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Two Clinical Prediction Tools to Improve Tuberculosis Contact Investigation

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Background. Efficient contact investigation strategies are needed for the early diagnosis of tuberculosis (TB) disease and treatment of latent TB infections.

Methods. Between September 2009 and August 2012, we conducted a prospective cohort study in Lima, Peru, in which we enrolled and followed 14 044 household contacts of adults with pulmonary TB. We used information from a subset of this cohort to derive 2 clinical prediction tools that identify contacts of TB patients at elevated risk of progressing to active disease by training multivariable models that predict (1) coprevalent TB among all household contacts and (2) 1-year incident TB among adult contacts. We validated the models in a geographically distinct subcohort and compared the relative utilities of clinical decisions based on these tools to existing strategies.

Results. In our cohort, 296 (2.1%) household contacts had coprevalent TB and 145 (1.9%) adult contacts developed incident TB within 1 year of index patient diagnosis. We predicted coprevalent disease using information that could be readily obtained at the time an index patient was diagnosed and predicted 1-year incident TB by including additional contact-specific characteristics. The area under the receiver operating characteristic curves for coprevalent TB and incident TB were 0.86 (95% confidence interval [CI], .83–.89]) and 0.72 (95% CI, .67–.77), respectively. These clinical tools give 5%–10% higher relative utilities than existing methods.

Conclusions. We present 2 tools that identify household contacts at high risk for TB disease based on reportable information from patient and contacts alone. The performance of these tools is comparable to biomarkers that are both more costly and less feasible than this approach.

Keywords. tuberculosis; TB; clinical prediction rule; contact investigation.

Worldwide, an estimated 10.0 million people developed tuberculosis (TB) disease in 2017, of whom only 64% were detected and reported to the World Health Organization (WHO) [1]. Among diagnosed TB patients, self-reported delays in diagnosis have been estimated to range from 1 to 6 months after symptom onset [2], suggesting that by the time an infectious patient is put on treatment, many close contacts of that patient will have been exposed to *Mycobacterium tuberculosis* and at risk of developing active TB. The diagnosis of a TB patient thus provides a window of opportunity for TB clinics to screen for and treat active TB among patient contacts and to offer preventive therapy to those at risk of progressing to active disease.

Unfortunately, contacts are routinely lost from the contact screening and preventive therapy care cascades (Figure 1). While many national guidelines recommend systematic screening of contacts for TB disease [3–5], dropouts in high-burden settings are substantial. For example, the proportion of targeted contacts screened for TB disease was 8% of children aged <5 years in Indonesia [6], 14% of children aged <15 years in India [7], and 5% of all household contacts in urban Uganda [8]. Similarly, while many national guidelines recommend preventive therapy for subsets of contacts who screen negative for TB disease [5, 9], <20% of contacts 5 years or younger initiated therapy in India and rural Malawi despite the fact that national guidelines specified treatment for this group [7, 10]. A recent WHO guideline recommended expanding preventive therapy to household contacts aged ≥5 years in high-incidence countries [9], but dropouts in this age category have not yet been assessed [11].

Implementation barriers to contact screening and preventive therapy act at both the individual and healthcare system levels. For those targeted for screening, a lack of knowledge about TB transmission, perceived low risk of infection and disease, and long wait times at clinics have been identified as reasons for

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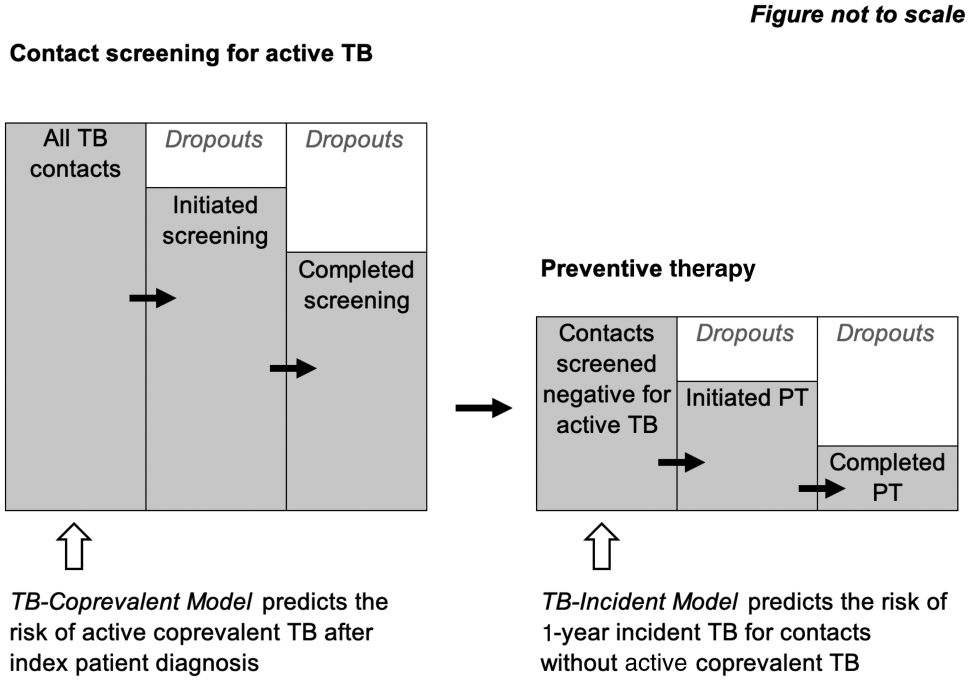

Figure 1. A simplified schematic of care cascades for tuberculosis contacts. Abbreviations: PT, preventive therapy; TB, tuberculosis.

losses at different steps in the cascades [11–13]. For TB clinics, identified barriers include insufficient time and space for counseling, lack of funds for contacts' travel [13], and low health provider knowledge about the benefits and risks of preventive therapy [11].

One way to address some of these barriers would be to use clinical prediction tools to quantify individual TB risks for contacts. Here, we describe 2 prediction tools to estimate and communicate the risk of TB to contacts and clinics (Figure 1). We designed the first tool to estimate the risk of coprevalent TB among household contacts at the time of index patient diagnosis and the second to estimate the risk of subsequent progression to TB.

METHODS

Between September 2009 and August 2012, we conducted a prospective cohort study of household contacts patients with pulmonary TB aged ≥16 years in Lima Province, Peru. Data collected at baseline included sociodemographic and clinical characteristics of both index patients and contacts (Table 1). We tested contacts for latent TB using tuberculin skin tests (TSTs). Contacts who reported symptoms of TB disease at the time of enrollment were referred to their local health clinic for clinical evaluation and diagnosis of TB disease. Contacts were then followed for 12 months. Incident TB was identified at routine household visits or from medical records at the participating study clinics. The design of this study has been reported previously [14, 15].

We developed 2 multivariable models to predict TB disease among contacts using these data. The first model predicts a TB diagnosis within 14 days after index patient diagnosis (coprevalent TB); the second model predicts a 1-year incident TB diagnosis among contacts in whom TB had been ruled out at baseline (incident TB).

