Supplementary Appendix

Table of Contents

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Methods

Recruitment

This study was conducted in Lima in 106 district health centers that provide care to a population of approximately three million residents. We enrolled all patients who were newly diagnosed with pulmonary tuberculosis and over 15 years of age. The diagnosis was performed by a health center clinician on the basis of sputum smear microscopy or chest radiography. We collected an additional sputum sample from consenting participants which we sent for repeat sputum smear microscopy, mycobacterial culture, and drug sensitivity testing. We confirmed the microbiological status of their pulmonary tuberculosis disease with either a positive sputum smear or mycobacterial culture. We requested permission to visit each patient's household and recruit his or her household contacts (household contacts) 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

We collected the following data from index patients at the time of enrollment: age, gender, occupation, symptoms of tuberculosis, duration of symptoms, history of tuberculosis disease, alcohol, intravenous drug, recreational drug, and tobacco history, and comorbidities including HIV and diabetes mellitus. Patients who did not know their HIV status had blood drawn for HIV and CD4 count. Signs associated with tuberculosis disease, height, and weight were recorded. Index patients also underwent HIV testing and were evaluated with a chest radiograph. The time to treatment was measured as the number of days the patient reported coughing prior to diagnosis.

Bacteriological cultures and drug susceptibility testing

Sputum samples were tested for the presence of acid-fast bacilli by Ziehl-Neelsen staining and cultured by inoculation in two tubes containing Lowenstein-Jensen or Ogawa medium. Indirect susceptibility testing to isoniazid, Rifampicin (RIF), Ethambutol (EMB) and Streptomycin (STR) was conducted by the Löwenstein-Jensen Proportion Method, using the following drug concentrations: isoniazid (0.2 and 1.0 μg/ml), RIF (40.0 μg/ml), EMB (2.0 μg/ml), and STR (4.0 μg/ml). Susceptibility to Pyrazinamide (PZA) (100 ug/ml) was tested using the Wayne method. DNA from each mycobacterial culture was extracted and genotyped by 24-loci mycobacterial interspersed repetitive units-variable-number tandem repeats (MIRU-VNTR) using standard methods (1).

Whole genome sequencing on culture positive isolates

Mtb strains were sequenced on an Illumina Hiseq 4000 in paired-end mode with a read-length of 100-150 base-pairs (bps) and at least a 50-fold coverage (2). The paired-end raw sequence data were mapped to the H37Rv reference genome using the BWA mem algorithm (3). We used SAMtools (default settings) and pilon to identify the single nucleotide polymorphisms (SNPs) across the whole genome using a coverage-based approach (4, 5). We assigned a call as missing if the valid depth of coverage at a specific site is less than 10 reads, if the mean read mapping

quality at the site does not reach 7, or if none of the alternative alleles account for at least 90% of the valid coverage.

Follow-up of index patients

Index patients received directly observed therapy at their district health clinics, as specified in the Peruvian National Tuberculosis Control Program (NTP) guidelines for drug-sensitive and drug-resistant tuberculosis. Patients with drug-sensitive tuberculosis received a standard 6-month course with a 2-month "intensification phase" of isoniazid, RIF, PZA, and EMB followed by a 4-month "consolidation phase" of isoniazid and RIF alone. Patients with MDR-tuberculosis, received treatment according to NTP guidelines. Since results for routine drug resistance testing were often not available for two to three months after initial diagnosis, patients who were not previously suspected of having MDR-tuberculosis, were started on a first-line drug regimen until MDR-tuberculosis, was confirmed.

Isoniazid preventive therapy for household contacts

The 2006 Peruvian National tuberculosis Program recommended that household contacts 19 years old or younger and those who had a specified comorbidity should receive six months of isoniazid preventive therapy while those with HIV should receive 12 months (6). Children aged 19 and under were offered isoniazid preventive therapy at the time index patients were diagnosed, regardless of tuberculin skin test (TST) status. Health care providers often chose to discontinue isoniazid preventive therapy in household contacts if the index patient was subsequently diagnosed with MDR-tuberculosis, but some MDR-exposed household contacts received a full course of isoniazid preventive therapy. We used medical records from participating hospitals and health clinics to determine the duration of isoniazid preventive therapy.

Enrollment of household contacts

At the time of the enrollment of household contacts, study workers collected the following data: whether isoniazid preventive therapy had been initiated, age, gender, relationship to index patient, housing information including number of rooms, building material, type of flooring, education, residential district, history of incarceration, occupation, alcohol, cigarette and illicit drug intake, general health history including previous history of tuberculosis, BCG vaccination, co-morbidities, BMI medications taken. Participants were assessed for symptoms associated with tuberculosis disease including cough, night sweats, weight loss, and fever. Those with symptoms were referred to their local health clinic for chest radiography and clinical evaluation for active tuberculosis disease. Household members with no known history of active tuberculosis disease or previously documented infection received a TST, and those with unknown HIV status were tested for HIV.

