified, 10–50% of household contacts (HHCs) of TB patients remain negative on tuberculin skin test (TST) despite substantial exposure (eg, living in the same house or same room) to an infectious source case [3–5]. These individuals may be resistant to *Mtb* infection, commonly referred to as *resisters* or *resister phenotype*. Limited knowledge about factors that mediate resistance to *Mtb* infection after exposure to an infectious case has hampered development of prevention measures for TB, including a TB vaccine [6, 7].

Challenges in identifying individuals who are truly infected with *Mtb*, given the lack of a gold standard for determining TB infection, have limited rigorous research of resister phenotype to date. The 2 main methods used for the diagnosis of TB infection are TST and interferon-gamma release assays (IGRA) [5, 8, 9]. However, both methods measure the immune response to *Mtb*, rather than the infection itself. Some of the disadvantages of these methods are false negativity due to anergy, persistent positivity after clearance of infection, and false-positivity of TST due to nontuberculosis mycobacteria and Bacillus Calmette-Guérin (BCG) vaccination [10, 11]. In addition, discordance

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between TST and IGRA is common and ranges from 8% to 15% [12–14], making clinical interpretation challenging.

Similar to measuring TB infection, the objective measurement of TB exposure is also challenging. Although a validated TB exposure risk score has been developed for children [15], there is no standard methodology for assessing the extent of exposure across all ages and in diverse epidemiological settings, making it difficult to distinguish between resisters and those who are TST- or IGRA-negative due to insufficient exposure. Exposure to *Mtb* is affected both by clinical characteristics of the index patient (bacillary burden, or presence of cavities as clinical proxy) and the intensity and duration of exposure, such as proximity of contact and ventilation in the home [16, 17].

In preparation for an interventional trial, a longitudinal study was conducted to investigate the feasibility of identifying, recruiting, and characterizing adult index patients and their HHCs. Using data from this study, we aimed to: (1) estimate the proportion of household contacts of rifampicin-resistant (RR) and multidrug-resistant (MDR) TB patients who might be resistant to *Mtb* infection, using varying definitions of infection and exposure; and (2) evaluate factors associated with resistance to *Mtb* among HHCs.

METHODS

Study Design and Setting

A multicenter longitudinal study was conducted during 2015–2017 at 16 study sites in 8 high and middle TB burden countries worldwide: Botswana (1 site), Brazil (1), Haiti (1), India (2), Kenya (1), Peru (2), South Africa (7), and Thailand (1). These sites are now participating in a randomized clinical trial to test the safety and efficacy of a novel drug, delamanid, compared to standard of care isoniazid, for prevention of TB among HHCs (NCT03568383).

Study Population

The study population consisted of a convenience sample of adult index patients who initiated treatment for pulmonary RR/MDR-TB within 6 months preceding study enrollment, and their HHCs. A HHC was defined as a person who lived in the same dwelling unit or plot of land as the index patient and shared the same housekeeping arrangements. Further details about eligibility and enrollment of index patients and HHCs are provided in the methods section of the supplementary material and have been previously described elsewhere [18].

Data Collection

Data collection procedures in the parent study have been previously described and details are also provided in the supplementary material [18]. HHCs were tested for TB infection by TST and/or IGRA using QuantiFERON Gold or Gold-in-tube (Qiagen, Venlo, The Netherlands). TST was not performed at 2 study sites in Peru and 1 study site in South Africa due to reagent shortages. Quantitative results for IGRA were not recorded, and results <0.35 IU/mL were classified as negative. Among HHCs ≥5 years of age with a negative or missing result on IGRA at baseline, IGRA was repeated at 1 year of follow-up. Because the focus of the parent study was to inform the upcoming clinical trial, repeated testing was not performed among children <5 considering that this subpopulation is considered high risk regardless of their LTBI testing results. TST was not repeated in any age group. Previous human immunodeficiency virus (HIV) testing and TB history in HHCs was obtained through self-report during interviews. An HIV test was performed for those with unknown HIV status or last negative result documented more than 1 year prior to study entry. All HHCs not already on TB treatment were screened for active TB both at baseline and after 1-year follow-up with a symptom questionnaire, chest radiograph, and a collected sputum sample, as well as a gastric aspirate for children, if disease was suspected.

