Title: Isoniazid preventive therapy protects against tuberculosis among household contacts of isoniazid-resistant patients.

1. Chuan-Chin Huang, Sc.D., Brigham and Women's Hospital, Division of Global Health Equity, Boston, Massachusetts, United States
2. Mercedes C. Becerra, Sc.D., Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, United States.
3. Roger Calderon, M.S., Socios En Salud, Lima, Peru
4. Carmen Contreras, M.P.H., Socios En Salud, Lima, Peru
5. Jerome Galea, Ph.D., School of Social Work, University of South Florida, Florida, United States
6. Louis Grandjean, M.D., Ph.D., Wellcome Centre for Clinical Tropical Medicine, Imperial College London, London, United Kingdom; Universidad Peruana Cayetano Heredia, Lima, Peru; TB Centre, London School of Hygiene & Tropical Medicine, London, United Kingdom
7. Leonid Lecca, M.D., Socios En Salud, Lima, Peru
8. Rosa Yataco, Socios En Salud, Lima, Peru
9. Zibiao Zhang, M.S., Brigham and Women's Hospital, Division of Global Health Equity, Boston, Massachusetts, United States
10. Megan Murray, M.D., Sc.D., Harvard Medical School, Department of Global Health and Social Medicine, Boston, Massachusetts, United States and Brigham and Women's Hospital, Division of Global Health Equity, Boston, Massachusetts, United States

Corresponding authors: Megan Murray, Harvard Medical School, 641 Huntington Avenue, Boston, MA 02115 megan.murray.epi@gmail.com, 617-432-2781.

ABSTRACT

Background: World Health Organization recommend the use of isoniazid (INH) only, or INH and rifapentine therapy, to treat the latent tuberculosis infection (LTBI). The recent rise of isoniazid and multi-drug resistant (MDR) tuberculosis has complicated the choice of LTBI treatment regimen. The current lack of evidence on optimal regimens prevents the formulation of definitive recommendations for latent drug-resistant tuberculosis. We examine the risk of disease progression of individuals exposed to sensitive, INH, or MDR tuberculosis who received INH as part of routine tuberculosis management.

Methods: This study is a prospective cohort study conducted in Lima, Peru. Between September 2009 and August 2012, we identified and enrolled 4,500 tuberculosis patients and their 14,044 household contacts. We measured the incident tuberculosis of the household contacts (HHCs) over a one-year follow-up. We used a Cox frailty proportional hazards model to evaluate whether the effect of INH preventive therapy (IPT) on tuberculosis progression varied by the resistance profile of the index case.

Findings: We restricted the analyses to 4,216 HHCs who were ≤ 19 years old. 2,106 HHCs (50%) had initiated isoniazid prevention therapy at enrollment. We found that the protective effect of INH against tuberculosis was stronger in HHCs exposed to drug-sensitive or MDR TB than in those exposed to mono-INH-resistant strains (IPT vs. No-IPT aHR[95% confidence interval]: 0.32 [0.20-0.50] in INH-sensitive subgroup; 0.26 [0.08-0.77] in MDR; 0.80 [0.23 to 2.79] in mono-INH-resistant). When we further restricted the analyses to those who received a ≥ 3 months of INH, the protective effect of IPT became even stronger across all three groups (0.2 [0.1 to 0.4] in INH-sensitive subgroup; 0.16 [0.02-1.27] in MDR; 0.72 [0.16-3.16] in mono-INH-resistant).

Interpretation: We found that INH prevention therapy protected against TB among contacts of INH-resistant TB patients. This finding suggests that INH may have a role in the management of MDR-LTBI.

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Research in Context

Evidence before this study

Few data exist on the efficacy of INH in preventing TB progression among people exposed to MDR-TB. One study done in Brazil, following 190 TST-positive contacts of MDR-TB patients, found a 2.3 times increased risk among contacts who received IPT than among those who did not. In Israel, investigators followed contacts of MDR-TB and reported no cases among 71 contacts receiving IPT in a 6-year follow-up. In South Africa, researchers reported that children who did not receive preventive therapy were four times more likely to develop TB disease than those who received less than 6 months of individualized preventive therapy that contained a high dose of INH (15-20 mg/kg/d). Several other studies reported the use of regimens that included INH for contacts of MDR-TB patients, but these studies lacked control arms and thus the efficacy of INH could not be measured.

