Understanding Epidemiologic Risks for Infectious Disease Control

UNDERSTANDING EPIDEMIOLOGIC RISKS FOR INFECTIOUS DISEASE CONTROL

RUORAN LI

A Dissertation Submitted to the Faculty of

The Harvard T. H. Chan School of Public Health

in Partial Fulfillment of the Requirements

for the Degree of *Doctor of Science*

in the Department of Epidemiology

Harvard University

Boston, Massachusetts

May, 2020

Dissertation Advisor: Megan B. Murray Ruoran Li

Understanding epidemiologic risks for infectious disease control

Abstract

As of April 2020, the coronavirus disease 2019 (COVID-19) pandemic has already irreversibly changed our perception of the field of infectious diseases. The first two chapters in this thesis were completed in the pre-2020 era, when we focused on developing tools to inform tuberculosis (TB) control programs in high-burden countries. The last chapter is our quick response to the emerging COVID-19 pandemic, in which we described the disease burden on healthcare resources in cities in China and explored its implication for cities in the United States.

One common theme in all three chapters is our focus on epidemiologic risks. In Lima, Peru, can we predict the risk of disease progression among household contacts of TB patients to better their clinical management (Chapter 1)? In India, how can we use information about the distribution of TB risk factors to identify populations who were missed by disease surveillance systems (Chapter 2)? And finally, how to translate experience from one city to another during a pandemic, when the underlying populations have potentially different risk profiles (Chapter 3)?

While TB continues to plague our most vulnerable population, knowledge about risk and risk factors for the COVID-19 will start to accumulate. The enclosed three chapters are our exploration of how epidemiologic risks could help with infectious disease control programs.

Table of Contents

List of Figures with Captions

List of Tables with Captions

Acknowledgements

I would like to express my deepest gratitude to my academic advisor, Dr. Megan Murray, on constantly challenging me to leave my comfort zone of being a student and a junior analyst. By the end of these five years, through countless conversations and dozens of paper drafts, I have learned from Megan the skills to explore topics that I am interested in, assess the merits of different research questions, stand my ground, and write, and the wisdom to give up an idea or ask for help. These are the things that I have sought to learn five years ago, and I will treasure and use for the rest of my career, so I cannot overstate my appreciation for being advised by Megan.

I would like to extend my sincere gratitude to my two committee members, Dr. Marc Lipsitch and Dr. Francesco Nordio. Marc has been an exemplar scientist and a patient teacher to me, and I particular appreciate the opportunity to work with him more closely over the last several months during the COVID-19 pandemic. His good humor and passion for working through impactful scientific problems even under the most strenuous situation have moved me deeply. Francesco was instrumental for helping me build a foundation for doing good research by always providing helpful advice, practical suggestions, and unwavering support.

I would also like to thank other mentors and friends who have guided and supported me over the past five years, Dr. Lindsay Jaacks, Dr. Kayla Laserson, Dr. Fran Cook, Dr. Chuan-Chin Huang, Dr. Limei Jing, Kathy Brenner, Donald Halstead, Dr. Edward Nardell, Dr. Nancy Cook, Dr. Courtney Yuen, Dr. Eric Mooring, Dr. Letizia Trevisi, Dr. I-Min Lee, Dr. Howard Sesso, Dr. Jennifer Stuart, Dr. Natalie DuPré, Dr. Corey Peak, Dr. Bernard Rachet, Dr. Bethany Hedt, Dr. Miguel Hernan, Dr. Goodarz Danaei, Dr. Caroline Buckee, Dr. Bill Hanage, and all other coauthors and teachers.

I would like to thank all staff members in the Department of Epidemiology in Chan School of Public Health, the Department of Global Health and Social Medicine in Harvard Medical School, and other school- and university-wide colleagues who have made this work possible. Special thanks to Eric DiGiovanni and Germaine Palmer, who brought me constant warmth in trying times through their humanity and openness.

I would like to thank all of my friends and colleagues who have supported me intellectually and emotionally over the past five years. In particular, my doctoral cohort study group (in order of their defense), Hari Iyer, Gyeyoon Yim, Katrina Mott, Chris Andersen. Special thanks also to a group of mandarin-speaking friends, with whom I had the deepest conversions on public health and on life over many takeout dinners and hotpots: Ruijia Chen, Dr. Fang Yang, Yi Wang, You Wu, Dr. Qian Di, Rui Yang, Han Zhang, Yingxiang Lu. Special mentions to Rebecca Khan and Taylor Chin, who helped me come up with the title of this thesis.

Finally, I am deeply indebted to my family. My partner, Puyiran Zhu, to whom I will save my words here but suffice to say that without whom this work would not have been remotely possible. My extended family, who have always been simultaneous understanding and proud of what I am doing. One aunt said to me in my first year of the doctoral program that “the whole family will be very understanding” if I decided to quit; these are the words that have kept me going. Lastly, my parents and grandparents, for their great personalities and life-long inspirations, and for sheltering me from the burdens that could have been mine.

I would like to dedicate this dissertation to my mother and paternal grandparents, all of whom have passed away in the past five years.