Definitions of Exposure and Resistance to *Mtb*

The primary outcome of interest was resistance to *Mtb* infection among adult and child HHCs ≥5 years of age. Inclusion criteria for the main analysis were the following: (1) age ≥5 years; (2) available TST result at baseline; and (3) complete IGRA result, defined as either positive IGRA result at baseline or valid results from 1-year follow-up testing (ie, positive or negative), if the baseline IGRA was negative or missing. Borderline/indeterminate IGRA results were counted as missing (n = 8 at baseline and n = 1 at the follow-up testing).

To assess the level of exposure among HHCs, a 3-level variable was created by adapting factors validated in published literature, which included infectiousness factors of index patient, index patient and HHC interaction factors, and age of HHC [15, 19]. Although all HHCs were considered exposed to an infectious TB case, we combined these factors to classify HHCs into low-, medium-, or high-exposure categories for the purposes of our analysis (Figure 1).

There is no universally accepted definition of resistance to *Mtb* infection or validated tools for assessing level of exposure in adults. As such, we used several classification criteria that varied the specificity of the definition of resister phenotype. Specifically, we explored different definitions of TB infection by varying the cutoff for baseline TST negativity (0 mm vs <5 mm). We also varied how we classified HHCs with incomplete TST or IGRA test results. Finally, we conducted a subset analysis to assess how the proportion of resister phenotype changed if we restricted to only those with high exposure. Our primary outcome definition was based on the most restrictive definition of resistance (ie, high specificity).

Data Analysis

Descriptive analysis was conducted on index patients, HHCs and household characteristics. The distribution of resisters

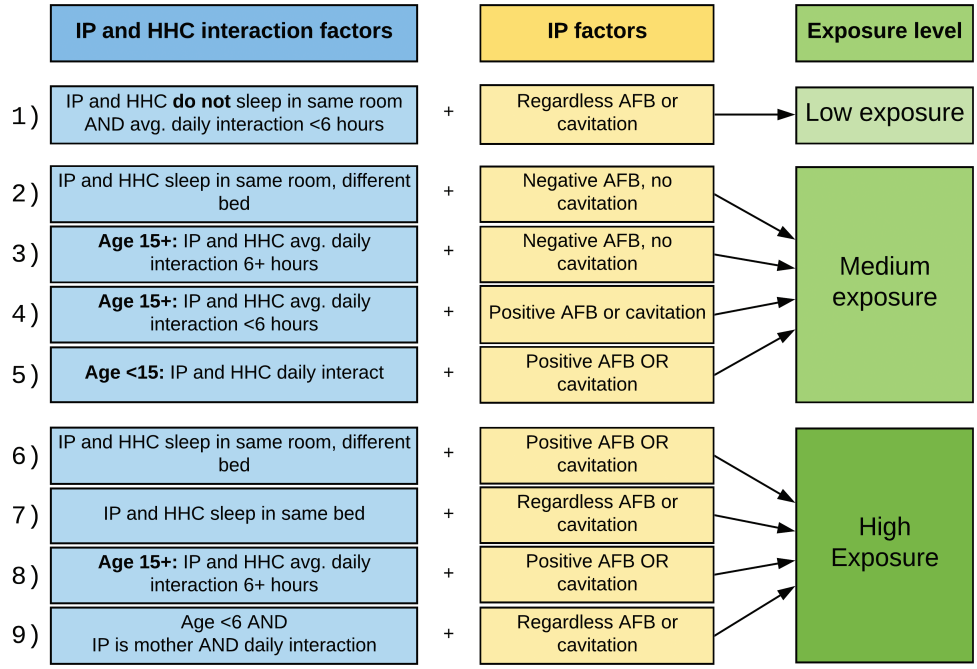

Figure 1. Components of exposure score and classification scheme. Abbreviations: AFB, acid-fast bacilli; HHC, household contact; IP, index patient.

across households was examined to identify any potential association between resisters and their household characteristics. Multivariable analysis using log-binomial regression was used to identify factors associated with resister phenotype. The models were fitted using generalized estimating equations (GEE) using a working exchangeable correlation structure to account for the clustering of contacts within households, and prevalence ratios with confidence intervals using robust standard errors were calculated. In order to evaluate whether any difference between groups was due to actual resistance to *Mtb* rather than lack of exposure, all models were adjusted for the 3-level exposure variable. Statistical analyses were carried out using SAS 9.4 and R package "digraph."