Added value of this study

We found that INH prevention therapy protected against TB among contacts of INH-resistant TB patients.

The protective effect was stronger among contacts who received a longer period course of INH or among those who were less than 5 years old.

Implications of all the available evidence

Our findings suggest that INH may have role in the management of MDR-LTBI

Introduction

The worldwide TB pandemic remains one of today's greatest global health challenges. The World Health Organization (WHO) estimates that there were 10.4 million new cases of TB in 2016 (1). Between one third and a quarter of the world's population is estimated to have latent TB infection (LTBI) (2). Although treatment of LTBI has been shown to protect against the development of TB disease, only a tiny minority of those at risk receive preventive therapy (2). WHO's recently revised guidelines on treating LTBI now recommend systematic testing and treatment of LTBI for an expanded group of people at high risk of TB progression including child and adults contacts of pulmonary TB patients. Recommended regimens for LTBI include 6 to 9 month isoniazid (INH), a 3-month regimen of rifapentine plus INH, 3–4 months INH and rifampicin, and 3–4 months rifampicin alone (2).

The recent rise of INH-resistant and multi-drug resistant TB has complicated the choice of an LTBI treatment regimen. Although several small studies have shown that regimens tailored to specific drug sensitivity profiles can be effective, most of these lacked control arms or compared these individually tailored regimens to no treatment rather than an alternative regimen (3). WHO concludes that the current lack of evidence on optimal regimens prevents the formulation of definitive recommendations for INH-resistant and MDR-exposed contacts (2).

In countries that implement preventive therapy for those at high risk, close contacts of MDR-TB patients often receive standard LTBI regimens prior to time that the index patient's drug sensitivity tests are available to the treating clinician. In areas where rapid diagnostic tests for MDR are not yet available, contacts may receive INH for months prior to the eventual diagnosis

of MDR (4, 5). Here, we examined the risk of disease progression of individuals exposed to sensitive, INH or MDR-TB who received INH as part of routine TB management.

Methods

Recruitment

This study was conducted in Lima in 106 district health centers that provide care to a population of approximately three million residents. Patients were referred to study staff if they were over 15 years of age and had been diagnosed with pulmonary TB (PTB) disease by a health center clinician. We requested permission to visit each patient's household and recruit his or her household contacts (HHCs) into a prospective cohort study. Study workers aimed to enroll all household members within one week of the diagnosis of the index case.

Baseline assessment of index patients and household contacts

We collected the following data from index patients and HHCs at the time of enrollment: age, height, weight, gender, occupation, history of TB disease, alcohol, education, housing information, intravenous drug and tobacco history, symptoms of TB, BCG vaccination, and comorbidities including HIV and diabetes mellitus. For index cases, we additionally collected the duration of coughing symptoms before diagnosis, presence of cavitary disease, sputum smear status, and culture results. For those with positive cultures, isolated underwent drug-susceptibility test and MIRU-based genotyping (detail information in Supplement 1). For HHCs, we additionally collected whether IPT had been initiated and their relationship to the index patient. Household contacts with symptoms were referred to their local health clinic for chest radiography and clinical evaluation for active TB disease. Household members with no known history of active TB disease or previously documented infection received a tuberculin skin test.

INH preventive therapy for HHCs

The 2006 Peruvian National TB Program recommended that HHCs 19 years old or younger or those who had a specified comorbidity should receive 6 months of INH preventive therapy (IPT) (Ref 6) while those with HIV should receive 12 months. Children under 19 were offered IPT at the time index patients were diagnosed, regardless of whether they were infected or not. Health care providers often chose to discontinue IPT if the index patient to whom HHCs had been exposed was subsequently diagnosed with MDR-TB but some MDR-exposed HHCs received a full course of IPT. We used medical records from participating hospitals and health clinics to determine the duration of IPT.

Follow-up of household contacts

Participants were revisited in their household at 2, 6, and 12 months and were asked whether they had been diagnosed with TB or if they had had symptoms of active disease. Those who reported symptoms were referred to their local health center for further clinical evaluation including a chest radiograph and sputum smear.