Follow-up of household contacts

Participants were revisited in their household at two, six, and 12 months and were asked whether they had been diagnosed with tuberculosis 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. Participants who tested negative at the initial study visit and who had not developed active tuberculosis disease at the time of the follow-up visit underwent repeat TST and clinical evaluation at six and 12 months. We used medical records from participating hospitals and health clinics to determine the duration of isoniazid preventive therapy.

Data categorization

We considered household contacts to have received isoniazid preventive therapy in response to the exposure to the index patient if isoniazid was initiated within three months of that patient's diagnosis. We categorized participants according to their alcohol intake as nondrinkers if they reported having consumed no alcoholic drinks per day, light drinkers if they reported drinking <40 grams or <3 alcoholic drinks per day, and heavy drinkers if they reported drinking 40 grams or more of alcohol or three or more drinks per day. A large proportion of smokers reported smoking only a single cigarette per day. We classified people as nonsmokers if they reported no cigarette smoking, as light smokers if they reported smoking one cigarette per day, and as heavy smokers if they reported smoking more than one cigarette per day. We defined nutritional status for children based on the WHO body mass index (BMI) z-score tables (7). We assigned people with BMI z-scores of less than two as underweight and those greater than two as overweight.

We created a continuous variable to capture household socioeconomic status (SES) by including variables on housing quality, water supply, and sanitation in a principal component analysis (PCA). PCA is a data reduction statistical technique that extracts a set of uncorrelated 'principal components' from a set of correlated variables, where each principal component is a weighted linear combination of the original variables. The continuous SES score was categorized into tertiles corresponding to relative "low," "middle," and "upper" SES. We categorized household average education into "low," "middle," and "upper" levels.

Outcome definition

We identified incident tuberculosis among household contacts during scheduled household visits and from a systematic review of tuberculosis registries at the participating health clinics to ensure we obtained all the incident tuberculosis among household contacts during the one-year follow-up. We considered household contacts to have co-prevalent tuberculosis if they were diagnosed within two weeks of the diagnosis of the index case. If household contacts were diagnosed between two weeks and 15 months after diagnosis of the index case, we considered them "secondary" cases. Diagnosis of adult secondary tuberculosis followed the same criteria as outlined above for index cases. We defined secondary tuberculosis disease among contacts younger than 18 years of age according to the consensus guidelines for classifying tuberculosis disease in children (8).

Analyses

We included in our analysis only household contacts under 19 because older contacts were only offered isoniazid preventive therapy if they had comorbidities that substantially increased their risk of tuberculosis disease. We used a Cox frailty proportional hazards model to evaluate risk factors for incident tuberculosis disease, accounting for clustering within households (9). We first performed a univariate analysis to examine the effect of isoniazid preventive therapy on tuberculosis incidence, followed by a multivariate model in which we adjusted for the age of the index case age and the age, SES and tuberculosis history of the household contact. To evaluate whether the effect of isoniazid preventive therapy on tuberculosis incidence varied by resistance profile of the index case, we added a variable representing isoniazid resistance in the index case and an interaction term for isoniazid-resistance and isoniazid preventive therapy. Because the spectrum of isoniazid resistance-causing mutations that lead to isoniazid mono-resistance may differ from those that lead to MDR-tuberculosis, we classified strains as sensitive, mono-isoniazid-resistant, or MDR-tuberculosis, (resistant to both isoniazid and RIF). Previous studies have shown that the efficacy of isoniazid preventive therapy treatment is reduced if the treatment is ended within three months (10). We therefore repeated these analyses stratifying by a dichotomous variable that captured treatment for more or less than three months. We also considered the possibility that household contacts ≤ 5 years of age would be more likely to acquire tuberculosis 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 isoniazid preventive therapy on disease in the household contacts was a function of the mean inhibitory concentrations (MICs) of the infecting organism, we repeated these analyses for the subset of household contacts exposed to index cases for whom quantitative isoniazid-resistance was available.

Verifying our finding with an independent dataset

We conducted a similar 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. (11). This study enrolled 1,055 household contacts of 213 MDR-tuberculosis, index cases and 2,362 household contacts of 487 drug-susceptible index cases and measured incident tuberculosis over 2-years of follow-up. Drug susceptibility testing for isoniazid and RIF was performed for all index cases' samples using microscopic observation drug susceptibility assays in regional laboratories and results were confirmed in the national reference laboratory using proportions methods (12). The investigators note that isoniazid preventive therapy was discontinued in this group after MDR-tuberculosis, index cases were confirmed but data on the duration of isoniazid preventive therapy were not available.

