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Protective effects of household-based TB interventions are robust to neighbourhood-level variation in exposure risk in Lima, Peru: a model-based analysis

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Abstract

Background: Untargeted active screening and treatment programmes for tuberculosis (TB) have not been shown to be more effective than passive screening and isoniazid preventive therapy (IPT) for reducing TB incidence. In this manuscript, we compare the efficacy of targeting screening and IPT on high-risk household contacts of diagnosed TB cases, with less-targeted active screening approaches in Lima, Peru.

Methods: We conducted a population-based prospective cohort study within households of TB cases in Lima. We identified all adults diagnosed with incident pulmonary TB from 2009 through 2012 at 106 participating public health centres (HC) within our catchment area of ~3.3 million inhabitants. We estimated combined effects of community and household exposure on the risk of latent TB infection (LTBI) and incident TB disease. We used simulation modelling to assess the efficacy of TB screening programmes for reducing the risk of incident TB in these contacts.

Results: Individuals with household exposure to TB are more likely to present with LTBI and TB disease than those without this exposure, despite wide variation in community exposure. Simulations suggest that more cases are prevented by 1000 administrations of IPT to tuberculin skin test (TST)-positive household contacts of identified TB cases (30, 95% CI = 16,47) than from blanket screening and treatment in the community (7, 95% CI = 2,17).

Conclusions: Household exposure remains a major driver of incident TB risk among household contacts of identified TB cases. Targeting interventions on these individuals is likely to prevent more cases of TB than blanket screening of individuals in the community.

Key words: Tuberculosis, targeting, intervention, hierarchical modeling

Key Messages

- Passive detection and treatment of TB is not sufficient to bring TB under control in many high-incidence settings, but community-wide active screening and treatment have not been shown to be more effective.
- More targeted active approaches focusing on the high-risk household contacts of identified TB cases are a promising alternative. However, it is not yet clear if high rates of community exposure to infection may undermine the expected efficiency gains of interventions targeted to at-risk household contacts.
- Our analysis suggests that targeting TB screening and treatment on household contacts with latent TB infection will prevent more cases on a per-screening basis than untargeted community-wide screening and treatment, and that this type of targeting is robust to observed variation in community exposure in Lima, Peru.

Introduction

Global progress toward the control of tuberculosis (TB) is not on pace to meet post-2015 TB elimination goals of by 2030 an 80% reduction in TB deaths, 60% reduction in TB incidence and zero catastrophic costs for families affected by TB, compared with 2015 levels.[1] It is now clear that the standard public health approach used against TB, which relies primarily on passive detection and treatment, is not sufficient to bring TB under control in many high-incidence settings.[2] Although new tools such as better diagnostics, shortened drug regimens, better treatments for drug-resistant disease and novel vaccines may eventually facilitate TB control efforts, we cannot wait on these technologies to accelerate our response to this ongoing public health crisis.

Options for accelerating reductions in TB using existing tools may include active case finding and expanded use of preventive therapy. These approaches aim to reduce TB incidence by finding cases more promptly, thus interrupting transmission. Despite the sound rationale for these interventions, the results of a systematic review,[3] large cluster randomized clinical trials of community-wide approaches for active case finding[4] and cluster-wide provision of preventive therapy[5] have been disappointing. Each of these studies found a lack of significant impact of untargeted use of these interventions for reducing TB transmission in high-incidence settings.

In light of the unclear benefits of untargeted active case finding and preventive therapy, we are interested in understanding whether concentrating these interventions among high-risk household contacts of TB cases in Lima, Peru can improve their impact. Analyses of routine TB programme data[6] and prospective cohort studies from Lima[7] have revealed the high risk of infection and disease among household contacts of TB cases as well as spatial variability in TB infection and disease risk within this city. In the current analysis, we use statistical and simulation models to determine whether targeted screening and treatment are likely to be robust to neighbourhood variation in TB exposure.

Methods

Data

We conducted a population-based prospective cohort study within households of tuberculosis index cases in contiguous areas of Lima Ciudad and Lima Este. Between September 2009 and August 2012, we identified all adults (> 15 years old) diagnosed with incident pulmonary tuberculosis at any of 106 public health centres (HC) in our study catchment area of ~3.3 million inhabitants. This area includes 12 of the 43 districts of metropolitan Lima, and reflects a mix of urban and peri-urban areas and informal settlements. Within Lima, individuals must present at their locally assigned HC for TB diagnosis and treatment. Within 1 month of diagnosis of tuberculosis in these 'index patients', a study nurse visited the patient's home and invited all other individuals in the household to participate in a baseline assessment of tuberculosis infection and disease. Household contacts were followed for incident infection and disease for 12 months. Informed consent was

obtained from all study participants; study design is described in further detail in reference 8.