Ethical Considerations

The parent study was approved by the local IRB or Ethics Committee at each site. Written informed consent was obtained from all participants and assent in children as per local guidelines. This secondary analysis of resister phenotype was also approved by the institutional review board (IRB) at Emory University.

RESULTS

Description of Study Population

A total of 284 index patients were enrolled. The highest proportion of index patients were enrolled in South Africa (121, 43%), followed by India (58, 20%) and Peru (54, 19%). There were 102 (36%) index patients who were HIV-positive, 135 (48%) with a positive acid-fast bacilli (AFB) smear result, and 138 (49%) with a positive Xpert result prior to study enrollment. Of 184 index patients with documented chest X-ray, 80 (43%) had cavitation.

A total of 1016 HHCs were included and evaluated (Supplementary Table 1). 913 (90%) of them were ≥5 years old, of which 63 (7%) were HIV-infected (including both newly diagnosed and known HIV infection), 89 (9%) had been previously treated for TB, and 212 (23%) reported current or past smoking. TST and IGRA discordance at baseline was observed in approximately 31% of HHCs, regardless of TST cutoff.

Proportion of Resister Phenotype Based on Varying Definitions of Infection and Exposure

Using a restrictive (ie, high specificity) definition of resistance to *Mtb* as TST of <5 mm, IGRA <0.35 IU/mL after 1 year of follow-up, no evidence of active TB at baseline or 1-year follow-up, and all levels of exposure, we were able to determine resister status for 572 HHCs ≥5 years of age based on the availability of complete TST and IGRA test results (Figure 2, Table 1). Among these, 77 (13%) HHCs were classified as resisters (Table 1, Supplemental Table 2). Using the most restrictive TST cutoff of 0 mm, there were 71 (12%) HHCs classified as resisters (Supplemental Table 3). Of the 572 HHCs, 263 were highly exposed. Among these highly exposed HHCs, 29 (11%) were classified as resisters using a TST of <5 mm, and 26 (10%) with a TST of 0 mm (Figure 1, Table 1).

Expanding our analysis population to include HHCs with baseline TST and IGRA data available but no follow-up IGRA testing, we were able to determine resister status for additional 44 HHCs, with total of 616 HHCs included (Table 1). Among