We used a Cox frailty proportional hazards model to evaluate the association between isoniazid preventive therapy and incident tuberculosis infection in individuals aged 19 and under, accounting for clustering within each matched set. We first performed univariate analysis, followed by a multivariate model adjusted for household contacts' age, SES, and previous tuberculosis history. We then added a dichotomous variable for the drug resistance status (MDR

or sensitive) in the index case, as well as interaction terms for the resistance profile and isoniazid preventive therapy to evaluate whether the effect of isoniazid preventive therapy on tuberculosis incidence varied by the resistance profile of index cases.

Figure S1. Flow diagram of household contacts of household contacts of index tuberculosis patients

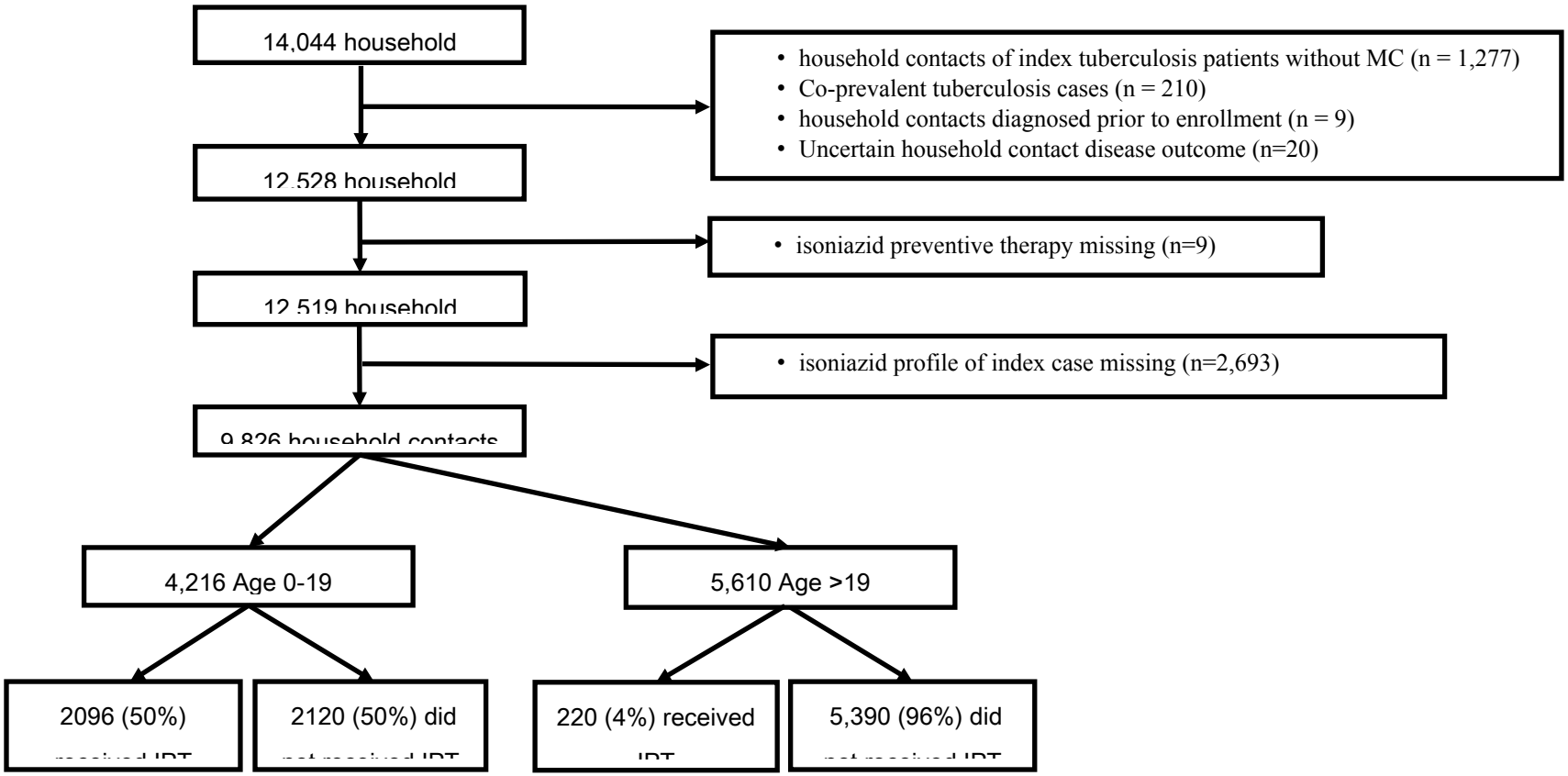


Figure S2. Duration of isoniazid prevention therapy by isoniazid resistant profile pattern of tuberculosis index cases