We built the TB-Coprevalent Model including those baseline characteristics of the index patient, the household, and the contact that could be readily obtained at the time the index patient was diagnosed. We trained the model on the subset of contacts from the districts of North Lima, East Lima, and Rimac (training sample, Figure 2). We initially included 24 candidate predictors that had been previously associated with risk of TB (Table 2) [16]. We then used a 10-fold cross-validation procedure to fit a multivariable least absolute shrinkage and selection operator (Lasso) logistic regression model with the *glmnet* package [17] in R (3.5.0), imputing missing data for candidate predictors (Supplementary Materials). We used out-of-sample model deviance in cross-validation to select an optimal Lasso shrinkage parameter for fitting the final logistic regression training model. We assessed the goodness of fit of this final model by computing the area under a receiver operating characteristic curve (*C* statistic [AUC]) and the Hosmer-Lemeshow test, where low *P* values (eg, $P < .05$) indicate poor calibration. We used the coefficients from this final model to compute a risk score for coprevalent TB by dividing its Lasso coefficient for each predictor by the largest coefficient among all predictors, multiplied by 10, and rounded to the nearest integer. We evaluated the score's ability to classify patients

Table 1. Baseline Characteristics of Index Tuberculosis Patients, Households, and Household Contacts, Lima, Peru, September 2009–August 2012 (N = 14 044)

Characteristic	Training[a]	Validation[b]	*P* Value
No. of household contacts	10 062	3982	
Index TB patient characteristics			
Female sex	41.5	39.4	.02
Age, y			
Median (IQR)	27 (21–41)	28 (21–44)	.09
16–30	58.8	57.0	< .001
31–45	20.2	19.1	
46–60	10.8	11.4	
> 60	10.1	12.5	
College education or higher	28.8	23.7	< .001
Smoking			
None	97.4	97.0	< .001
≤ 1 cigarette a day	1.3	0.8	
> 1 cigarette a day	1.3	2.2	
Living with HIV	3.8	4.9	.003
TB history	17.7	17.2	.52
Cavitary disease	24.0	28.2	< .001
Smear positive	63.4	71.0	< .001
Culture positive	80.2	85.5	< .001
Diagnostic delay ≥ 4 wk	45.8	43.2	.007
Season of diagnosis			
Spring (September–November)	27.3	27.5	< .001
Summer (December–February)	24.8	28.5	
Fall (March–May)	26.3	23.9	
Winter (June–August)	21.7	20.1	
Symptom of coughing	85.4	87.8	< .001
Household characteristics			
Socioeconomic status			
Low	32.9	38.9	< .001
Medium	46.4	38.3	
High	20.7	22.8	
Crowding > 4 people per room	19.6	29.9	< .001
Type of housing			
House	12.2	26.7	< .001
Apartment	82.5	51.6	
Other	5.3	21.8	
Household TB history	39.3	42.5	.001
Contact characteristics			
Relationship between the contact and the index patient			
Child of index patient	19.0	19.3	.11
Parent	15.0	14.1	
Sibling	20.9	19.4	
Spouse	7.6	8.1	
Other	37.6	39.0	
Male sex	44.9	44.2	.48
Age, y			
Median (IQR)	23 (11–41)	24 (10–43)	.05
<5	12.6	13.2	< .001
5–19	30.5	28.7	
20–30	19.2	19.2	
31–45	18.4	16.6	
46–60	13.1	13.4	
> 60	6.3	8.8	
College education or higher[d]	30.5	29.7	.50
Smoking[d]			
None	90.2	88.6	.11
≤ 1 cigarette a day	5.1	5.9	
> 1 cigarette a day	4.7	5.5	
Drinking[d]			
None	58.6	61.3	.07
≤ 2 units per day	32.8	30.3	
> 2 units per day	8.6	8.4	
Self-reported diabetes	1.5	2.4	.001
Living with HIV	0.4	0.5	.26
Nutrition[c]			
Normal	58.2	55.8	.02
Underweight	1.9	1.8	
Overweight	39.9	42.4	
BMI[d], kg/m^2, mean (SD)	26.7 (4.7)	27.0 (5.1)	.03
TB history	7.5	8.1	.23
No. of BCG scars			
0	13.5	14.9	< .001
1	63.1	66.0	
2	18.4	16.1	
≥ 3	5.0	2.9	
Cough			
None	90.5	92.1	.007
1–7 d	3.1	2.8	
8–14 d	0.5	0.5	
15–30 d	5.1	3.7	
> 30 d	0.8	0.8	
Tuberculin skin test			
TST contraindicated	12.1	19.9	< .001
< 5 mm	42.4	34.4	
5–9 mm	12.1	9.9	
10–14 mm	21.7	20.9	
≥ 15 mm	11.6	14.9	
Endpoints			
Coprevalent TB	2.0	2.5	.08
1-y incident TB	2.1	2.3	.38
1-y incident TB[d]	1.8	2.1	.43

Data are presented as percentage unless otherwise indicated. *P* values were based on χ^2 tests for categorical variables, Wilcoxon rank-sum test for continuous variables with nonnormal distributions (age of index patient and age of contact), and *t* test with equal variance for BMI.

Abbreviations: BCG, bacille Calmette Guerin; BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation; TB, tuberculosis; TST, tuberculin skin test.

[a]We trained the models on the subset of contacts with index patients diagnosed in North Lima, East Lima, and Rimac.

[b]We validated the models among the subset of contacts diagnosed within central Lima. Using a geographically external sample for validation allows our models to be tested in demographically different households than those represented by the training sample.

[c]Nutrition was defined as follows: Underweight: for under-5, *z* score for weight for length/height ≤ −2 from World Health Organization (WHO) mean; for age 5–19: *z* score for BMI for age ≤ −2 from WHO mean; for age ≥20: BMI <18.5 kg/m^2. Overweight: for under-5, *z* score for weight for length/height >2 from WHO mean; for age 5–19: *z* score for BMI for age >2 from WHO mean; for age ≥20: BMI ≥25 kg/m^2. Normal: otherwise. Using weight for length may result in an underestimation in the prevalence of underweight for infants aged <2 years, particularly in settings with high burden of stunting.

[d]For adults (≥20 years of age) only.

by comparing observed and predicted risks within 3 risk groups. We then estimated the score's sensitivity and specificity using plausible cutoffs indicated by its distribution. Finally, we validated the score among the subset of contacts diagnosed within