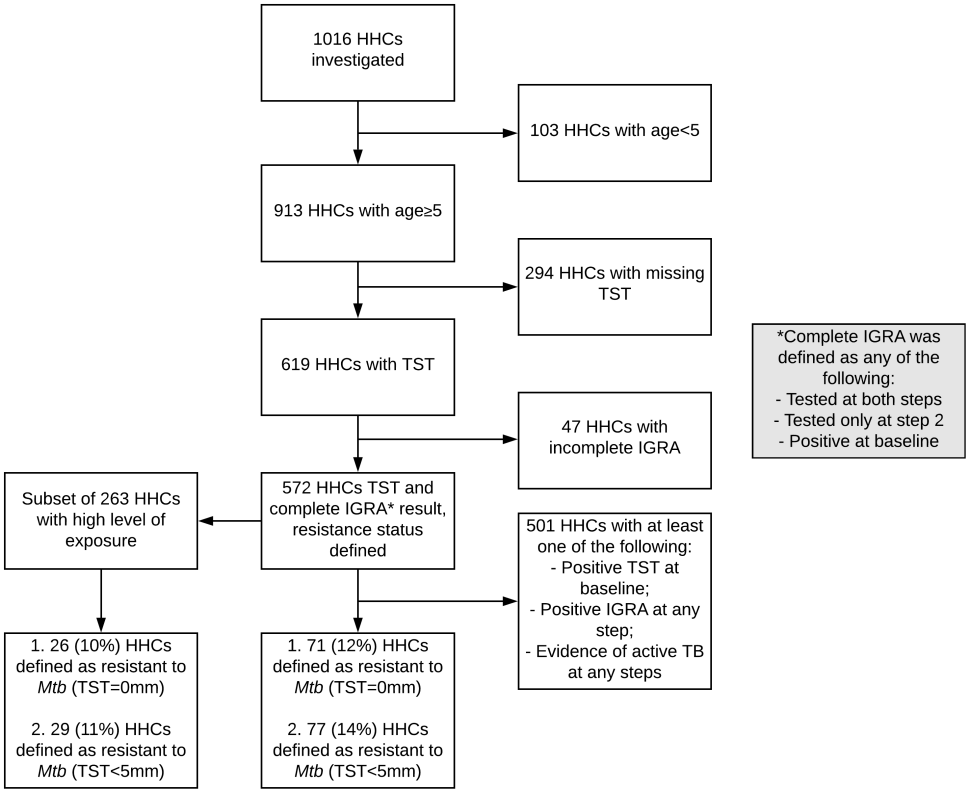

Figure 2. Flow diagram of household contacts with complete testing and exposure data to determine resistance to *Mtb* infection. Abbreviations: HHC, household contact; IGRA, interferon-gamma release; *Mtb, Mycobacterium tuberculosis*; TB, tuberculosis; TST, tuberculin skin test.

them, 101 (16%) HHCs were classified as resisters using TST <5 mm and 93 (15%) using 0 mm. When exposure was added to the definition, 285 HHCs were highly exposed; among these, 38 (13%) were classified as resisters using a TST of <5 mm and 35 (12%) using 0 mm.

Finally, including HHCs with at least 1 negative TST or IGRA test at baseline or follow-up, resister status was available for additional 282 HHCs, with a total of 898 HHCs included (Table 1). Among these, 188 (21%) HHCs were resistant to *Mtb* infection using TST <5 mm and 180 (20%) using 0 mm. Among 415 HHCs in this group who were highly exposed, 63 (15%) were resisters using a TST of <5 mm and 60 (14%) using 0 mm.

Characteristics of Participants With Resistance to *Mtb* Infection

Table 2 shows the characteristics of HHCs with the resister phenotype, using the most restrictive TST (0 mm cutoff) and IGRA definitions, along with exposure level. The proportion of resisters differed by country and ranged from 0% in Brazil to 46% in Thailand. However, proportion in 2 of the largest enrolling countries (India and South Africa) was similar. The

Table 1. Proportion of Household Contacts Classified as Resistant to *Mtb* Infection Using Varying Definitions for Infection and Exposure

	All HHCs			Highly Exposed HHCs		
Criteria for Defining HHC as a resister[a]	HHCs Included	n (%) Resistant, TST Cutoff <5 mm	n (%) Resistant, TST Cutoff 0 mm	HHCs Included	n (%) Resistant, TST Cutoff <5 mm	n (%) Resistant, TST Cutoff 0 mm
TST- and IGRA2-[b]	572	77 (13.5)	71 (12.4)	263	29 (11.0)	26 (10.0)
TST- and IGRA2-; TST- and IGRA1- and IGRA2 missing	616	101 (16.4)	93 (15.1)	285	38 (13.3)	35 (12.3)
All tests negative or any test negative while others missing	898	188 (20.9)	180 (20.0)	415	63 (15.2)	60 (14.5)

Abbreviations: HHC, household contact; IGRA1, interferon gamma release assay at baseline; IGRA2, interferon gamma release assay after 1-year follow-up; *Mtb, Mycobacterium tuberculosis*; TB, tuberculosis; TST, tuberculin skin test at baseline.

[a] Age ≥5 was a required criterion for inclusion in the analysis population. No evidence of active TB was required criteria for classifying a HHC as a resister in all definitions.

[b] IGRA2 was only performed if IGRA1 was negative or missing.