As in reference 9, we take advantage of the fact that 22% of enrolled index cases diagnosed with TB based on clinical presentation had both negative sputum smear and negative culture results. Although such individuals are included in official notification statistics, they are known to be less infectious than microbiologically confirmed cases.[10]

We isolated household exposure from community exposure by contrasting the latent TB infection (LTBI) status of household contacts of smear-positive/culture-positive index cases (SCPIs) and smear-negative/culture-positive index cases (CPIs) with those who were exposed to a smear-negative/culture-negative index case (NIs). Consistent with previous observations,[10–12] we hypothesized that SCPIs are the most infectious household index cases, followed by CPIs and then NIs. LTBI was measured using the tuberculin skin test (TST) with a 10-mm cutoff. We refer to individuals with a TST $\geq$ 10 mm as TST+ individuals and those with a TST $<$ 10 mm as TST-.

In the current analysis, we focus on household contacts aged $\leq$30 years, because of the concentration of household infection risk among younger individuals demonstrated in previous analyses[9] and to minimize the potential effect of decreasing TST reactivity with age.[13] In the original dataset, there were 14 044 household contacts exposed to 3446 index cases. From this dataset, 5345 individuals were excluded because they were aged >30 years, leaving 8487 household contacts $\leq$30 years. An additional 343 contacts were excluded because of missing information on their BCG or IPT status, or because the bacteriological status of their household index case was missing. Our final dataset contains 8144 household contacts exposed to 2829 household index cases. Of these, 4637 (56.9%) were exposed to an SCPI, 1517 (18.6%) were exposed to a CPI and 1990 (24.4%) were exposed to an NI; 488 (6.0%) contacts had a co-prevalent household case diagnosed with TB at the same time as the index case. In the final dataset, 733 (9.0%) individuals were not administered a TST at baseline because they had received a TST in the 6 months preceding enrolment. An additional 544 (6.7%) household contacts had neither a baseline administered TST nor a TST within the 6 months preceding enrolment. The unobserved LTBI status of these individuals is modelled by a latent variable; for additional information, see the supplementary materials, available as Supplementary data at *IJE* online.

Data model

We developed a statistical model to estimate the combined effects of heterogeneous community and household exposure on LTBI prevalence. This model also relates source of infection to risk of developing TB disease. Each individual's LTBI status is indicated by the binary variable y_i; $y_i = 1$ denoting TST+. The binary variable z_i indicates whether the individual developed TB disease during the year-long follow-up period.

Household and community risks of TB infection

LTBI in an individual with household TB exposure may be attributable to the known episode of household exposure or to unobserved exposure in the community from birth until current age a_i. To capture these different sources of risk, our model includes an explicit representation of heterogeneous exposure in the community as well as the risk associated with a single episode of household exposure to an SCPI or CPI. This model is meant specifically to capture first TB infections, represented by the transition from TST-negativity (TST $<$ 10 mm) to TST-positivity (TST $\geq$ 10 mm). First infections have been demonstrated to be more likely to result in disease than subsequent reinfections, which are less likely to result in a TST status conversion.[14,15]

To capture local variation in community TB exposure, we allow the annual risk of TB infection (ARTI) to vary across HC areas. We denote α_j to be the baseline ARTI in health centre catchment j. We model variation across HC catchment areas using a Gaussian prior, where μ_α is the average baseline ARTI across all HC areas and σ_α is the standard deviation of log-ARTI across HC catchments:

$$log(\alpha_j) \sim Normal(log(\mu_\alpha), \sigma_\alpha)$$

We denote an individual's total community exposure from birth to age a_i as $\lambda_{ij}^{COM} = \alpha_j a_i$. We denote X_i^H to be a binary vector indicating whether an individual was exposed to a CPI or SCPI and if there were any co-prevalent cases at the time of diagnosis of the index case. β^H is a vector of coefficients corresponding to the rate of infection for each type of household exposure, so to the force of infection (FOI) from household exposure, $\lambda_i^{HH} = X_i^H \beta^H$. Finally, λ_{ij} indicates the total FOI on individual i living in HC j:

$$\lambda_{ij} = (\lambda_{ij}^{COM} + \lambda_i^{HH}) e^{X i \gamma}$$

Since the TST is left-censored, i.e. only indicating infection at age $\leq a_i$, we model the probability of observing a positive TST at age a_i using the cumulative distribution function (CDF) of the exponential distribution:

$$Pr(y_i = 1) = 1 - e^{-\lambda_{ij}}$$

Incident TB disease risk

We use a logistic regression model to estimate the risk of incident TB disease attributable to household exposure

during the year-long follow-up period. Because the source of an individual's LTBI is unobserved, we use a latent variable, ζ_i, to indicate whether TST-positive individual i was infected in the household or community. $\zeta_i = 1$ indicates that the individual was infected in the home and $\zeta_i = 0$ indicates that she or he was infected in the community. Following Cauchemez *et al.*,[16] we can then model the probability that a TST-positive individual was infected in the home, using the ratio of the probability of infection in the household and the total probability of LTBI:

$$Pr(\zeta_i = 1|y_i = 1) = \frac{\left(1.0 - exp(-\lambda_i^{HH})\right) exp(-\lambda_{ij}^{COM})}{1.0 - exp(-\lambda_{ij})}$$

To determine whether individuals with household-acquired LTBI are more likely to develop TB disease than those infected in the community, we allow the risk of TB disease to vary by infection source. α_{HH} and α_{COM} indicate the log odds ratio (OR) of incident TB disease associated with household-acquired LTBI and community-acquired LTBI, relative to TST-negativity. β is a vector of regression coefficients including terms for BCG and IPT as well as effects of SCPI/CPI exposure on TB disease not captured by α_{HH}. We can then estimate the individual's probability of incident TB, conditional on LTBI status and infection source:

$$Pr(z_i = 1|y_i, \zeta_i) = \begin{cases} logit^{-1}(x'\beta), & \text{if } y_i = 0 \\ logit^{-1}(\alpha_{COM} + x'\beta), & \text{if } y_i = 1,\ \zeta_i = 0 \\ logit^{-1}(\alpha_{HH} + x'\beta), & \text{otherwise} \end{cases}$$

All parameter estimation was performed using Stan v2.9 via the RStan package for R v3.2.[17]

Policy model

WHO guidelines for resource-limited settings with high ARTI recommend that only the young-child (≤5 years) household contacts of identified TB cases and all HIV-positive individuals receive isonaizid preventive therapy (IPT).[1] However, recent results suggest that >40% of latent TB infections among child and young adult household contacts (≤15 years) of identified TB cases in Lima, Peru, may be attributable to household exposure[9] and that household contacts ≤ age 30 who received IPT were half as likely to develop TB disease during the year following exposure[8] than those who did not.

To understand the implications of heterogeneity in community exposure for surveillance and intervention, we use predictions from the statistical model defined above to estimate the number of cases expected to be prevented by 1000 administrations of IPT, under three scenarios reflecting increasing intensity of targeting:

i. Community-based screening and IPT: individuals aged ≤30 are selected at random from the community and screened for LTBI. Individuals with LTBI are administered IPT.
ii. Household-based IPT: all household contacts ≤30 years old of bacteriologically positive TB cases (i.e. smear-positive/culture-positive and smear-negative/culture-positive) are administered IPT.
iii. Household-based screening and IPT: household contacts ≤30 years old of bacteriologically-positive TB cases are screened for LTBI, and TST-positive individuals are administered IPT.

For a detailed description of this model, see the supplementary materials, available as Supplementary Data at *IJE* online.

Results

Household and community LTBI risk

Table 1 shows parameter estimates for risks of LTBI associated with household and community exposure. This shows that FOI from a single episode of household exposure to an SCPI, $\beta_{SCPI} = 0.14$ (95% CI = 0.12,0.17), and to a CPI is $\beta_{CPI} = 0.07$ (95 % CI = 0.04,0.10). Individuals living with at least one co-prevalent case experienced additional infection risks similar to SCPI exposure (0.18, 95% CI = 0.10,0.27). Across all HC catchment areas, ARTI is approximately 2% per year. This confirms earlier results at the city level, showing that each episode of household exposure is equivalent to approximately a decade of exposure in the community.[9]