Outcome definition

We identified incident TB among HHCs during scheduled household visits and from a systematic review of TB registries at the participating health clinics. We considered HHCs to have co-prevalent TB if they were diagnosed within 2 weeks of the diagnosis of the index case. If HHCs were diagnosed between 2 weeks and 15 months after diagnosis of the index case, we considered them “secondary” cases. Diagnosis of adult secondary TB followed the same criteria as outlined above for index cases. We defined secondary TB disease among contacts younger

than 18 years of age according to the consensus guidelines for classifying TB disease in children (7).

Data categorization

The information of data categorization is provided in Supplement Appendix (Supplement 1)

Analyses

We included in our analysis only HHCs under 19 because older contacts were only offered IPT if they had comorbidities that substantially increased their risk of TB disease. We used a Cox frailty proportional hazards model to evaluate risk factors for incident TB disease, accounting for clustering within households (8). We first performed a univariate analysis to examine the effect of IPT on TB incidence, followed by a multivariate model in which we adjusted for the age of the index case age and the age, social economic status (SES), and TB history of the HHC. To evaluate whether the effect of IPT on TB incidence varied by resistance profile of the index case, we added a variable representing INH resistance in the index case and an interaction term for INH-resistance and IPT. Because the spectrum of INH resistance-causing mutations that lead to INH mono-resistance may differ from those that lead to MDR-TB, we classified strains as sensitive, mono-INH-resistant, or MDR-TB (resistant to both INH and RIF). Previous studies have shown that the efficacy of IPT treatment is reduced if the treatment is ended within 3 months (9). We therefore repeated these analyses stratifying by a dichotomous variable that captured treatment for more or less than 3 months. We also considered the possibility that HHCs $\leq$ 5 years of age would be more likely to acquire TB at home than in the community compared to older contacts and we thus conducted sensitivity analyses restricted to this subgroup.

To determine whether the effect of IPT on disease in the HHCs was a function of the mean inhibitory concentrations (MICs) of the infecting organism, we repeated these analyses for the subset of HHCs exposed to index cases for whom quantitative INH-resistance was available.

Verifying our finding with an independent dataset

We conducted a seperate analysis using publically available data from an independent dataset collected from a prospective cohort study in South Lima and Callao, Peru between 2010 and 2013, posted by Grandjean et al. (10). This study enrolled 1,055 HHCs of 213 MDR-TB index cases and 2,362 HHCs of 487 drug-susceptible index cases and measured incident TB over 2-years of follow-up. Drug susceptibility testing for INH and RIF was performed for all index cases' samples using microscopic observation drug susceptibility assays (11) in regional laboratories and results were confirmed in the national reference laboratory using proportions methods. The investigators note that IPT was discontinued in this group after MDR-TB index cases were confirmed but data on the duration of IPT were not available. We applied the same analytic plan which we used for our own data to this independent dataset.

Results

Data collection

We enrolled 14,044 HHCs of 4,500 patients suspected of having PTB, of whom 12,767 had been exposed to index patients with microbiologically confirmed TB. Of these, 5,496 (43%) were ≤ 19 years of age. We restricted our analyses to 4,216 HHCs who were exposed to an index case whose INH resistant profile was available (Figure 1). At the time of enrollment, 2,106 HHCs (50%) had initiated IPT while the remainder had declined it. On average, the duration of IPT was shorter among HHCs of MDR-TB cases (115 days) than those of drug-sensitive TB (142 days)

and mono-INH-resistant TB cases (148 days) (Figure 2). The baseline characteristics stratified by IPT are shown in Table 1.

At 12-months follow-up, 146 HHCs developed TB disease. Of these, 48 (33%) had complete 24-loci MIRU-typing. Twenty-nine of the 48 (64%) had at least 23 loci that matched their index cases' MIRU-typing.

Univariate analyses and multivariate adjustment

In univariate analyses, we found that HHCs under age 15 who received IPT were less likely to develop TB disease compared to those who did not (HR=0.33, 95% CI = 0.22 to 0.48). The INH-resistance profile of the index patient was not associated with subsequent disease in the HHCs (Table 2). HHCs who received IPT experienced a lower incidence of secondary TB disease and this signal was retained after we adjusted for age, SES, and history of TB, as well as the age of the index case (adjusted HR=0.34, 95% CI = 0.23 to 0.5) (Table 2).