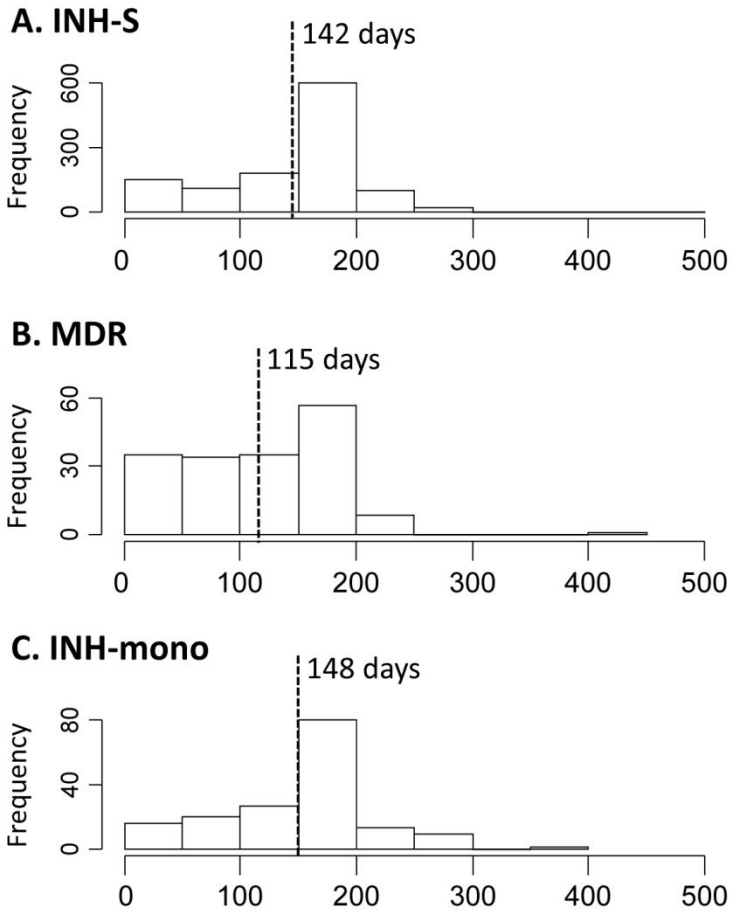
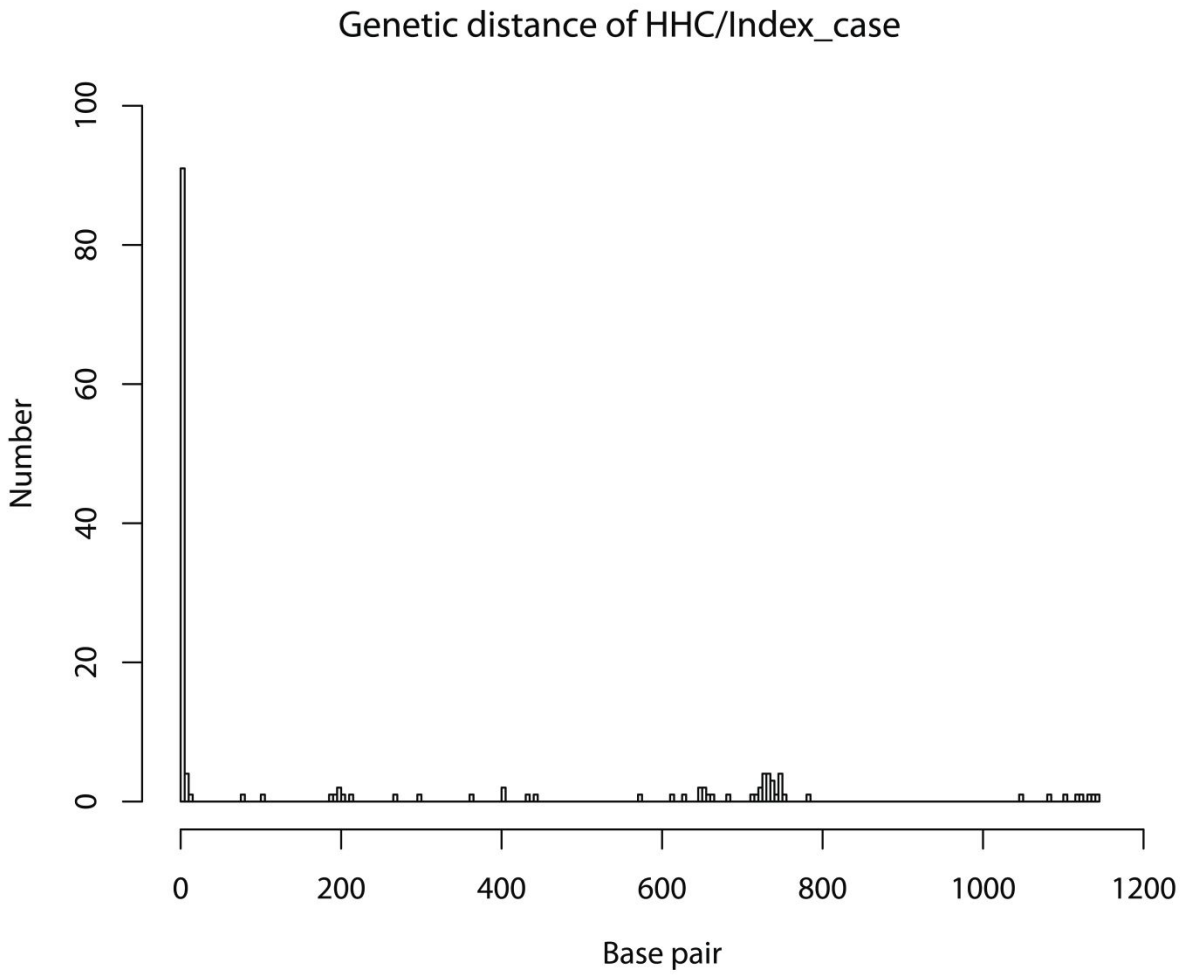