Figure 1 illustrates variation in HC-specific cumulative FOI from birth until age 10 (for more information on Figure 1, see the supplementary materials available as Supplementary data at *IJE* online.) We can understand HC variation in ARTI in terms of its relationship to the annual per capita incidence of TB disease in the community, which is illustrated in Figure 2. This shows that an increase in incidence of 100 cases/100 000 population is associated with a 1.36 times increase in HC-level ARTI (95% CI = 1.06, 1.78). We can relate this to the 'Styblo ratio' which has been used to estimate ARTI indirectly from incidence. The classic Styblo ratio suggests that an increase in incidence of 50 smear-positive TB cases/100 000 population corresponds to a 1% increase in ARTI,[18] although the validity of this assumption has been called into question with the growth of HIV and use of supervised short-course chemotherapy.[19,20] In our data, an increase of 148/100 000 of all

Table 1. Risk factors for LTBI. Table contains estimates and 95% posterior credible intervals (CIs) for risk of infection associated with culture-positive (CPI), smear/culture-positive (SCPI) household exposure, as well as the risk of infection associated with exposure to a co-prevalent household case with unknown smear and culture status. The table also contains estimates of hazard ratios for factors associated with individual- and household-level risks, such as overcrowding (more than three people per bedroom), living in a household with a thatch or mud roof as compared with a metal or wood roof, and BCG vaccination

Type	Variable	Median	95% CI	Units
Household exposure	CPI	0.07	0.04,0.10	Infections/exposure
	SCPI	0.14	0.12,0.17	Infections/exposure
	Co-prevalent	0.18	0.10,0.27	Infections/exposure
Susceptibility risks	Crowding	1.13	1.00,1.27	Hazard ratio
	Poor roof	0.91	0.71,1.20	Hazard ratio
	BCG	0.92	0.80,1.09	Hazard ratio

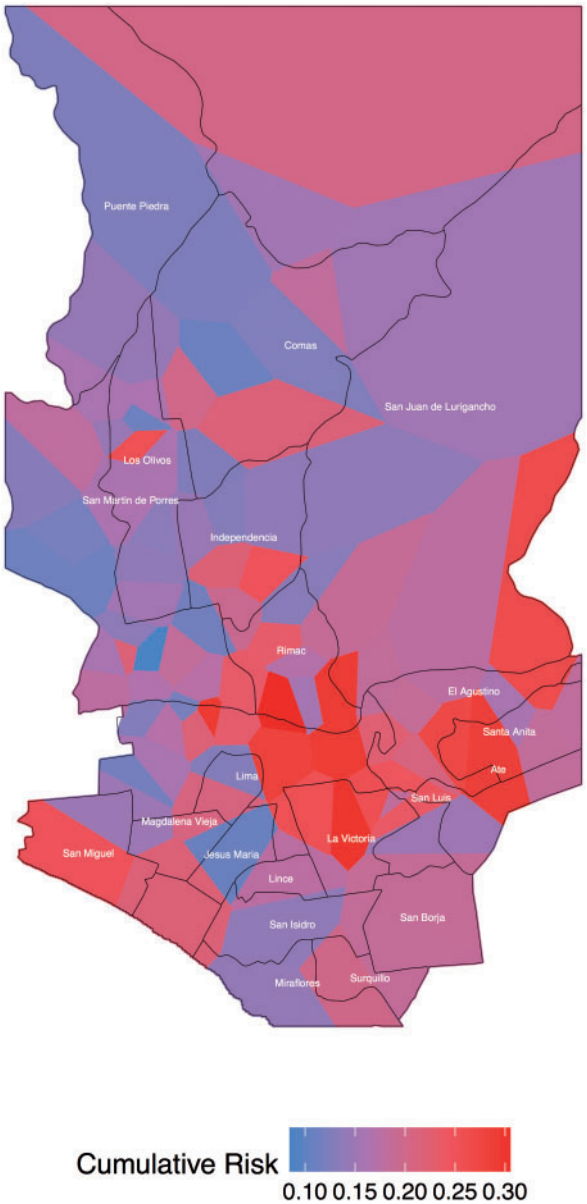

Figure 1. Health Center (HC) Cumulative FOI from Birth to Age 10. Polygons indicate HC catchment areas and fill color (increasing fill intensity) indicates the intensity of exposure to TB in the community.