Adding IPT and INH-resistant profile of index case as interaction terms

We found that the protective effect of IPT was significantly stronger in HHCs exposed to drug-sensitive or MDR-TB than in those exposed to mono-INH-resistant strains (IPT vs. No-IPT adjusted HR= 0.32, 95% CI; 0.20 to 0.50 in INH-sensitive subgroup; 0.26, 95% CI = 0.08 to 0.77 in MDR; 0.80, 95% CI; 0.23 to 2.79 in mono-INH-resistant) (Table 3A). When we restricted the analysis to a subgroup of HHCs who received IPT for more than 3 months, we found that the protective effect of IPT became even more extreme across all three INH groups (IPT vs. No-IPT adjusted HR= 0.2, 95% CI = 0.1 to 0.4 in INH-sensitive subgroup; 0.16, 95% CI = 0.02 to 1.27 in MDR; 0.72, 95% CI: 0.16 to 3.16 in mono-INH-resistant) (Table 3B). Conversely, the

protective effect of IPT was reduced across all three groups in those who received less than 3 months treatment (IPT vs. No-IPT adjusted HR 0.89, 95% CI = 0.44 to 1.82 in INH-sensitive subgroup; 0.52, 95% CI: 0.09 to 1.84 in MDR; 1.02, 95% CI: 0.1 to 8.46 in mono-INH-resistant) (Table 3C). These results persisted when we restricted the analyses to HHCs ≤ 5 years of age among whom the protective effect of IPT was almost 100% effective among all those who received ≥ 3 months IPT treatment (Table 4A-4C). When we evaluated HHCs for whom index patient minimal inhibitory concentration (MIC) data was available (N = 1,276), we found that the protective effect of IPT remained strong among those HHCs exposed to index cases with INH-sensitive and INH-moderate phenotypes (MIC ≤ 5μg/ml) (IPT vs. No-IPT HR = 0.37, 95% CI = 0.1 to 1.37). None of the HHCs (0/92) who received IPT after being exposed to an index patient with an MIC >5 μg/ml developed active TB, while 4% (14/368) of those who didn't receive IPT developed disease.

Second independent dataset

The second dataset included 1,121 HHCs ≤ 19 years age who had available IPT data. Here again, we found that IPT strongly protected HHCs from incident TB in both the univariate and in an analysis that adjusted for age, SES, and TB history (HR = 0.1; 95% CI = 0.03 to 0.3). When we further evaluated whether the effect of IPT varied by the resistance pattern of index cases, we found that IPT not only protected HHCs of drug-sensitive index cases (adjusted HR= 0.13 95% CI = 0.03 to 0.57) but also perfectly protected 76 HHCs of MDR-TB index cases from developing TB.

Discussion

Here, we found that INH prevention therapy protected HHCs of index TB patients against TB disease even when the index patients were infected with MDR and mono-INH-resistant Mtb strains. This protective effect was greater among HHCs of MDR-TB cases than among those exposed to mono-INH resistant strains. As expected, the risk of incident TB was higher among HHCs who received less than 3 months treatment, especially among children under five. No child who received ≥ 3 months of IPT developed TB disease. We also showed that the effect of IPT in preventing TB progression is unrelated to the MIC of the index patient's TB strain; no HHC who was exposed to an index patient with a >5 μg/ml MIC developed disease. We verified our findings in a second independent dataset in which the protective effect of IPT against TB in HHCs of MDR-TB cases was also demonstrated.

Few data exist on the efficacy of INH in preventing TB progression among people exposed to MDR-TB. In Brazil, Kritski et al., investigators followed 190 TST-positive contacts of MDR-TB patients and found that disease developed in two of 45 (4%) contacts who received IPT and in 13 of 145 (9%) contacts who did not (12). In Israel, Attamna et al. followed contacts of MDR-TB cases for up to 6 years and reported no cases among 71 contacts receiving IPT, suggesting that IPT might have been effective in preventing the progression of MDR-LBTI. (13). In South Africa, Schaaf et al. reported that children who did not receive preventive therapy were four times more likely to develop TB disease than those who received less than 6 months of individualized preventive therapy that contained a high dose of INH (15-20 mg/kg/d). Although this suggests that INH could have been effective against MDR-LTBI, the efficacy of INH cannot be measured as the regimens contained other drugs tailored to the drug susceptibility profile of