Figure S3. Genetic distance of secondary cases and their index cases



Tables

Table S1. Baseline characteristics of household contacts ≤ 19 years old and exposed to an index case with drug-sensitive tuberculosis, stratified by isoniazid prevention therapy.

Characteristic	No isoniazid preventive therapy		Isoniazid preventive therapy		p-value*
	N	%	N	%	
Age in years (N=3,164)					<0.01
0 to 5	484	32%	659	40%	
6 to 10	324	21%	417	26%	
11 to 15	349	23%	354	22%	
16 to 19	377	25%	200	12%	
Gender (N=3,164)					0.33
Female	786	51%	806	49%	
Male	748	49%	824	51%	
HIV seropositive (N=3,128)					0.12
No	1,508	100%	1,616	100	
Yes	4	0%	0	0%	
Diabetes Mellitus (N=3,157)					0.98
No	1,529	100%	1,627	100	
Yes	1	0%	0	0%	
BCG scars (N=3,164)					0.52
0	299	19%	294	18%	
1	1,197	78%	1,299	80%	
≥2	38	2%	37	2%	
Smoking status (N=3,159)					<0.01
Non-smoker	1,494	98%	1,621	100	
1 cigarette per day	19	1%	5	0%	
>1 cigarette per day	17	1%	3	0%	
Alcohol use (N=3,151)					<0.01
Non-drinker	1,384	91%	1,557	96%	
0 to <3 drinks per day	111	7%	60	4%	
≥3 drinks per day	31	2%	8	0%	
Nutritional status† (N=3,132)					0.07
Normal weight	1,269	84%	1,299	81%	
Underweight	31	2%	46	3%	
Overweight	219	14%	268	17%	
Use of public transportation (N=3,105)					0.12
Non-user	530	35%	629	40%	

1 to 3 days per week	510	34%	484	30%	
4 to 7 days per week	477	31%	475	30%	
Socioeconomic status‡ (N=3,099)					0.19
Low	593	40%	617	39%	
Middle	675	45%	694	43%	
High	233	16%	287	18%	
Tuberculosis infected at baseline (N=3,056)					0.72
No	1,060	72%	1,154	73%	
Yes	410	28%	432	27%	
TB history (N=3,164)					<0.01
No	1,478	96%	1,624	100	
Yes	56	4%	6	0%	
Employment (N=3,162)					<0.01
No	1,373	90%	1,544	73%	
Yes	160	10%	85	27%	
Being a student (N=3,162)					<0.01
No	591	39%	546	34%	
Yes	943	61%	1,082	66%	
Index-case age in years (N=3,164)					<0.01
16-30	915	60%	942	58%	
31 to 45	307	20%	439	27%	
46 to 60	179	12%	118	7%	
>60	133	9%	131	8%	
Index-case sex (N=3,164)					<0.01
Female	599	39%	838	51%	
Male	935	61%	792	49%	
Index-case smoking status (N=3,110)					0.53
None or light smoker	1,486	99%	1,588	99%	
Heavy smoker	15	1%	21	1%	
Index-case drinking status (N=3,035)					0.46
None or light drinker	1,291	89%	1,429	90%	
Light drinker	157	11%	158	10%	
Index-case employment (N=3,150)					0.17
No	1,000	66%	1,104	68%	
Yes	525	34%	521	32%	
Index-case Marijuana use (N=3,159)					<0.01
No	1,213	79%	1,430	88%	
Yes	316	21%	200	12%	
Index-case Cocaine (N=3,159)					<0.01
No	1,275	83%	1,485	91%	
Yes	254	17%	145	9%	
Household incarceration (N=3,164)					<0.01
No	1,343	88%	1,511	93%	
Yes	191	12%	119	7%	
Household education (N=3,164)					<0.01