Table 2. Characteristics of Household Contacts With Resistance to *Mtb* Infection (0 mm TST cutoff), for All Levels of Exposure and for Highly Exposed HHCs

	All Levels of Exposure						High Exposure					
			Resistant		Not Resistant				Resistant		Not Resistant	
	Total	% (column)	n	% (row)	n	% (row)	Total	% (column)	n	% (row)	n	% (row)
Total	572		71	12%	501	88%	263		26	10%	237	90%
Qualitative exposure variable												
Low exposure	75	13%	18	24%	57	76%						
Medium exposure	234	41%	27	12%	207	88%						
High exposure	263	46%	26	10%	237	90%	263		26	10%	237	90%
HHC demographics												
Country[a]												
Botswana	28	5%	10	36%	18	64%	15	6%	5	33%	10	67%
Brazil	9	2%	0	0%	9	100%	7	3%	0	0%	7	100%
Haiti	38	7%	3	8%	35	92%	19	7%	1	5%	18	95%
India	159	28%	16	10%	143	90%	68	26%	7	10%	61	90%
Kenya	6	1%	0	0%	6	100%	5	2%	0	0%	5	100%
Peru	0		0	-	0	-	0	-	0		0	-
South Africa	304	53%	29	10%	275	90%	145	55%	12	8%	133	92%
Thailand	28	5%	13	46%	15	54%	4	2%	1	25%	3	75%
Sex												
Male	233	41%	35	15%	198	85%	97	37%	8	8%	89	92%
Female	339	59%	36	11%	303	89%	166	63%	18	11%	148	89%
Age, y												
<15	113	20%	18	16%	95	84%	38	14%	4	11%	34	89%
15+	459	80%	53	12%	406	88%	225	86%	22	10%	203	90%
Employed												
Yes	145	25%	17	12%	128	88%	69	26%	9	13%	60	87%
No	425	74%	54	13%	371	87%	193	73%	17	9%	176	91%
Refused	2	0%	0	0%	2	100%	1	0%	0	0%	1	100%
Highest education												
None	107	19%	15	14%	92	86%	49	19%	7	14%	42	86%
Primary	207	36%	23	11%	184	89%	93	35%	7	8%	86	92%
Secondary	214	37%	29	14%	185	86%	99	38%	11	11%	88	89%
College/University or higher	44	8%	4	9%	40	91%	22	8%	1	5%	21	95%
Relationship of index patient to HHC												
Spouse	42	7%	5	12%	37	88%	35	13%	5	14%	30	86%
Cohabitant	34	6%	7	21%	27	79%	15	6%	4	27%	11	73%
Child	78	14%	8	10%	70	90%	34	13%	3	9%	31	91%
Mother	66	12%	6	9%	60	91%	36	14%	2	6%	34	94%
Father	40	7%	2	5%	38	95%	16	6%	1	6%	15	94%
Sibling	104	18%	8	8%	96	92%	45	17%	4	9%	41	91%
Missing/other	208	36%	35	17%	173	83%	82	31%	7	9%	75	91%
Comorbidities												
HIV												
Positive	45	8%	5	11%	40	89%	26	10%	3	12%	23	88%
Negative	444	78%	50	11%	394	89%	208	79%	18	9%	190	91%
Missing	83	15%	16	19%	67	81%	29	11%	5	17%	24	83%
Diabetes	19	3%	2	11%	17	89%	9	3%	2	22%	7	78%
COPD	7	1%	0	0%	7	100%	3	1%	0	0%	3	100%
Asthma	18	3%	2	11%	16	89%	7	3%	0	0%	7	100%
HHC behavioral factors												
Ever smoke tobacco	139	24%	13	9%	126	91%	76	29%	6	8%	70	92%
Currently smoke tobacco	116	20%	12	10%	104	90%	64	24%	5	8%	59	92%
HHC use substances[b]	44	8%	1	2%	43	98%	21	8%	0	0%	21	100%
HHC drank alcohol	38	7%	3	8%	35	92%	22	8%	0	0%	22	100%
Index patient characteristics[c]												
Index patient's cavitation												
Yes	199	35%	27	14%	172	86%	118	45%	15	13%	103	87%