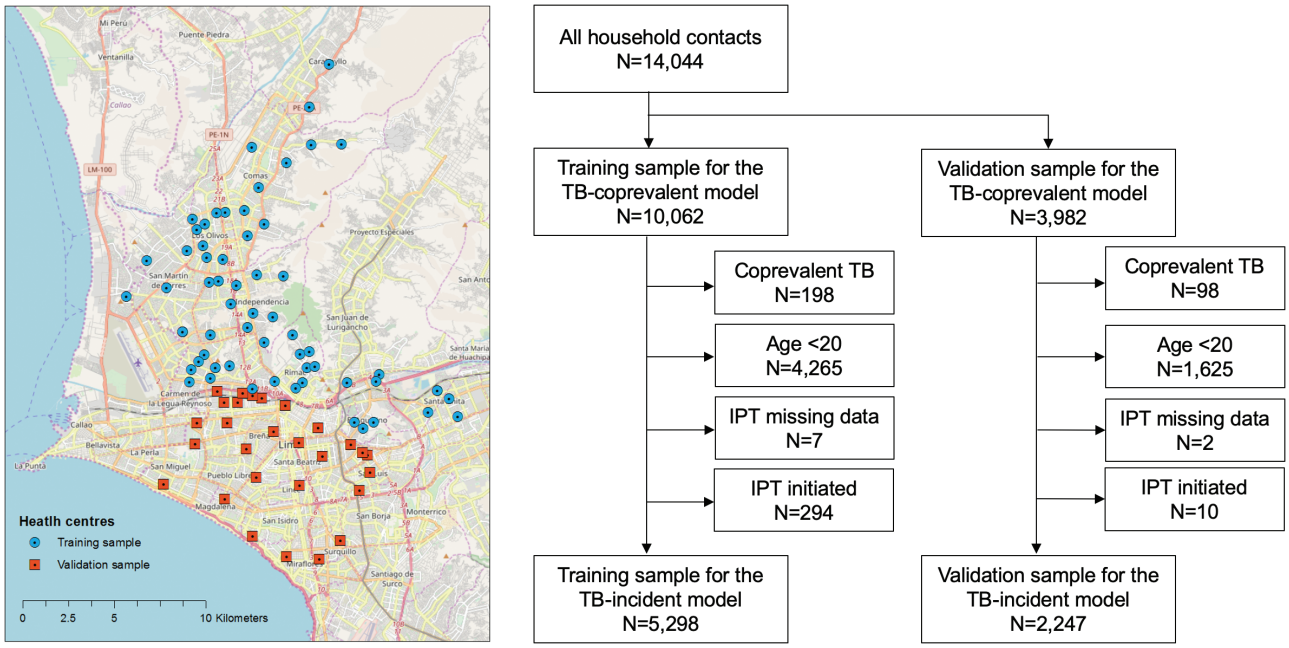

Figure 2. Flow diagram and map for participants included in the prediction models. Training sample: contacts of adults with pulmonary tuberculosis (TB) diagnosed in health centers in North Lima, East Lima, and Rimac, Peru. For the TB-Coprevalent Model, n = 10 062; for the TB-Incident Model (restricted to contacts aged ≥20 years who did not receive preventive therapy), n = 5298. Validation sample: contacts of adults with pulmonary TB diagnosed in health centers in central Lima (except Rimac). For the TB-Coprevalent Model, n = 3982; for the TB-Incident Model (restricted to contacts aged ≥20 years who did not receive preventive therapy), n = 2247. Using a geographically external sample for validation allows our models to be tested in demographically different households than those represented by the training sample. Abbreviations: IPT, isoniazid preventive therapy; TB, tuberculosis.

central Lima (validation sample, Figure 2). We tested for homogeneity of baseline characteristics between the validation and the training sample using χ^2 tests for categorical variables, Wilcoxon rank-sum test for continuous variables with nonnormal distributions, and *t* test for body mass index (BMI). To further illustrate the utility of the risk score in aiding decision-making processes during contact screening, we compared the relative utility curves [18] (Supplementary Materials) of the TB-Coprevalent Model risk score and the current WHO recommendations for contact investigation in low- and middle-income countries [3], assuming that the cost of index patient surveys is negligible relative to the utility of identifying a coprevalent TB patient.

Using the same approach, we next developed a prediction model for 1-year incident TB (TB-Incident Model) among contacts aged ≥20 years who did not have coprevalent disease and had not received preventive therapy. (We note that Peru national TB policy specifies that preventive therapy is only offered to contacts aged <20 years and to individuals with specified comorbidities [19]). Here, we included the variables used in the previous model as well as contact-specific information that might be routinely collected during screening including socioeconomic status, BMI, diabetes mellitus, and the presence/number of visible scars from BCG immunization (Table 3). After obtaining a final Lasso logistic regression model in the training sample, we computed the risk score for 1-year incident TB by dividing the Lasso coefficients of predictors by the absolute value of the coefficient of BMI and rounded to the nearest integer to ensure 1 unit' difference in BMI translates into 1 unit change in the risk score. We added 30 to the sum of predictor scores in order to have a score distribution similar to the TB-Coprevalent Model score. We conducted a sensitivity analysis in which we added TST as a candidate predictor before the Lasso procedure and compared the performance of both models (the TB-TST [Incident] Model). We also validated a previously developed model (Saunders risk score) [20]. for predicting 1-year incident TB in our cohort. We classified contacts into 3 arbitrary risk groups based on their incident TB risks and calculated the net reclassification improvement [21] comparing our model to the Saunders risk score. Finally, we compared the relative utility curves of (1) TB-Incident Model, (2) TB-TST (Incident) Model, (3) Saunders risk score [20], (4) latent TB identification based on TST results alone, and (5) the current WHO recommendation for preventive therapy [9], and computed test thresholds for the difference in utility between the TB-Incident Model and the TB-Incident TST Model.

RESULTS

TB-Coprevalent Model Risk Score

The training sample for the TB-Coprevalent Model included 10 062 contacts of adult pulmonary TB patients (Figure 2), among whom 2.0% (198) were found to have coprevalent TB (Table 1). Of the 24 candidate predictors shown in Table 2, 17 remained in the best Lasso model, which had an AUC of

Table 2. TB-Coprevalent Model: Penalized Multivariate Logistic Regression Analysis Using Candidate Predictors for Coprevalent Tuberculosis, Training Cohort (n = 10 062)

	Univariate		Multivariate			Lasso Model	
Characteristic	OR[a]	*P* Value	aOR[b]	(95% CI)	*P* Value	OR[c]	Score[d]
Index TB patient characteristics							
Female sex	0.86	.4	1.02	(.65–1.49)	.9	…	…
Age, y							
16–30	ref		ref				
31–45	1.23	.4	0.81	(.48–1.37)	.4	…	…
46–60	0.86	.7	0.58	(.27–1.23)	.2	0.83	…
> 60	1.33	.4	0.91	(.45–1.83)	.8	…	…
Living with HIV	0.62	.4	0.54	(.15–1.96)	.4	0.77	–1
Cavitary disease	1.05	.8	1.14	(.72–1.81)	.6	1.03	…
TB history	1.44	.12	1.59	(.84–3.01)	.2	1.17	…
Smear positive	1.00	.98	1.02	(.66–1.60)	.9	…	…
Culture positive	0.94	.8	0.83	(.49–1.42)	.5	…	…
Smoking status							
None	ref		ref				
≤ 1 cigarette a day	1.39	.7	0.56	(.11–2.90)	.5	0.78	–1
> 1 cigarette a day	3.01	.09	2.14	(.53–8.58)	.3	1.58	1
Diagnostic delay ≥ 4 wk	1.93	< .001	2.27	(1.45–3.57)	< .001	1.67	1
Season of diagnosis							
Spring (September–November)	2.18	< .01	1.96	(1.13–3.40)	.02	1.45	1
Summer (December–February)	1.28	.4	1.36	(.76–2.42)	.3	…	…
Fall (March–May)	ref		ref				
Winter (June–August)	1.13	.7	1.33	(.72–2.48)	.4	…	…
Symptom of coughing	1.39	.2	0.86	(.43–1.70)	.7	…	…
College education or higher	0.53	< .01	0.59	(.36–.98)	.04	0.72	–1
Household characteristics							
Crowding (> 4 people per room)	1.52	.07	1.41	(.86–2.31)	.2	1.19	…
Type of housing							
House	ref		ref				
Apartment	0.84	.6	0.96	(.52–1.78)	.9	…	…
Other	0.85	.7	0.49	(.20–1.25)	.1	0.74	–1
Household TB history	1.47	.04	0.76	(.43–1.34)	.3	…	…
Contact characteristics collectible from index patients during TB diagnosis							
Relationship between the contact and the index patient							
Child of index patient	1.24	.4	2.00	(1.15–3.50)	.01	1.35	1
Parent	1.29	.3	1.21	(.63–2.32)	.6	…	…
Sibling	1.09	.7	1.11	(.64–1.92)	.7	…	…
Spouse	1.45	.2	1.27	(.61–2.65)	.5	…	…
Other	ref		ref				
Male sex	1.29	.11	1.40	(.95–2.05)	.09	1.15	…
Age, coughing duration							
≥ 20 y, ≤ 7 d	ref		ref				
≥ 20 y, > 7 d	95.9	< .001	87.7	(49–157)	< .001	47.8	10
5–19 y, ≤ 7d	1.27	.4	0.98	(.50–1.90)	.9	…	…
5–19 y, > 7 d	46.9	< .001	33.92	(16–72)	< .001	25.1	8
< 5 y, ≤ 7 d	0.92	.9	0.65	(.25–1.71)	.4	1.00	…
< 5 y, > 7 d	7.85	< .001	5.44	(1.70–17.4)	< .01	4.71	4
Nutrition[e]							
Normal	ref		ref				
Underweight	2.63	.02	1.54	(.53–4.47)	.4	1.30	1
Overweight	0.86	.4	0.69	(.45–1.06)	.09	0.82	–1
TB history	2.47	< .001	1.68	(.89–3.15)	.11	1.53	1
Current smoker	0.93	.8	0.57	(.25–1.26)	.2	0.81	–1