Low	361	24%	302	19%	
Medium	887	58%	927	57%	
High	286	19%	401	25%	
Household district (N=3,164)					<0.01
Cercado de Lima	180	12%	96	6%	
Comas	97	6%	117	7%	
El Agustino	193	13%	36	2%	
La Victoria	193	13%	153	9%	
Los Olivos	144	9%	188	12%	
Rimac	60	4%	250	15%	
San Martin de Porres	261	17%	452	28%	
Santa Anita	115	7%	71	4%	
Others	291	19%	267	16%	

* Compared the two groups used a χ^2 test

† Nutritional status was defined by the WHO body mass index z-score tables

‡ Socioeconomic status was defined using a principal component analysis based on housing quality,

Abbreviation: N: number; MDR: multi-drug resistant

Table S2. Baseline characteristics of household contacts ≤ 19 years old and exposed to an index case with MDR tuberculosis, stratified by isoniazid prevention therapy.

Characteristic	No isoniazid preventive therapy		Isoniazid preventive therapy		p-value[a]
	N	%	N	%	
Age in years (N=666)					<0.01
0 to 5	124	31%	118	45%	
6 to 10	83	21%	67	25%	
11 to 15	101	25%	51	19%	
16 to 19	93	23%	29	11%	
Gender (N=666)					0.07
Female	215	54%	122	46%	
Male	186	46%	143	54%	
HIV seropositive (N=658)					NA
No	398	100	260	100%	
Yes	0	0%	0	0%	
Diabetes Mellitus (N=663)					1
No	399	100	262	100%	
Yes	1	0%	1	0%	
BCG scars (N=666)					0.54
0	88	22%	53	20%	
1	301	75%	207	78%	
≥2	12	3%	5	2%	
Smoking status (N=666)					0.19
Non-smoker	396	99%	265	100%	
1 cigarette per day	2	0%	0	0%	
>1 cigarette per day	3	1%	0	0%	
Alcohol use (N=661)					<0.01
Non-drinker	366	92%	259	98%	
0 to <3 drinks per day	24	6%	4	2%	
≥3 drinks per day	7	2%	1	0%	
Nutritional status[b] (N=658)					0.35
Normal weight	331	83%	214	83%	
Underweight	7	2%	9	3%	
Overweight	61	15%	36	14%	
Use of public transportation (N=643)					0.49
Non-user	145	37%	92	37%	
1 to 3 days per week	129	33%	89	36%	
4 to 7 days per week	122	31%	66	27%	
Socioeconomic status[c] (N=664)					0.09
Low	149	37%	119	45%	

Middle	183	46%	100	38%	
High	68	17%	45	17%	
Tuberculosis infected at baseline (N=638)					<0.01
No	236	62%	205	80%	
Yes	146	38%	51	20%	
TB history (N=666)					<0.01
No	386	96%	265	100%	
Yes	15	4%	0	0%	
Employment (N=666)					0.04
No	357	89%	249	94%	
Yes	44	11%	16	6%	
Being a student (N=666)					0.76
No	153	38%	105	40%	
Yes	248	62%	160	60%	
Index-case age in years (N=666)					<0.01
16-30	247	60%	942	58%	
31 to 45	82	20%	439	27%	
46 to 60	50	12%	118	7%	
>60	22	9%	131	8%	
Index-case sex (N=666)					0.99
Female	174	43%	114	43%	
Male	227	57%	151	57%	
Index-case smoking status (N=638)					0.89
None or light smoker	373	97%	248	98%	
Heavy smoker	11	3%	6	2%	
Index-case employment(N=665)					0.15
No	285	71%	174	66%	
Yes	115	29%	91	34%	
Index-case Marijuana use (N=662)					0.58
No	340	86%	222	88%	
Yes	57	14%	43	12%	
Index-case Cocaine (N=661)					0.52
No	340	86%	233	91%	
Yes	56	14%	32	9%	
Household incarceration (N=666)					0.32
No	347	87%	237	93%	
Yes	57	13%	28	7%	
Household education (N=666)					0.21
Low	88	22%	45	19%	
Middle	240	60%	162	57%	
High	73	18%	58	25%	
Household district (N=666)					<0.01
Cercado de Lima	30	7%	21	8%	
Comas	3	1%	10	4%	
El Agustino	83	21%	16	6%	

La Victoria	62	15%	19	7%
Los Olivos	51	13%	28	11%
Rimac	7	2%	30	11%
San Martin de Porres	81	20%	87	33%
Santa Anita	18	4%	10	4%
Others	66	16%	44	17%

[a] Compared the two groups used a χ^2 test

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

[c] Socioeconomic status was defined using a principal component analysis based on housing quality,

Abbreviation: N: number; MDR: multi-drug resistant

Table S3. Baseline characteristics of household contacts ≤ 19 years old and exposed to an index case with isoniazid-mono resistant tuberculosis, stratified by isoniazid prevention therapy.