Table 2. Continued

	All Levels of Exposure						High Exposure					
			Resistant		Not Resistant				Resistant		Not Resistant	
	Total	% (column)	n	% (row)	n	% (row)	Total	% (column)	n	% (row)	n	% (row)
No	190	33%	20	11%	170	89%	74	28%	6	8%	68	92%
Unknown	183	32%	24	13%	159	87%	71	27%	5	7%	66	93%
Index patient's AFB result[d]												
Negative	229	40%	27	12%	202	88%	58	22%	5	9%	53	91%
Scanty positive	56	10%	6	11%	50	89%	38	14%	5	13%	33	87%
(1+)	52	9%	4	8%	48	92%	33	13%	1	3%	32	97%
(2+)	70	12%	10	14%	60	86%	42	16%	3	7%	39	93%
(3+)	120	21%	16	13%	104	87%	83	32%	8	10%	75	90%
Unknown	45	8%	8	18%	37	82%	9	3%	4	44%	5	56%

Abbreviations: AFB, acid-fast bacilli; COPD, chronic obstructive pulmonary disease; HHC, household contact; HIV, human immunodeficiency virus; *Mtb*, *Mycobacterium tuberculosis*; TST, tuberculin skin test.

[a] TST was not performed in Peru due to reagent shortage. All countries followed the same protocol, and there was no other substantial difference across countries in terms of study procedures.

[b] In the past 12 months, has the household contact used any other substances (eg, marijuana, cocaine, etc.).

[c] Based on testing before or at study enrollment, whichever result was highest.

[d] Numbers included in this section are of HHCs who have an index patient with given characteristic, not the number of index patients itself.

proportion of resisters did not differ substantially by sex, age, employment status, HIV coinfection, or comorbid diabetes or asthma. The only factor with considerable variation in proportion of resisters was based on the relationship to the index patient, where HHCs who were first-degree relatives (eg, parent, spouse, sibling) had a lower proportion of resisters than other cohabitants. Substance and alcohol use among HHCs were also associated with a lower proportion of resisters, although tobacco use was not. In multivariable analysis, we were unable to find any meaningful clinical or behavioral factor associated with the resister phenotype (Supplementary Table 4).