Table 2. Continued

Characteristic	Univariate		Multivariate			Lasso Model	
	OR[a]	*P* Value	aOR[b]	(95% CI)	*P* Value	OR[c]	Score[d]
Drinks alcohol	1.30	.13	1.04	(.67–1.62)	.8	…	…
College education or higher	0.89	.6	0.96	(.55–1.68)	.9	…	…

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; TB, tuberculosis.

[a]Univariate odds ratio estimated using mixed-effect models with random intercept and fixed slope, accounting for clustering at household level.

[b]Adjusted odds ratios from a similar mixed-effect model using all candidate predictors, with random intercept and fixed slope, accounting for clustering at household level.

[c]Lasso model: The lasso model fitted using the shrinkage parameter that gives best external model performance (in terms of deviance) in a cross-validation procedure. We selected interaction terms to be entered into the Lasso model-fitting strategy based on the *P*-values of plausible bi-variable interactions, using likelihood ratio tests with .05 cutoffs: between contact age group and contact cough ($P < .001$), relationship and contact age group ($P = .6$), index case sex and relationship ($P = .4$), and index case smear and index case cough ($P = .12$).

[d]Score: A score corresponding to each predictor that is used to calculate the TB-Coprevalent Model risk score, estimated by dividing the lasso coefficient of a predictor by the coefficient for coughing among TB contacts 20 years or older, multiplied by 10 and rounded to the nearest integer.

[e]Nutrition was defined as: *Underweight*: for under 5s, z-score for weight for length/height ≤ -2 from WHO mean; for age 5–19: z-score for BMI for age ≤ –2 from WHO mean; for age ≥ 20: BMI < 18.5 kg/m^2. *Overweight*: for under 5s, z-score for weight for length/height > 2 from WHO mean; for age 5–19: z-score for BMI for age > 2 from WHO mean; for age ≥ 20: BMI ≥ 25 kg/m^2. *Normal*: otherwise.

0.86 (95% confidence interval [CI], .83–.89) (Figure 3) and a Hosmer-Lemeshow test of $P = .72$. The final risk score included the 12 predictors shown in Table 2. The risk scores were distributed bimodally (Figure 4B): the majority of contacts (94%) had scores <6 and 0.7% of this group had coprevalent TB, while 18.4% of those with scores between 6 and 10 and 36.5% of those with scores >10 had coprevalent TB (Figure 4C). We found no significant differences between predicted and observed prevalences (Supplementary Figure 1, Supplementary Table 1). When we considered those with scores ≥6 as the high-risk group, our tool had 65% sensitivity and 96% specificity in identifying contacts with coprevalent disease, with a positive predictive value (PPV) of 22.4% and a negative predictive value (NPV) of 99.3% (Table 4).

Table 3. TB-Incident Model: Penalized Multivariate Logistic Regression Analysis Using Candidate Predictors for 1-Year Incident Tuberculosis Among Adult Contacts, Training Cohort (n = 5298)

Characteristic	Univariate		Multivariate				
	OR[a]	*P* Value	aOR[b]	(95% CI)	*P* Value	OR[c]	Score[d]
Index TB patient characteristics							30+
Female sex	1.34	.2	1.40	(.91–2.15)	.13	1.02	…
Age, y							
16–30	ref		ref				
31–45	0.63	.2	0.53	(.27–1.02)	.06	…	…
46–60	0.54	.14	0.57	(.23–1.41)	.2	0.996	…
> 60	0.61	.2	0.74	(.29–1.88)	.5	…	…
Living with HIV	1.22	.7	1.32	(.49–3.57)	.6	…	…
Cavitary disease	1.30	.3	1.40	(.87–2.24)	.2	…	…
TB history	1.38	.2	1.84	(.95–3.56)	.07	…	…
Smear positive	1.42	.14	1.33	(.82–2.17)	.2	1.04	…
Culture positive	1.34	.3	1.12	(.61–2.04)	.7	…	…
Smoking							
None	ref		ref				
≤ 1 cigarette a day	0.87	.9	0.91	(.12–6.93)	.9	…	…
> 1 cigarette a day	2.97	.12	2.47	(.69–8.83)	.2	…	…
Diagnostic delay ≥4 wk	1.05	.8	1.02	(.65–1.60)	.9	…	…
Season of diagnosis							
Spring (September–November)	1.31	.4	1.32	(.73–2.39)	.3	…	…
Summer (December–February)	1.27	.4	1.38	(.76–2.48)	.3	…	…
Fall (March–May)	ref		ref				
Winter (June–August)	1.25	.5	1.38	(.74–2.56)	.3	…	…
Symptom of coughing	1.16	.6	0.93	(.48–1.80)	.8	…	…
College education or higher	0.92	.7	1.01	(.62–1.64)	.96	…	…
Household characteristics							
Socioeconomic status							