Characteristic	No isoniazid preventive therapy		Isoniazid preventive therapy		p-value[a]
	N	%	N	%	
Age in years (N=386)					<0.01
0 to 5	56	30%	78	39%	
6 to 10	32	17%	48	24%	
11 to 15	39	21%	46	23%	
16 to 19	58	31%	29	14%	
Gender (N=386)					0.3
Female	86	46%	105	52%	
Male	99	54%	96	48%	
HIV seropositive (N=378)					NA
No	180	100%	198	100%	
Yes	0	0%	0	0%	
Diabetes Mellitus (N=382)					1
No	183	100%	198	99%	
Yes	0	0%	1	1%	
BCG scars (N=386)					0.1
0	36	19%	54	27%	
1	142	77%	144	72%	
≥2	7	4%	3	1%	
Smoking status (N=384)					0.04
Non-smoker	178	97%	200	100%	
1 cigarette per day	4	2%	0	0%	
>1 cigarette per day	2	1%	0	0%	
Alcohol use (N=383)					0.11
Non-drinker	162	89%	190	95%	
0 to <3 drinks per day	14	8%	9	4%	
≥3 drinks per day	6	3%	2	1%	
Nutritional status[b] (N=383)					0.69
Normal weight	148	81%	168	84%	
Underweight	6	3%	4	2%	
Overweight	28	15%	29	14%	
Use of public transportation (N=372)					0.44
Non-user	61	33%	74	39%	
1 to 3 days per week	70	38%	67	36%	
4 to 7 days per week	53	29%	47	25%	
Socioeconomic status[c] (N=365)					0.12

Low	79	45%	65	34%	
Middle	73	41%	93	49%	
High	24	14%	31	16%	
TB infected at baseline (N=374)					0.94
No	121	68%	135	69%	
Yes	57	32%	61	31%	
TB history (N=386)					0.45
No	178	96%	197	98%	
Yes	7	4%	4	2%	
Employment (N=386)					0.09
No	163	88%	188	94%	
Yes	22	12%	13	6%	
Being a student (N=386)					0.66
No	65	35%	76	38%	
Yes	120	65%	126	62%	
Index-case age in years (N=386)					0.28
16-30	102	55%	102	51%	
31 to 45	49	26%	69	34%	
46 to 60	23	12%	17	8%	
>60	11	6%	13	6%	
Index-case sex (N=386)					0.8
Female	63	43%	72	43%	
Male	122	57%	129	57%	
Index-case smoking status (N=377)					0.22
None or light smoker	178	98%	185	95%	
Heavy smoker	4	2%	10	5%	
Index-case drinking status (N=378)					0.44
None or light drinker	155	86%	175	89%	
Heavy drinker	26	14%	22	11%	
Index-case employment (N=385)					<0.01
D	127	69%	106	53%	
Yes	57	31%	95	47%	
Index-case Marijuana use (N=385)					0.05
No	162	88%	159	90%	
Yes	23	12%	41	10%	
Index-case Cocaine (N=386)					0.61
No	159	86%	168	90%	
Yes	26	14%	33	10%	
Household incarceration (N=386)					0.86
No	173	94%	186	90%	
Yes	12	6%	15	10%	
Household education (N=386)					<0.01
Low	50	27%	27	68%	
Middle	75	41%	116	32%	

High	60	32%	58	68%	
Household district (N=386)					<0.01
Cercado de lima	28	15%	18	9%	
Comas	12	6%	8	4%	
El Agustino	18	10%	0	0%	
La Victoria	18	10%	6	3%	
Los Olivos	17	9%	22	11%	
Rimac	17	9%	43	21%	
San Martin de Porres	31	17%	66	33%	
Santa Anita	5	3%	2	1%	
Others	39	21%	36	18%	

[a] Compared the two groups used a χ^2 test

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

[c] Socioeconomic status was defined using a principal component analysis based on housing quality,

Abbreviation: N: number; MDR: multi-drug resistant

Table S4. Effect of isoniazid prevention therapy on disease incidence of household contacts ≤ 19 years of age by isoniazid resistant profile pattern of tuberculosis index cases