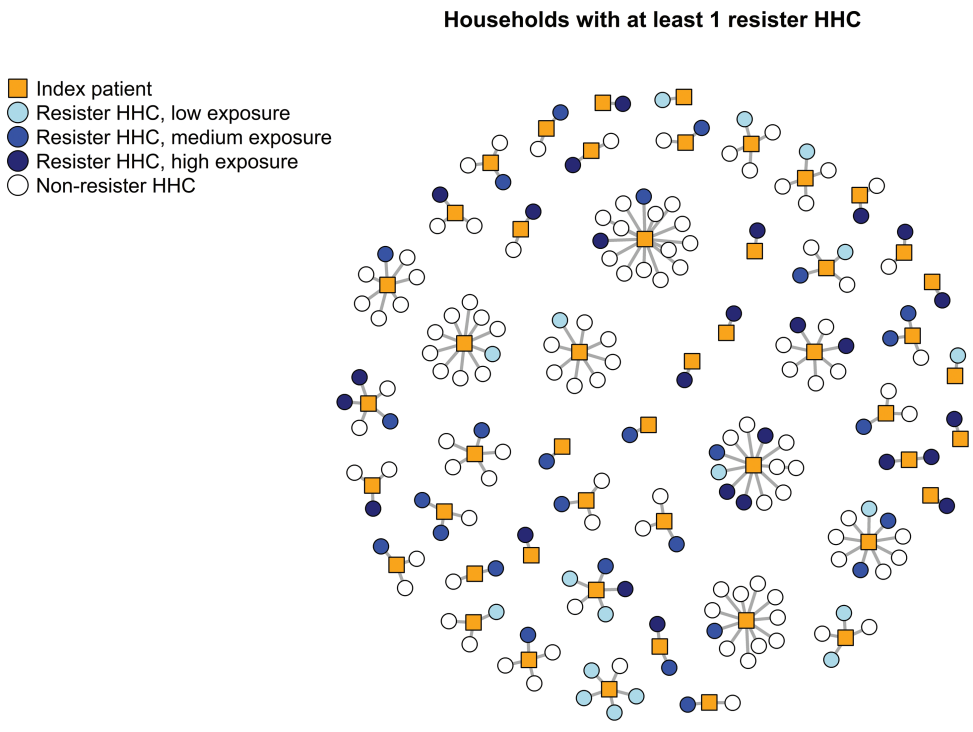

Figure 3. Clustering of persons with resistance[a] to *Mtb* infection in the subset of households with at least 1 resistor household contact (HHC; n = 49). Abbreviations: HHC, household contact; *Mtb*, *Mycobacterium tuberculosis*. [a]Using the definition with 71 resisters (all levels of exposure, tuberculin skin test [TST] 0 mm, negative follow-up interferon-gamma release [IGRA]).

Distribution of Participants With Resistance to *Mtb* Infection Across Households

The 71 HHCs among all exposure levels who were classified as resisters to *Mtb* infection based on the definition with 0 mm TST, and all exposure levels were distributed across 49 (17%) households in 5 countries (Figure 3). Visual examination of household clusters suggests uneven distribution of that resister phenotype across households, with several households with large clusters of resister HHCs (Figure 3). The median number of HHCs in these households was 3 (interquartile range [IQR] 2–5). Among the 38 households with >1 HHCs and ≥1 resister HHC, the percentage of HHCs resistant to *Mtb* infection varied from 8% to 100% (median 33%, IQR 25%–50%).

DISCUSSION

In this multinational study, we examined the proportion of individuals resistant to *Mtb* infection among HHCs who were exposed to active RR/MDR-TB index patients diagnosed in the preceding 6 months. Overall, we found that depending on the definition used, 10–21% of HHCs were resistant to *Mtb* infection, despite living in the same household as an infectious index patient. Even after applying stringent criteria to define resistance to *Mtb* with high specificity (0 mm induration on TST at baseline and negative IGRA at 1 year), at least 10% of HHCs were resistant to *Mtb* infection. To our knowledge, this is the first multinational study using consistent methods across countries to characterize a resister phenotype, supporting the idea that this phenotype exists in various geographic contexts.

The concept of resistance to *Mtb* infection has long existed; however, few rigorous studies characterizing the proportion and predictors of resister phenotype have been carried out to date. There are several notable challenges in studying resistance to *Mtb* infection. These include: the inherent limitations of TST and IGRA to detect the presence of *Mtb* infection; the lack of standardized methodology in measuring exposure to infectious index patients; a still rudimentary understanding of infectiousness of index patients; and no clear definition of resistance to *Mtb*, which incorporates these measures of infection, exposure, and infectiousness. In this study, we attempted to address these challenges using multiple strategies to improve the specificity of the definition. We used a combination of TST and IGRA—at baseline and after 1 year of follow-up, as well as using differing cutoffs of TST results—to examine the influence of varying definitions on the proportion of HHCs found to be resisters. Similarly, we created an exposure variable incorporating differing durations and proximity that contacts have spent with index patients, as well as clinical factors of the index patients' TB disease that have been previously associated with infectiousness. Finally, we utilized several definitions of resistance to *Mtb* to identify how each of these components impacts the proportion of resister HHCs identified.

Using our most stringent definition, which required a TST of 0 mm, a negative IGRA result after 1 year of follow-up, and a high level of exposure, 10% of HHCs were classified as resistant. As each of these components were varied stepwise in definitions that increased sensitivity, the proportion of HHCs classified as resisters increased. The most sensitive definition (HHCs with at least 1 negative TST or IGRA test at baseline or follow-up) classified 21% of HHCs as being resisters. Based on these data, future researchers can vary the definition of resistance to *Mtb* to suit their purposes. For example, very strict definition with high specificity could be used in studies that involve assessment of immune or genetic markers and might have limited resources for laboratory testing due to high cost. Other studies that aim to identify individuals potentially resistant to *Mtb* could use more encompassing definition with higher sensitivity for initial screening purposes. Regardless of the definition that is used to identify resisters, however, it is clear that a considerable group of HHCs remain uninfected with *Mtb*, lending considerable strength to the long-standing notion that resistance to *Mtb* infection exists.