the index strain. In that study, children who did not receive preventive therapy were four times more likely to develop TB disease (14). A study conducted in Australia considered people who received IPT after exposure to MDR-TB as controls and compared them to MDR-TB contacts who received other regimens of preventive therapy or no treatment (15). Of these, two contacts developed TB disease within 54 months, but the study did not specify what regimens these two incident patients received. Other studies reported the use of regimens that included INH for contacts of MDR-TB patients, but these studies lacked control arms and thus the efficacy of INH could not be measured (16-18).

We considered several possible explanations for the protective effect of IPT on contacts of INH-resistant TB patients. First, HHCs might have been infected in the community by index patients with drug-sensitive TB rather than by the patient with drug resistant TB living in their household and so their TB strains may have been susceptible to INH. However, MIRU-typing of the secondary cases showed that approximately two-thirds harbored strains that matched their index case, suggesting that no more than a third of the secondary cases acquired TB in the community. If IPT had had no effect among HHCs of MDR-TB index cases, we would expect to see an protective effect of no less than 0.32 (effect size of contacts exposed to drug sensitive strains, table 3A), rather than the 0.26 effect we observed. Furthermore, the observed protective effect was stronger in under-5 year olds, whom we considered much less likely than older contacts to have been infected by someone other than the index case. In the independent dataset, Grandjean et al. noted that 86% of MDR-TB secondary cases were exposed to MDR-TB index cases, again suggesting that most of the incident MDR-TB among HHCs in their study were infected at home rather than in the community (10).

Secondly, we considered the possibility that HHCs who chose to take IPT came from higher SES groups and thus were less likely to develop TB disease, regardless of the resistance profile of the index case. Although we attempted to adjust for SES, it is possible the principal component score we used did not completely capture its effect. However, in this case, we would not expect the INH effect to vary by duration of therapy as it did in our study (Table 3 and 4). The reduced efficacy of IPT among people who received less than one month of treatment is within the range reported in a highly referenced randomized trial, again suggesting that confounding introduced by SES could not explain our findings (10).

Finally, we considered the possibility that INH is effective against LTBI even when the relevant strains are found to be resistant to INH in media-based growth assays. This raises the possibility that the mechanism by which INH reduces TB risk among those with LTBI may differ from its mechanism in active disease. In the latter case, INH is known to be a pro-drug which is converted to its s active metabolite, an INH-NAD adduct, by an MTB catalase peroxidase encoded by the KatG gene (20). The INH-NAD adduct then binds to InhA (enoyl-acyl carrier protein reductase) and inhibits the synthesis of essential mycolic acids in MTB cell walls. The most common causes of INH resistance among clinical are mutations in KatG that reduce the activity of the catalase-peroxidase and thereby block the conversion of INH to its active form. Several studies have raised the possibility that this conversion may occur independently through other routes. Youatt et al. showed that the presence of copper increased the INH sensitivity of an INH-resistant strain, suggesting the interaction of INH and copper ions may facilitate the conversion of INH to its active form (19,20). In a second study, Mahapatra et al. identified metabolites of oxidized INH-NAD adducts in the urine of people who were not infected with

MTB, thereby demonstrating that INH can be activated by host enzymes (21). Other studies have suggested that INH may employ nonspecific antibacterial mechanisms against MTB in addition to its impact on mycolic acid synthesis. INH is a strong ligand for iron, copper and zinc and might be involved in metal ion uptake by MTB, which could disrupt metal homeostasis and inhibit MTB growth (22-24).

These hypotheses raise the question of why INH fails to cure INH-resistant TB patients. One possible explanation is that these mechanisms clear MTB in the early stage of infection when the bacterial load is low, but are less effective when the bacterial load is much higher. Another explanation is that INH may kill the latent TB through a host T-cell-mediated mechanism, as several studies have hypothesized that latent TB is in a cell-free form and so INH cannot have a bactericidal effect through the inhibition of cell wall synthesis (25).