	Cases/Person-year*	Univariate analysis	Multivariate**
		HR (95% CI)	HR (95% CI)
Isoniazid prevention therapy			
No	108/4,250	Ref	Ref
Yes	38/2,583	0.33 (0.22-0.48)	0.31 (0.2-0.47)
Isoniazid resistant profile			
Sensitive	108/3,849	Ref	Ref
MDR	27/806	1.17 (0.74-1.85)	0.97 (0.6-1.56)
Mono-isoniazid-resistant	11/470	0.82 (0.43-1.59)	0.8 (0.41-1.56)

** Numbers for univariate analyses

*Adjusted for index case age, recreational drug use, household contact age, gender, BCG-vaccination scar, nutritional status, being a student or not, tuberculosis history, household socio-economic status, and household residential district

Abbreviations: HR: Hazard ratio; CI: confidence interval; Ref: Reference group; MDR: multi-drug resistant.

Table S5. The effect of isoniazid prevention therapy on tuberculosis incidence in ≤19 year olds, by isoniazid resistance status of index patient, adjusted for index case age, household contact age, gender, BCG-vaccination scar, nutritional status, being a student or not, tuberculosis history, recreational use of index case, household socio-economic status, and household residential district.

A. Complete dataset

Isoniazid prevention therapy	Isoniazid-sensitive		MDR		Mono-isoniazid resistant	
	Cases/Person-year	HR (95% CI)	Cases/Person-year	HR (95% CI)	Cases/Person-year	HR (95% CI)
No	78/1,782	Ref	23/474	Ref	6/209	Ref
Yes	28/1,947	0.3 (0.18-0.48)	3/320	0.19 (0.05-0.66)	5/231	0.8 (0.23-2.8)

Likelihood ratio test for interaction term: <0.001

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

Isoniazid prevention therapy	Isoniazid-sensitive		MDR		Mono-isoniazid resistant	
	Cases/Person-year	HR (95% CI)	Cases/Person-year	HR (95% CI)	Cases/Person-year	HR (95% CI)
No	78/1,782	Ref	23/474	Ref	6/209	Ref
Yes	10/1133	0.17 (0.08-0.35)	1/127	0.17 (0.02-1.34)	3/150	0.69 (0.15-3.09)

Likelihood ratio test for interaction term: <0.001

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

Isoniazid prevention therapy	Isoniazid-sensitive		MDR		Mono-isoniazid resistant	
	Cases/Person-year	HR (95% CI)	Cases/Person-year	HR (95% CI)	Cases/Person-year	HR (95% CI)
No	78/1,782	Ref	23/474	Ref	6/209	Ref
Yes	10/273	0.89 (0.43-1.83)	1/77	0.31 (0.03-1.98)	1/42	1.31 (0.14-11.95)

Likelihood ratio test for interaction term: 0.255

Table S6. The effect of isoniazid prevention therapy on tuberculosis incidence in baseline infected ≤19 year olds, by isoniazid resistance status of index patient, adjusted for index case age, household contact age, gender, BCG-vaccination scar, nutritional status, being a student or not, tuberculosis history, recreational use of index case, household socio-economic status, and household residential district.

Isoniazid prevention therapy	Isoniazid-sensitive		MDR		Mono-isoniazid resistant	
	Cases/Person-year	HR (95% CI)	Cases/Person-year	HR (95% CI)	Cases/Person-year	HR (95% CI)
No	58/434	Ref	18/164	Ref	3/66	Ref
Yes	16/504	0.19 (0.1-0.35)	1/61	0.14 (0.02-1.07)	4/69	1.09 (0.23-5.3)

Likelihood ratio test for interaction term: <0.001

Table S7. Isoniazid preventive therapy provided and outcomes achieved.

Study	Region	Treatment	Treatment group (case/total N)	Control group (case/total N)	Follow up time
Kritski Brazil 1996 (13)	Brazil	High dose	2/45	145	10,604-person-months
Schaaf et al. 2002 (14)	South Africa	Various, all have isoniazid	2/41	13/64	30 months
Attamna et al. 2009 (15)	Israel	Isoniazid	0/71	0/387	2,666 person years
Tochon et al. 2011(16)	France	Isoniazid and rifampin up to 3 month	1/6	NA	NA
Denholm et al. 2012 (17)	Australia	Various (all were not under regular isoniazid preventive therapy)	0/11	2/38	Median 54 months
Seddon et al. 2013 (18)	South Africa	High dose isoniazid, ethionamide and ofloxacin	6/187	NA	219 patient-years
Garcia-Prat et al. 2014 (19)	South Africa	High dose isoniazid, ethionamide and ofloxacin	0/21	0/10	1 year
Wu et al. 2018 (20)	China	Isoniazid	2/5	4/16	6 months

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