Table 3. Continued

Characteristic	Univariate		Multivariate				
	OR[a]	*P* Value	aOR[b]	(95% CI)	*P* Value	OR[c]	Score[d]
Low	ref		ref				
Medium	0.62	.05	0.60	(.37–.95)	.03	…	…
High	0.54	.05	0.56	(.30–1.04)	.07	…	…
Crowding (>4 people per room)	1.06	.84	1.09	(.62–1.90)	.8	…	…
Type of housing							
House	ref		ref				
Apartment	1.13	.7	1.00	(.54–1.85)	.99	…	…
Other	0.41	.2	0.26	(.06–1.14)	.07	0.98	…
Household TB history	1.15	.53	0.59	(.31–1.13)	.11	…	…
Contact characteristics							
Relationship between the contact and the index patient							
Child of index patient	0.81	.7	1.09	(.36–3.24)	.9	…	…
Parent	1.12	.7	1.44	(.70–2.96)	.3	…	…
Sibling	1.59	.12	1.35	(.74–2.48)	.3	…	…
Spouse	1.96	.04	2.10	(1.09–4.05)	.03	1.18	2
Other	ref		ref				
Male sex	1.30	.2	1.27	(.81–1.99)	.3	…	…
Age, y							
20–30	1.21	.6	1.30	(.56–3.03)	.5	1.16	2
31–45	0.60	.2	0.83	(.37–1.85)	.6	…	…
46–60	0.60	.2	0.73	(.32–1.67)	.4	…	…
> 60	ref		ref				
Body mass index	0.87	< .001	0.88	(.83–.93)	< .001	0.91	−1
TB history	2.07	.007	2.06	(1.07–3.95)	.03	1.31	3
No. of BCG scars							
0	ref		ref				
1	0.65	.2	0.71	(.38–1.34)	.3	…	…
2	0.48	.04	0.60	(.29–1.22)	.16	…	…
≥ 3	0.62	.3	0.90	(.35–2.31)	.8	…	…
Diabetes	1.26	.7	1.58	(.46–5.36)	.5	…	…
Smoking							
None	ref		ref				
≤ 1 cigarette a day	0.79	.7	1.04	(.36–2.99)	.9	…	…
> 1 cigarette a day	1.00	1.0	1.22	(.46–3.28)	.7	…	…
Drinking							
None	ref		ref				
≤ 2 units per day	0.61	.05	0.61	(.37–1.02)	.06	0.89	−1
> 2 units per day	0.81	.6	0.70	(.31–1.57)	.4	…	…
College education or higher	0.54	.02	0.55	(.32–.95)	.03	0.73	−3
Coughing							
None	ref		ref				
1–14 d	0.39	.4	0.40	(.05–2.89)	.4	…	…
> 14 d	3.24	< .001	3.07	(1.61–5.87)	< .001	2.16	9

Abbreviations: aOR, adjusted odds ratio; BCG, bacille Calmette Guerin; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; TB, tuberculosis.

[a]Univariate odds ratio estimated using mixed-effect models with random intercept and fixed slope, accounting for clustering at household level.

[b]Adjusted odds ratios from a similar mixed-effect model using all candidate predictors, with random intercept and fixed slope, accounting for clustering at household level.

[c]Lasso OR: We selected interaction terms to be entered into the Lasso model-fitting strategy based on the *P* values of plausible bivariable interactions, using likelihood ratio tests with .05 cutoffs: between index case smear and index case cough ($P = .06$), BCG scar number and contact age group ($P = .4$), and contact cough and contact age group ($P = .4$).

[d]Score: a score corresponding to each predictor that is used to calculate the TB-Incident Model risk score, estimated by dividing the Lasso coefficient of a predictor by the absolute value of the coefficient for body mass index and rounded to the nearest digit. The TB-Incident Model risk score is calculated as 30 plus the scores for individual predictors present in the model.

Contacts in the validation sample (n = 3982) had a higher prevalence of coprevalent TB (2.5% [n = 98]) than those in the training sample (2.0%) ($P = .08$; Table 1). The validation AUC was 0.83 (95% CI, .78–.88) (Figure 3) and the Hosmer-Lemeshow statistic was $P = .005$. Calibration plots (Figure 4D, Supplementary Figure 1, Supplementary Table 1) indicate that the score tended to underestimate coprevalent TB risks for contacts in the median risk category.

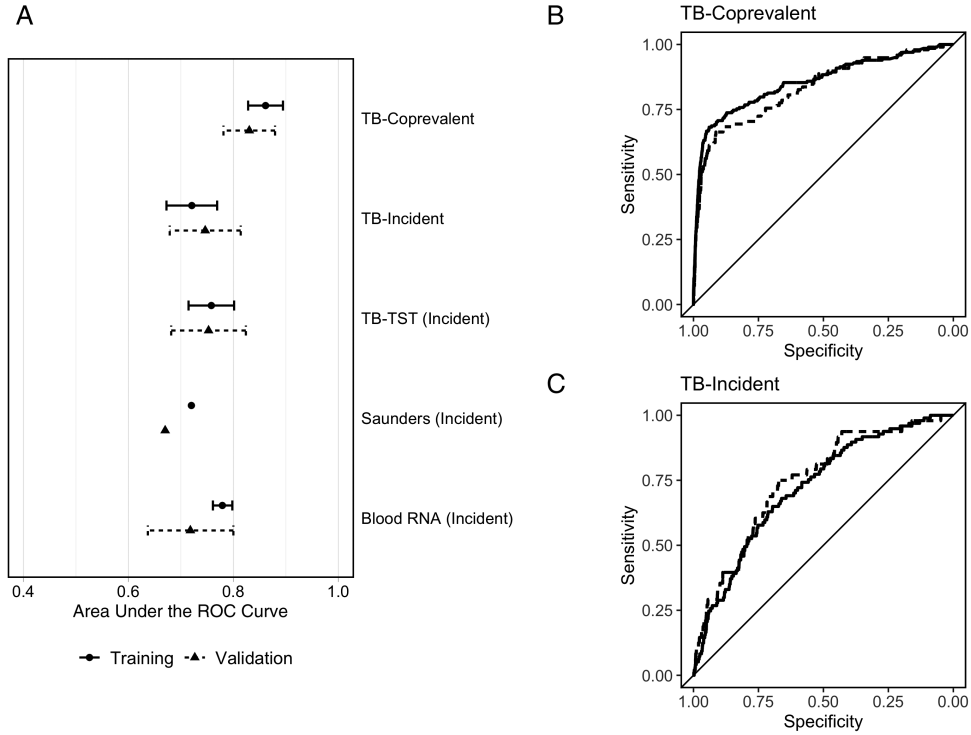

Figure 3. Receiver operating characteristic (ROC) curves for the Tuberculosis (TB)–Coprevalent Model and the TB-Incident Model, with area under the curve (AUC) statistics. *A*, Comparisons of the area under the ROC curves for various models that predict coprevalent and incident TB are as follows: *TB-Coprevalent*: performance of the TB-Coprevalent Model. *TB-Incident*: performance of the TB-Incident Model. *TB–Tuberculin Skin Test (TST) (Incident)*: performance of the TB-TST (Incident) Model. This is part of a sensitivity analysis, adding the contacts' TST results to the list of *a priori* predictors for incident TB. *Saunders (Incident)*: Performance of the Saunders model in Saunders' [20] training and validation cohorts. 95% confidence intervals (CIs) were not provided in the original publication. We also tested the performance of the Saunders model in our study and obtained an AUC of 0.65 (95% CI, .60–.69) (data not shown). *Blood RNA (Incident)*: performance of Zak et al's blood RNA signature [30] for predicting TB within 360 days prior to diagnosis. *B*, ROC curves for the TB-Coprevalent Model for the training and validation samples in our study. *C*, ROC curves for the TB-Incident Model for the training and validation samples in our study. Abbreviations: ROC, receiver operating characteristic; TB, Tuberculosis; TST, tuberculin skin test.

The relative utility of using the TB-Coprevalent Model to inform contact screening is substantially higher than the WHO recommendation (Figure 5) [3]; at a risk threshold of 5%, the relative utility of following the TB-Coprevalent Model is 20 percentage points higher than following the WHO recommendation.