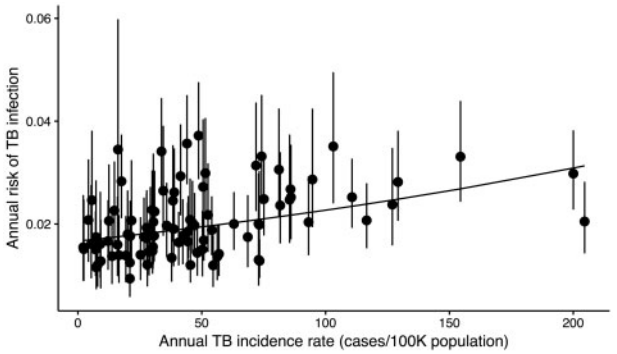

Figure 2. Health Center Annual TB Incidence vs. HC-level Annual Risk of TB Infection. Solid line indicates the predicted relationship between HC-level annual per-capita TB incidence and hc-level ARTI. Dots indicate posterior median values of ARTI for each HC and vertical bars indicate 80% uncertainty intervals for HC-level ARTI estimates.

types of incident TB cases (i.e. smear- and culture-negative, culture-positive and smear-positive) or 84/100 000 smear-positive cases corresponds to a 1% increase in ARTI. For a discussion of model fit, see the supplementary materials, available as Supplementary data at *IJE* online.

Risk of incident TB disease associated with household infection

Results in Table 2 show that there is an increased risk of TB disease associated with both household- and community-acquired LTBI as compared with TST-negativity. Despite the greater point estimate for household-acquired LTBI, the CI for the difference between these risks includes unity.

Adjusting for household-acquired and community-acquired LTBI, there is an increased risk of TB associated with SCPI exposure. This may reflect the fact that individuals with a reactive TST < 10 mm resulting from SCPI exposure are likely to be at increased risk of developing TB disease,[8] and that individuals with LTBI acquired in the community may be reinfected in the household. IPT and

Table 2. Risk factors for incident TB. Table contains odds ratios for incident TB disease during year-long following period, associated with household exposure as well as BCG vaccination and isoniazid preventive therapy

Type	Variable	Median	95% CI
	Intercept	−3.66	−4.37,−2.97
	Age	0.97	0.92,1.01
	HIV-positive	3.99	0.58,16.36
TST	TST-negative	REF	
	Community-acquired LTBI	2.32	1.09,4.27
	Household-acquired LTBI	5.78	1.48,11.98
Exposure	NI	REF	
	CPI	1.40	0.77,2.50
	SCPI	1.82	1.09,3.00
	Co-prevalent	1.24	0.69,2.10
Intervention	IPT	0.37	0.25,0.56
	BCG	0.36	0.19,0.71
	Age x BCG	1.03	0.99,1.08

BCG vaccination are associated with decreased TB risk in our dataset. To account for declining protection from BCG vaccination with age, we include an interaction term which suggests that there is no change in protection associated with BCG vaccination in our data. We also adjust for HIV status; although the coefficient is positive, the wide credible intervals reflect the small number (21) of HIV-positive individuals in our dataset.

Policy scenarios

Figure 3 shows the distribution of simulated outcomes for the three IPT scenarios. The figure shows that more cases are expected to be prevented from 1000 administrations of IPT in the household targeted scenarios (household targeted = 17, 95% posterior predictive interval (PPI) = 7,28; household TST-targeted = 30, 95% PPI = 15,47) than in the blanket community screening and treatment scenario (7 cases, 95% PPI = 2,17).

If we compare the outcomes from these scenarios within simulation steps, i.e. using the same set of parameters, we see that in 88% and 98% of simulations, the numbers of cases prevented in the household-targeted and household TST-targeted scenarios are greater than in the community scenario. In 96% of simulations, the number of cases prevented in the household TST-screening scenario is greater than in the household-targeted scenario. This indicates that overlaps in the outcome distributions in Figure 3 reflect uncertainty in model parameters rather than ambiguity in the relative efficacy of the interventions.

Because the cost of each IPT administration in the proposed interventions is unknown, it is not possible to estimate the cost of each policy scenario. We can, however, understand their relative cost-efficacy using the ratio of number of cases prevented in each scenario. For example, our simulation results suggest that the household-based IPT intervention will be more cost-effective than the community-screening intervention at up to approximately 2.2 times the cost for each IPT administration, although there is considerable uncertainty in this estimate (95% PPI = 0.6, 12.5). By contrast, the household TST-targeted intervention is expected to be more cost-effective than the community-screening intervention at up to 4.0 times the per-administration cost (95% PPI = 1.2, 21.0). TST-targeted household intervention is predicted to be more cost-effective than untargeted household-based administration of IPT at up to 1.8 times the per-administration cost (95% PPI = 1.0, 3.6).