Our study also showed that the protective effect of INH differs in contacts exposed to MDR-TB strains compared to mono-INH-resistant strains. While this could be due to random variation related to the small sample size of HHCs exposed to mono-INH-resistant TB, another possibility is suggested by the finding that INH mutation profiles differ between MDR and mono-INH-resistant strains. Alland et al. reported that mono-INH-resistant strains were more likely than MDR strains to harbor InhA promoter mutations and less likely to have KatG mutations (26). Since InhA is the downstream target of the INH-NAD adduct, mono-INH-resistant strains may remain resistant to INH regardless of whether INH conversion took place through an MTB-dependent or MTB-independent pathway.

IPT has been used for decades in tuberculosis control efforts and despite some concerns about hepatoxicity, it has been shown to have a good safety profile especially in children. Health

workers worldwide have extensive experience using this drug and handling its adverse effects. Establishing its efficacy against latent MDR TB would therefore be of great value and could set a bar against which alternative treatment could be measured. For example, the ongoing PHOENIx trial, designed to establish the efficacy of delamanid against MDR-LTBI uses INH as the control arm. If investigators consider that INH is ineffective against MDR TB and is serving only as a placebo, the effect of delamanid could be underestimated (27).

Our study has some limitations. The contacts of MDR-TB cases received INH for a shorter period of time than contacts of pan-sensitive or mono-INH-resistant cases, presumably because clinicians halted IPT once the index patients' MDR-TB status were confirmed. Given the dose effect we observed, we would expect to see an even more extreme effect of IPT had contacts of MDR-TB cases received the same duration of IPT as those exposed to drug-sensitive strains. Also, we were unable to assess the effect of IPT on adult contacts of MDR-TB cases given that IPT is not indicated for adult contacts without co-morbidities in Peru. Finally, almost all HHCs in our cohort were HIV-negative, so we were not able to evaluate the synergistic effect between IPT and highly active antiretroviral therapy in HIV-positive HHCs exposed to MDR-TB.

In conclusion, we found that IPT protected against TB among contacts of INH-resistant TB patients. Given the safety profile of INH and its wide use across the globe, INH may have a role in the management of MDR-LTBI.

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Figure 1. Flow diagram of household contacts of household contacts of index TB patients