TB-Incident Model Risk Score

Among 5298 adult contacts included in the TB-incidence model (Figure 2), 1.8% (n = 97) developed incident TB within 1 year of enrollment. Of 27 candidate predictors (Table 3), 11 remained in the best Lasso model, which had an AUC of 0.72 (95% CI, .67–.77) (Figure 3) and a Hosmer-Lemeshow test of $P = .65$. The final risk score consisted of 7 predictors after rounding model coefficients (Table 3). After we rounded model coefficients, the score was normally distributed in the training sample (Figure 6B), with scores <6 in 62% of contacts, of whom 0.9% developed TB; scores between 6 and 10 in 29% of contacts, of whom 2.6% developed TB; and scores >10 in 9.2% of contacts, of whom 5.5% developed TB (Figure 6C). Table 4 shows the sensitivity, specificity, PPV, and NPV at several arbitrary cutoff points.

Among 2247 contacts in the validation sample (Figure 2), 2.1% (n = 48) developed incident TB compared to 1.8% in the training sample ($P = .4$). The AUC was 0.75 (95% CI, .68–.81) (Figure 3) and the Hosmer-Lemeshow statistic was $P = .06$. The calibration plots (Figure 6D, Supplementary Figure 2, Supplementary Table 2) show that the score overestimated risk for contacts in the low-risk group, and underestimated risk for contacts in the high-risk group.

When we included TST results in the model-fitting strategy (full model in Supplementary Table 3), the model improved only slightly with an AUC of 0.76 (95% CI, .71–.80) in the training sample and 0.75 (95% CI, .68–.82) in the validation sample (Figure 3).

The Saunders score [20] gave an AUC of 0.65 (95% CI, .60–.69) in our cohort; it overestimated risk for the high- and medium-risk contacts and underestimated risk in the low-risk group (Supplementary Figure 3). Compared to the Saunders score, the TB-Incident Model classified more contacts into risk categories that better represent their risk of incident TB (Table 5): the reclassification improvement [21] using the TB-Incident Model risk score is 13.1% for contacts who progressed to TB and 4.6%

Ask these questions to an index TB patient who are over 15 years of age, during or shortly after his/her TB diagnosis

		Index patient score
Were you diagnosed with TB in the spring?	+1	
Have you ever tested positive for HIV?	-1	
If you smoke: do you smoke at most 1 cigarette a day?	-1	
If you smoke: do you smoke >1 cigarette a day?	+1	
Have you had TB symptom(s) for at least 4 weeks prior to your TB diagnosis?	+1	
Have you started or finished college education?	-1	
Do you live somewhere other than an apartment building or a house?	-1	

Index patient score: _____ *Add up the index patient score*

Then ask the following questions about EACH household contact of the index patient:

Name of your contact: _____

		Contact score
Is the contact your child?	+1	
Is the contact older than 19 years of age, and has coughed for over a week?	+20	
Is the contact between 5 and 19 years of age, and has coughed for over a week?	+8	
Is the contact under 5 years of age, and has coughed for over a week?	+4	
Is the contact underweight for his/her age?	+1	
Is the contact overweight for his/her age?	-1	
Does the contact currently smoke cigarettes?	-1	
Has the contact had TB before?	+1	

Contact score: _____ *Add up the contact scores for contact*

Contact's risk score for coprevalent TB is: _____ *Sum the index patient score with the contact score*

Read the risk of coprevalent TB using the calculated total score:

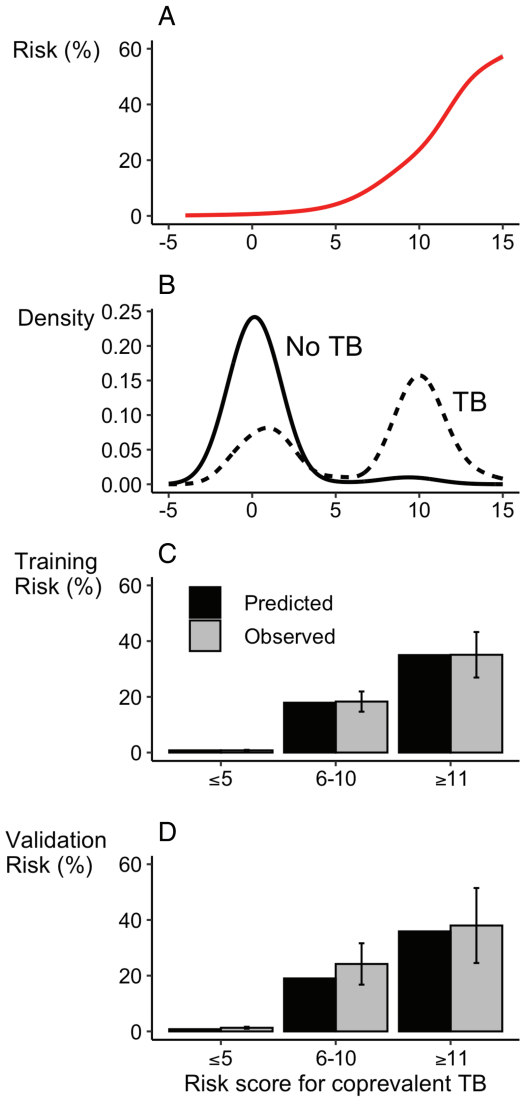

Figure 4. Distribution of Tuberculosis (TB)–Coprevalent Model risk scores and predicted coprevalent TB risk in the training and validation samples. *A*, Relationship between the TB-Coprevalent Model risk score and predicted risk for coprevalent TB. *B*, Distribution of TB-Coprevalent Model risk scores in the training and validation samples. *C*, Calibration of the TB-Coprevalent Model risk scores in the training sample. *D*, Calibration of the TB-Coprevalent Model risk scores in the validation sample. Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.

for contacts who did not progress, giving net reclassification improvement of 17.7%.

For risk thresholds between 1% and 5%—that is, for a person who would only get preventive therapy if he or she had a 1%–5% risk of 1-year incident TB or higher, treatment decisions informed by the TB-Incident Model gave at least 5%–10% higher relative utility compared to all previous methods (Figure 7). Including the TST in the TB-Incident Model was only worthwhile if one is willing perform at least 800 TSTs to find a single true-positive case. For risk thresholds <1%, different tests yielded similar utilities whereas for risk thresholds >5%, test utilities were no better than treating no one in the population.

DISCUSSION

We developed 2 tools that are predictive of TB risks for household contacts of adults with pulmonary TB using clinical and demographic predictors that are easily collected in clinical settings, without the need for obtaining measurements that would delay contact screening and preventive therapy. The TB-Coprevalent Model uses information that could be obtained

Table 4. Sensitivity and Specificity at Different Cutoff Points for Contacts at High Risk of Tuberculosis, Based on the TB-Coprevalent Model and the TB-Incident Model Risk Scores

Endpoint	Risk Score Model	High-risk Definition	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Contacts at High Risk, %	All Contacts: High Risk and Have TB, %	All Contacts: Low Risk but Have TB, %
Coprevalent TB	TB-Coprevalent	≥ 6	65	96	22.4	99.3	6	1.3	0.7
1-year incident TB	TB-Incident	≥ 1	94	27	2.3	99.6	74	1.7	0.1
		≥ 6	69	62	3.3	99.1	38	1.3	0.6
		≥ 11	28	91	5.5	98.5	9	0.5	1.3

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; TB, tuberculosis.

from patients at the time of their TB diagnosis to distinguish high- and low-risk contacts. The TB-Incident Model incorporates additional contact-specific demographic variables and predicts the probability of an adult contact progressing to active disease within 1 year of the diagnosis of the index patient. Both tools performed well in terms of the AUC and were validated in a geographically and demographically distinct sample of contacts. Clinical decisions for contact screening and preventive therapy based on predicted risks from these tools might be more effective than current practice in reducing secondary TB cases.