We did not find any meaningful behavioral or clinical factors associated with resister phenotype, despite our large sample size. We hypothesize that resistance to *Mtb* infection has an underlying biologic mechanism, mediated through innate immune responses, genetic or epigenetic factors. If that hypothesis is true, we would not expect that behavioral or clinical factors would be associated with resistance to *Mtb*, because the underlying biologic mechanisms would not be expected to vary by these factors. This hypothesis is further supported by recent studies that found enhanced innate immune response and distinct adaptive immune response profile among resister HHCs. [20, 21] However, more definitive acceptance of this hypothesis is hindered by the lack of tools to accurately assess the extent of exposure.

The findings of this large multinational study contribute to an evidence base from published single-site studies. A recent study in India found that the proportion of HHCs who were persistently LTBI-negative was 8.4% overall and 6.5% among HHCs with high exposure. [22]. The slightly higher estimates in our analysis could be explained by the fact that only IGRA testing was repeated after 1 year of follow-up in our study, although both IGRA and TST were repeated in the study from India, and lack of infection was defined as negative TST and negative IGRA at both baseline and up to 12 months following exposure to index patient. Due to common discrepancy between TST and IGRA, if TST were also repeated in our study, some of the HHCs currently classified as resisters in our definitions could have positive TST, and the total proportion of resisters would decrease. Similar to our analysis, the study from India did not identify any epidemiologic factors associated with resister phenotype. Two other studies from Uganda describe HHCs who remain

persistently TST negative after exposure to index patient and report similar findings: Ma et al (2014) report that 11.7% of HHCs were persistently TST negative after 2 years of follow-up, and Stein et al (2018) report 10.7% of HHCs persistently TST-negative after at least 1 year of follow-up [19, 23]; IGRA testing was not done in either of these 2 studies. The participants from the latter study were later retraced, and 82.7% of those who were originally persistently TST-negative were concordantly negative on TST and IGRA after an average of 9.5 years, suggesting that resistance to *Mtb* is a stable phenomenon [24].

The exact mechanism of resistance against *Mtb* infection remains unknown. Simmons et al (2018) discuss several potential explanations for persistently negative TB infection tests [25]. One hypothesis suggests that HHCs have negative TST or IGRA test results only because they have not had substantial exposure to index patient. Our analysis, as well as studies from India and Uganda, suggest that resistance to *Mtb* infection is observed even when we restrict the study population to highly exposed HHCs. Another explanation suggests that the resister phenotype is actually observed due to false-negative results in tests of TB infection. A recent study in Uganda found that HHCs classified as resisters had developed non-interferon-gamma immune response to *Mtb,* which could explain negative results on traditional TB infection testing methods [21]. Whether this means that these contacts are actually infected and at higher risk of active TB or whether this different type of immune response provides protection to progression to TB has yet to be determined and will require larger studies that will synthesize epidemiologic, genetic and immunologic data.

Our study had several limitations. First, the study population was not a random sample of all eligible individuals in the target population, which might have introduced selection bias. Second, TST was not performed on almost one-third of the initial study population due in part to a shortage of reagent, which limited our ability to determine their TB infection status and reduced our final sample size. Third, repeated testing after 1 year of follow-up was only performed using IGRA without TST and was not performed at all among children <5 years. For this reason, we had to exclude a large proportion of participants from our main analysis, including children with age <5 years. Fourth, we did not have quantitative results of IGRA testing available. IGRA is interpreted as positive if the result is above the cutoff of 0.35 IU/mL. However, borderline results around this cutoff have been shown to fluctuate substantially. We were not able to explore how our findings would change using different cutoffs for IGRA [26–28].

Despite these limitations, our study contributes to the emerging literature that supports the resister phenotype as part of the spectrum of TB infection to disease. This is the first report to our knowledge that describes the proportion of resister phenotype using multiple definitions and explores the extent to which different classification schemes might affect the proportion of resisters. Immunogenomic studies of resister phenotype are important in order to improve our understanding of genetic or immunologic mechanisms underlying resistance to *Mtb* infection, which will in turn help in developing novel strategies for vaccines, diagnostics, and therapies for TB infection and disease.

Notes

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