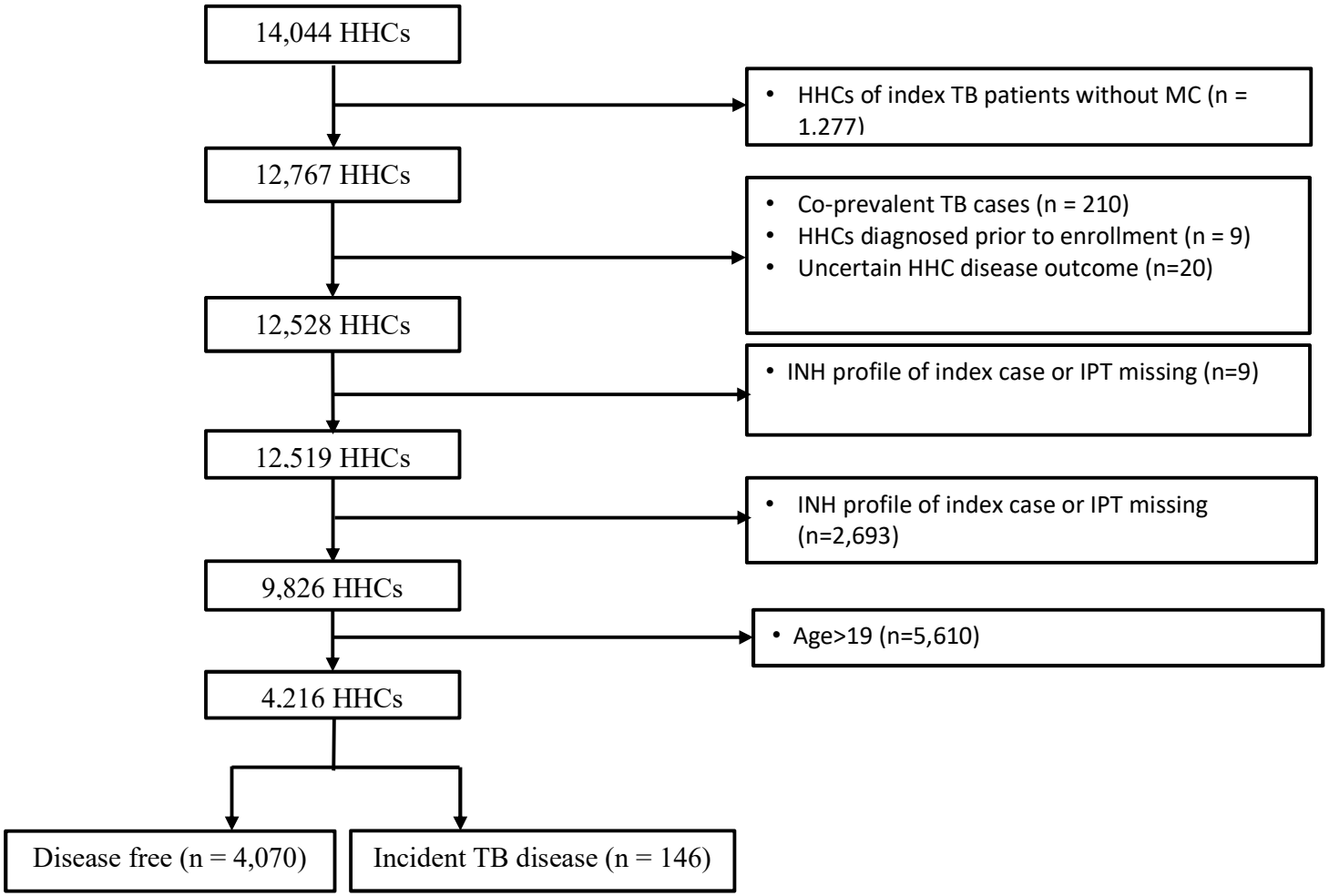

Table 1. Baseline characteristics of household contacts with age ≤ 19, stratified by receiving isoniazid prevention therapy or not.

Characteristic (total N with data)	Not received IPT		Received IPT	
Age years (N=4,216)	N	%	N	%
0 to 5	664	31%	855	41%
6 to 10	439	21%	532	25%
11 to 15	489	23%	451	22%
16 to 19	528	25%	258	12%
Male gender (N=4,216)				
Female	1,087	51%	1,033	49%
Male	1,033	49%	1,063	51%
HIV seropositive (N=4,164)				
No	2,086	100%	2,074	100%
Yes	4	0%	0	0%
Diabetes (N=4,202)				
No	2,111	100%	2,087	100%
Yes	2	0%	2	0%
BCG scars (N=4,216)				
0	423	20%	401	19%
1	1,640	77%	1,650	79%
≥2	57	3%	45	2%
Smoking status (N=4,209)				
Non-smoker	2,068	98%	2,086	100%
1 cigarette per day	25	1%	5	0%
>1 cigarette per day	22	1%	3	0%
Alcohol use (N=4,195)				
Non-drinker	1,912	91%	2,006	96%
0 to <3 drinks per day	149	7%	73	4%
≥3 drinks per day	44	2%	11	1%
Nutritional status[a] (N=4,173)				
Normal weight	1,748	83%	1,681	81%
Underweight	44	2%	59	3%
Overweight	308	15%	333	16%
Employed outside the home (N=4,214)				
No	1,893	89%	1,981	95%
Yes	226	11%	114	5%

Use of public transportation (N=4,120)				
Non-user	736	35%	795	39%
1 to 3 days per week	709	34%	640	32%
4 to 7 days per week	652	31%	588	29%
Socioeconomic status[b] (N=4,128)				
Low	821	40%	801	39%
Middle	931	45%	887	43%
High	325	16%	363	18%
TB infected at baseline (N=4,068)				
No	1,417	70%	1,494	73%
Yes	613	30%	544	27%
Index-case INH-profile (N=4,216)				
Sensitive	1,534	72%	1,630	78%
Mono-resistant	185	9%	201	10%
MDR	401	19%	265	13%

[a] Nutritional status was defined by the WHO body mass index z-score tables

[b] Socioeconomic status was defined using a principal component analysis based on housing quality, water supply, and sanitation.