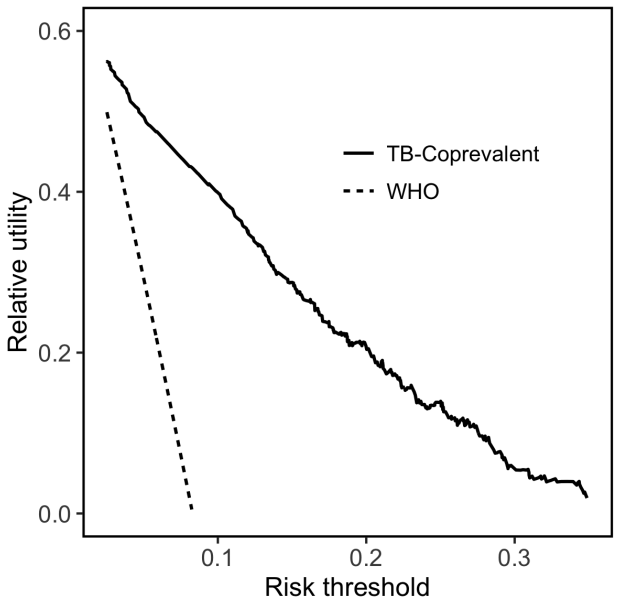

Figure 5. Relative utility curves comparing the Tuberculosis (TB)–Coprevalent Model vs the World Health Organization (WHO) recommendations for identifying high-risk household contacts for contact investigation. We assumed the cost of index patient survey is negligible compared to the utility of identifying 1 coprevalent TB case. The relative utility curves are plotted for the relevant region of risk thresholds above the observed prevalence (2%) of coprevalent TB among household contacts. TB-Coprevalent: scenarios where TB contacts were investigated if they have a predicted risk of coprevalent TB above a given risk threshold, based on the TB-Coprevalent Model. WHO: A scenario following the WHO recommendation ([3], recommendation 3) of targeting contact investigation in low- and middle-income countries to people of all ages with symptoms suggestive of TB, approximated by coughing for >2 weeks; children < 5 years of age; people with known or suspected immunocompromising conditions (especially persons living with human immunodeficiency virus); and contacts of index cases with multidrug-resistant or extensively drug-resistant TB (we did not use information on drug resistance in this comparison). Abbreviations: TB, tuberculosis; WHO, World Health Organization.

Although investigators have previously developed algorithms for screening for TB disease with symptom questionnaires and/or chest radiography [22–24], to our knowledge, the TB-Coprevalent Model is the first validated prediction model for coprevalent disease among household contacts. A limited number of studies have also incorporated TB risk factors into screening algorithms; these target specific high-risk groups such as symptomatic individuals [24], hospital inpatients [25], human immunodeficiency virus (HIV)–infected individuals [24, 26], immigrants [27], and prisoners [28], but none focus on household contacts. Whereas most other tools require that the relevant information is obtained directly from the individuals being screened, the TB-Coprevalent Model can be used before the contacts are engaged in the healthcare system.

In contrast to screening for coprevalent disease, the prediction of incident TB often involves both epidemiological risk factors and/or biomarkers such as TST, interferon-γ release assay (IGRA), and more recently, RNA-based signatures. A systematic review and meta-analysis of TST and IGRA to predict TB progression in high-risk groups estimated summary sensitivities and specificities of 72% and 50%, respectively, for enzyme-linked immunospot assay and 72% and 41% for the TST [29]. Blood RNA signatures have performed similarly in several African cohorts [30, 31]; the most recent 4-gene signature had an AUC of 0.69 when validated among household contacts [31].

Tools that rely on epidemiological and clinical risk factors of the index cases and their contacts have performed equally well and, in some cases, better than biomarkers. In 1 study, the addition of epidemiological indicators to the TST improved the prediction of TB disease among child contacts from an AUC of 0.80–0.87 [32]. Another recent study developed and assessed the performance of a tool that used a range of risk factors to stratify adult contacts of smear-positive TB patients by their risk of developing TB up to 10 years postenrollment [20]. With AUCs of 0.72 in the training cohort and 0.67 in the validation cohort, this tool performs similarly to the TB-Incident Model. Although both tools were developed and validated in Peruvian cohorts, our model pertains to contacts of all index pulmonary TB patients regardless of microbiological confirmation, while

Ask these questions to a household contact of adults (>15 years of age) with pulmonary TB:

If you do **not** know whether you currently have TB...	This questionnaire is not for you. You should be screened for TB now. Then, answer this only if you do not have TB.	
If you are under 20 years of age...	This questionnaire is not for you. You may be eligible for TB preventive therapy - check with your healthcare provider	
Are you the spouse of the index TB patient in your household?	+2	
Are you between 20 and 30 years of age?	+2	
Have you had TB before?	+3	
If you drink alcohol, on average, do you drink no more than 2 units of alcohol per day?	-1	
Have you started or finished college education?	-3	
Have you been coughing for >2 weeks?	+9	

Step 1 score: _____ *Add up all the numbers above*

What's your body mass index?	BMI	

*BMI=weight/(height*height), where weight is in kg and height is in meters.*

Step 2 score = 30 - BMI = _____ *Calculate (30 - BMI): this is the normalized contribution of BMI to risk*

Risk score for incident TB: _____ *Add up the Step 1 and Step 2 scores*

Read the risk of incident TB using the calculated total score:

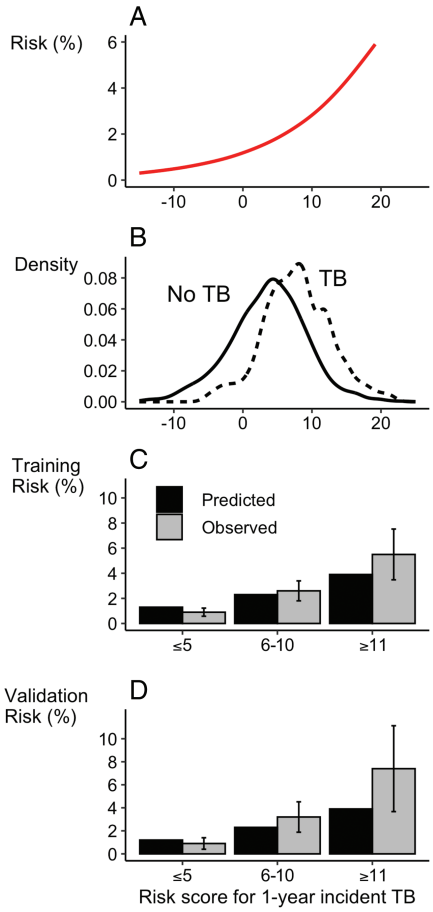

Figure 6. Distribution of Tuberculosis (TB)–Incident Model risk scores and predicted 1-year incident tuberculosis risk in the training and validation samples. *A*, Relationship between the TB-Incident Model risk score and predicted risk for incident TB. *B*, Distribution of TB-Incident Model risk scores in the training and validation samples. *C*, Calibration of the TB-Incident Model risk scores in the training sample. *D*, Calibration of TB-Incident Model risk scores in the validation sample. Abbreviations: BMI, body mass index; TB, tuberculosis.

the previous model focuses on contacts of patients with smear-positive TB. In addition, our model did not use household socioeconomic status, which may be difficult to rapidly assess in practice.