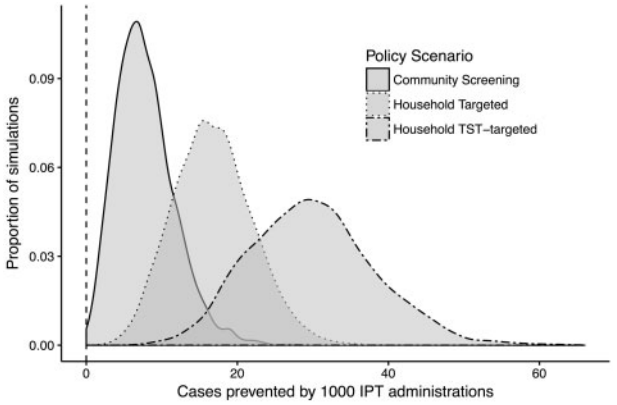

Figure 3. Cases prevented by 1000 administrations isoniazid preventive therapy (IPT) under three screening and treatment scenarios. Densities reflect posterior distributions of the number of cases prevented by 1000 administrations of IPT under three scenarios: 1. Community-based screening and IPT (solid line): Individuals aged ≤30 are selected at random from the community and screened for LTBI. Individuals with LTBI are administered IPT. 2. Household-based IPT (dotted line): All household contacts ≤30 years old of bacteriologically-positive (smear or culture positive) TB cases are administered IPT. 3. Household-based screening and IPT (dashed line): Household contacts ≤30 years old of bacteriologically-positive TB cases are screened for LTBI and TST-positive individuals are administered IPT.

Discussion

Isoniazid preventive therapy (IPT) is an underused tool for preventing TB disease among exposed individuals. In the current analysis, we have explored the potential benefits of three scenarios for providing IPT, each representing an increasing level of targeting of screening and treatment. We found that provision of IPT to household contacts of identified TB cases is likely to be more effective on a per-administration basis than provision of IPT to TST-positive individuals in the community at large, particularly when IPT is concentrated on household contacts with LTBI. This

is consistent with theory and models that suggest that where there is heterogeneity in infection risk, untargeted interventions are expected to underperform.[21] Importantly, our results show that the benefits of household-targeted interventions are robust to heterogeneity in ARTI across neighbourhoods of Lima.

The results presented here extend the findings in Zelner *et al.*,[9] to demonstrate that household-acquired LTBI among household contacts of identified TB cases translates into increased risk of incident TB disease, particularly among those exposed to smear-positive household cases. These results may also have population-level implications. Theoretical modelling of household-based screening and treatment interventions in a low HIV setting has suggested that household-targeted interventions may result in a population-level incidence reduction of around 2% over the long term.[22] Our results provide important inputs for transmission models that incorporate both realistic heterogeneity in community exposure risk and empirically derived estimates of the intensity of household transmission. Such models are critical for developing more comprehensive policy recommendations: In addition to the direct protection demonstrated in the current analysis, an important part of this calculation would be the indirect protection afforded by preventing individuals from transmitting to their household and community contacts, which necessitates transmission modelling.

It is also important to note that our conclusions rest on the comparison of outcomes among household contacts of bacteriologically confirmed (SCPI and CPI) TB cases to those of household contacts of bacteriologically negative (NI) household cases. To the extent to which NI-exposed individuals are different in their LTBI and TB disease risk from randomly sampled community controls, they likely experience greater community and household exposure risks. As a result, our estimates should be more conservative than what would be found if contacts of bacteriologically positive cases were compared with community controls.

Our findings suggest that targeted screening is likely to be effective in other low-HIV, high-TB incidence settings. However, it is not possible to draw conclusions about their general applicability beyond Lima without additional analyses. For example, we note that a previous cluster randomized trial of community-wide IPT in very high TB incidence, high-HIV prevalence mines in South Africa,[5] and subsequent modelling,[23] suggest that even optimal use of community-wide IPT as a stand-alone intervention was insufficient to reduce tuberculosis incidence in these communities. This highlights the necessity of understanding the specific transmission context for making concrete policy recommendations.

Supplementary Data

Supplementary data are available at *IJE* online.

Conflict of interest: None declared.

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