Abbreviation: N: number; TB: tuberculosis; INH: isoniazid; IPT: isoniazid prevention therapy; MDR: multi-drug resistant

Table 2. Univariate- and multivariate-adjusted effects of isoniazid prevention therapy, and the isoniazid resistant profile pattern of tuberculosis index cases on disease incidence of household contacts ≤ 19 years of age

	Univariate analysis	Multivariate*
	HR (95% CI)	HR (95% CI)
Isoniazid prevention therapy		
No	Ref	Ref
Yes	0.33 (0.22 - 0.48)	0.34 (0.23 - 0.5)
Isoniazid resistant profile		
Sensitive	Ref	Ref
MDR	1.17 (0.74 - 1.85)	1.02 (0.64 - 1.63)
mono-INH-resistant	0.82 (0.43 - 1.59)	0.81 (0.41 - 1.58)

*Adjusted for index case age, HHC age, TB history, and Social economics status
Abbreviation: HR: Hazard ratio; CI: confidence interval; Ref: Reference group; INH: isoniazid; MDR: multi-drug resistant

Table 3. The effect of isoniazid prevention therapy on disease incidence of children ≤19 years of age, stratified by INH profiles of index cases; adjusted for index case age, HHC age, TB history and social economics status.

A. Complete dataset

	Isoniazid-sensitive N=3099; event=106	MDR N=664; event=27	Mono-isoniazid resistant N=365; event=11
INH prevention therapy	HR (95% CI)	HR (95% CI)	HR (95% CI)
No	Ref	Ref	Ref
Yes	0.32 (0.2 - 0.5)	0.26 (0.08 - 0.77)	0.8 (0.23 - 2.79)

Likelihood ratio test for interaction term: 0.015

B. Household contacts who received isoniazid prevention therapy ≥ 3 months

	Isoniazid-sensitive N=2429; event=88	MDR N=505; event=24	Mono-isoniazid resistant N=299; event=9
INH prevention therapy	HR (95% CI)	HR (95% CI)	HR (95% CI)
No	Ref	Ref	Ref
Yes	0.2 (0.1 - 0.4)	0.16 (0.02 - 1.27)	0.72 (0.16 - 3.16)

Likelihood ratio test for interaction term: <0.001

C. Household contacts who received isoniazid prevention therapy < 3 months

	Isoniazid-sensitive N=1727; event=88	MDR N=465; event=25	Mono-isoniazid resistant N=210; event=7
INH prevention therapy	HR (95% CI)	HR (95% CI)	HR (95% CI)
No	Ref	Ref	Ref
Yes	0.89 (0.44 – 1.82)	0.52 (0.11 - 2.38)	1.02 (0.11 - 9.4)

Likelihood ratio test for interaction term: 0.367

Table 4. The effect of isoniazid prevention therapy on disease incidence of children ≤5 years of age, stratified by INH profiles of index cases; adjusted for index case age, HHC age, TB history and social economics status.

A. Complete dataset

	Isoniazid-sensitive	MDR	Mono-isoniazid resistant
	N=1257; event=32	N=277; event=13	N=137; event=5
INH prevention therapy	HR (95% CI)	HR (95% CI)	HR (95% CI)
No	Ref	Ref	Ref
Yes	0.33 (0.15 - 0.73)	0.18 (0.04 - 0.89)	0.46 (0.06 - 3.35)

Likelihood ratio test for interaction term: 0.726

B. Household contacts who received isoniazid prevention therapy ≥ 3 months

	Isoniazid-sensitive	MDR	Mono-isoniazid resistant
	N=970; event=23	N=193; event=11	N=113 event=3
INH prevention therapy	HR (95% CI)	HR (95% CI)	HR (95% CI)
No	Ref	Ref	Ref
Yes	0.06 (0.01 - 0.43)	0 (0 to infinity)	0 (0 to infinity)

Likelihood ratio test for interaction term: 0.801

C. Household contacts who received isoniazid prevention therapy < 3 months

	Isoniazid-sensitive	MDR	Mono-isoniazid resistant
	N=1727; event=88	N=465; event=25	N=210; event=7
INH prevention therapy	HR (95% CI)	HR (95% CI)	HR (95% CI)
No	Ref	Ref	Ref
Yes	1.65 (0.62 – 4.4)	0.31 (0.03 - 2.82)	1.9 (0.13 - 27.14)

Likelihood ratio test for interaction term: 0.797