Although the AUCs for predicting incident TB are reasonable, none of the currently available tests have high prognostic value despite the strong associations between the identified markers or scores and TB incidence [29]. In our study, the distribution of the TB-Incident Model risk score for contacts with and without incident TB overlapped substantially (Figure 6B). Therefore, although the TB-Incident Model is similar to other tools [29, 33] in having a relatively a high NPV, the low PPV means that there are comparable numbers of TB cases in the low-risk and high-risk groups. Nonetheless, the value of using an individualized TB risk score may go beyond efficiently prioritizing interventions; in randomized trials for cancer screenings, communicating individualized cancer risk scores to patients resulted in higher adherence to recommended protocols than providing them with general risk information [34]. Because low awareness of TB risks has been associated with both delays in care-seeking behavior and poor adherence to treatment and preventive therapy [11, 35], score-based tools might empower contacts to make informed decisions on initiating or adhering to TB screening and preventive therapy.

We note some limitations to our study. First, although the TB-Coprevalent Model uses information about contacts that we believe could be obtained directly from index patients, the data used in this study were collected from the contacts during household visits. It is possible that index patients undergoing an initial diagnostic workup for TB may provide different information on contact characteristics than the contacts provided. To minimize this potential misclassification, we collapsed some categorical variables into coarser dichotomous predictors such as coughing and smoking that might be more easily reported

Table 5. Reclassification Among Household Contacts of Patients With Pulmonary Tuberculosis, Comparing the TB-Incident Model Risk Score to Saunders Risk Score

	TB-Incident Model Risk Score			
Saunders Risk Score	Low Risk (≤ 5)	Medium Risk (6–10)	High Risk (≥ 11)	Total
Contacts who developed incident TB within 1 year				
Low risk	31 (62.0)	**13 (26.0)**	**6 (12.0)**	50
Medium risk	*11 (15.5)*	41 (57.7)	**19 (26.8)**	71
High risk	0*(0.0)*	*8 (33.3)*	16 (66.7)	24
Total	42	62	41	145
Contacts who did not develop incident TB within 1 year				
Low risk	3621(83.9)	**609 (14.1)**	**88 (2.0)**	4318
Medium risk	*939 (38.7)*	1211 (49.9)	**278 (11.4)**	2428
High risk	*43 (6.6)*	*336 (51.4)*	275 (42.0)	654
Total	4603	2156	641	7400

Data are presented as frequency (row %). Boldface text indicates positive reclassification; italic text indicates negative reclassification.

Abbreviation: TB, tuberculosis.

by an index patient, and we classified our continuous BMI variable into 3 categories: normal, overweight, and underweight. In practice, collecting contact information from the index patient could also be improved by asking the patient to communicate with their contacts by phone or text during the initial encounter. However, without actually implementing this strategy, it is difficult to assess its feasibility. Second, we assumed that index patients are aware of their HIV status. While TB patients are routinely tested for HIV if they do not already know their status, the results of these tests are often not available at the time of TB diagnosis. However, the index patient's HIV status is only a weak predictor for coprevalent TB and does not impact the

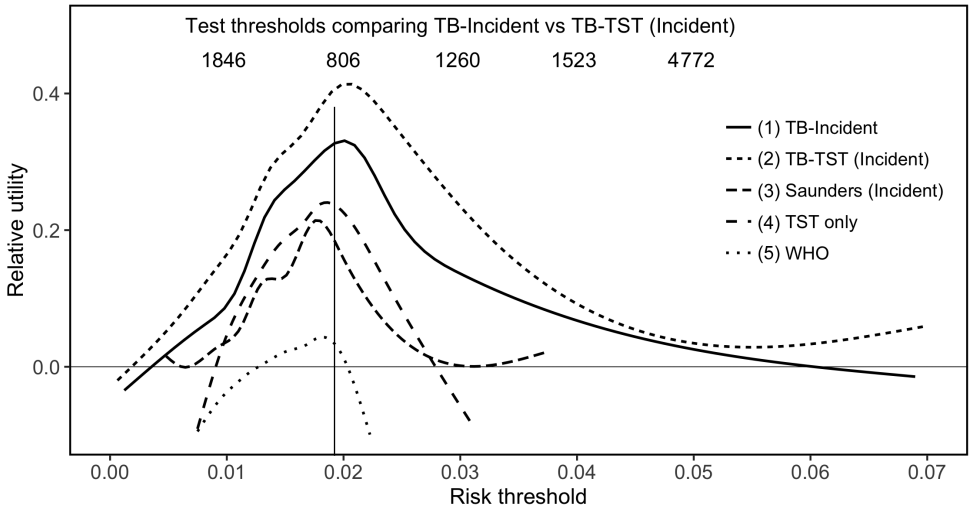

Figure 7. Relative utility curves comparing the Tuberculosis (TB)–Incident Model to other strategies for identifying high-risk household contacts for preventive treatment. Vertical line indicates the overall prevalence of 1-year incident TB among adult household contacts. (1) TB-Incident: scenarios where TB contacts were prescribed preventive treatment if they have a predicted risk of 1-year incident TB above a given risk threshold, based on the TB-Incident Model. (2) TB–Tuberculin Skin Test (TST) (Incident): scenarios where TB contacts were prescribed preventive treatment if they have a predicted risk of 1-year incident TB above a given risk threshold, based on the TB-TST (Incident) Model (sensitivity analysis is shown in Supplementary Table 3). (3) Saunders (Incident): scenarios where TB contacts were prescribed preventive treatment if they have a predicted risk of 1-year incident TB above a given risk threshold, based on the Saunders risk score [20]. We used the our data to estimate the risk of 1-year incident TB among household contacts for each value of Saunders risk score (because this was not reported in Saunders et al). (4) TST: a scenario where positive TST results (≥10 mm if tested, or contraindicated because of previous known positive results or TB history) were used as the cutoff point for prescribing preventive treatment for household contacts. (5) World Health Organization (WHO): a scenario following the WHO recommendation of targeting preventive treatment [9] to contacts who are human immunodeficiency virus positive or who have a microbiologically confirmed index pulmonary TB patient. Test thresholds comparing TB-Incident vs TB-TST (Incident) models: Test threshold is the minimum number of TST tests (using TB-TST [Incident] Model) that have to be traded for a true-positive prediction compared to using the TB-Incident Model for the expected utility to be nonnegative at a given risk threshold. For a person with a risk threshold of 0.03 (meaning that they would only receive preventive therapy if they had a 1-year risk of incident TB of 3% or higher), using TST in addition to questionnaires for prediction is only worthwhile if one is willing trade at least 803 TSTs for a true-positive prediction. For other risk thresholds, >1000 TSTs must be traded for a true-positive prediction for testing with TST to be worthwhile. Abbreviations: TB, tuberculosis; TST, tuberculin skin test; WHO, World Health Organization.

predictive ability of the model when we removed it in a sensitivity analysis (results not shown). Our cohort differed from what might be encountered in other settings in that HIV prevalence was extremely low and HIV status of the exposed contact was not found to be a significant predictor in our model. In areas with higher HIV burden, the HIV status of contacts would be expected to contribute substantially to the risk of progression and our tools may require further modification in these settings.

In summary, we developed 2 tools to predict TB in household contacts of index TB patients on the basis of easily obtained information and showed that in Lima, Peru, the performance of these tools may be comparable to biomarkers that are both more costly and less feasible than this approach.

Supplementary Data

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

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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