Chapter 1: Two clinical prediction tools to improve tuberculosis contact investigation

Ruoran Li[1], Francesco Nordio[2], Chuan-Chin Huang[3], Carmen Contreras[4], Roger Calderon[4], Rosa Yataco[4], Jerome T. Galea[5], Zibiao Zhang[6], Mercedes C Becerra[7], Leonid Lecca[4,7], Megan B Murray[1,7]

[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, Massachusetts, United States

[2]TIMI Study Group, Brigham and Women's Hospital, 75 Francis St, Boston, Massachusetts, United States

[3]Brigham and Women's Hospital, Department of Medicine. Division of Global Health Equity, Department of Medicine, 75 Francis Street, Boston, Massachusetts, United States

[4]Socios En Salud, Lima, Peru

[5]School of Social Work, College of Behavioral and Community Sciences, University of South Florida, Tampa, Florida, United States

[6]Division of Global Health Equity, Brigham and Women's Hospital, Boston, Massachusetts, United States

[7]Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Avenue, Boston, Massachusetts, United States

Abstract

Background

Efficient contact investigation strategies are needed for the early diagnosis of 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 adult pulmonary TB patients. We used information from a subset of this cohort to derive two clinical prediction tools that identify contacts of TB patients at elevated risk of progressing to active disease by training multivariable models that predict (1) co-prevalent TB among all household contacts and (2) one-year incident TB among adult contacts. We validated the models in a geographically distinct sub-cohort 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 co-prevalent TB and 145 (1.9%) adult contacts developed incident TB within one year of index patient diagnosis. We predicted co-prevalent disease using information that could be readily obtained at the time an index patient was diagnosed and predicted one-year incident TB by including additional contact-specific characteristics. The area under the receiver-operating-characteristic curves for co-prevalent TB and incident TB were 0.86 (95%CI 0.83 – 0.89) and 0.72 (0.67 – 0.77). These clinical tools give 5-10% higher relative utilities than existing methods.

Conclusions

We present two 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.

Introduction

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 has been estimated to range from one to six 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 (*M.tb*) 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.

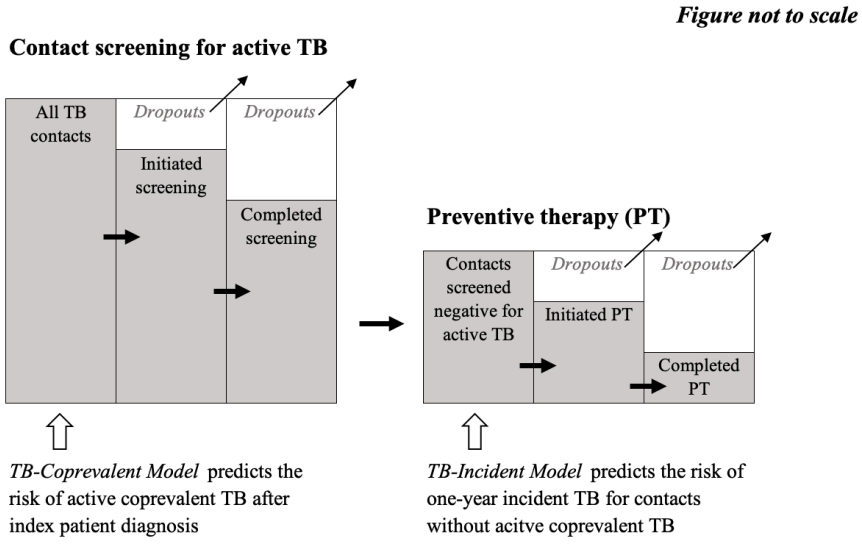

Figure 1.1. A simplified schematic of care cascade for tuberculosis contacts
Abbreviations: PT, preventive therapy; TB, tuberculosis.

Unfortunately, contacts are routinely lost from the contact screening and preventive therapy care cascades (Figure 1.1). 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 under-5 year

olds in Indonesia [6]; 14% of under 15-year olds 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], fewer than 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 ≥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 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 two prediction tools to estimate and communicate the risk of TB to contacts and clinics (Figure 1.1). We designed the first tool to estimate the risk of co-prevalent 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 of pulmonary TB patients aged ≥16 years in Lima Province, Peru. Data

collected at baseline included sociodemographic and clinical characteristics of both index patients and contacts (Table 1.1). We tested contacts for LTBI using tuberculin skin tests (TST). 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 were 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].

Table 1.1. Baseline characteristics of index tuberculosis patients, households, and household contacts, Lima, Peru, Sep 2009 - August 2012

Number of household contacts		**Training**[†] *10,062 (%)*	**Validation**[‡] *3,982 (%)*	***p value***
Index TB patient characteristics				
Sex	Female	41.5	39.4	*0.02*
Age	*Median [IQR]*	27 [21, 41]	28 [21, 44]	*0.09*
	16-30	58.8	57.0	*<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	*<0.001*
Smoking	None	97.4	97.0	*<0.001*
	≤ 1 cigarette a day	1.3	0.8	
	> 1 cigarette a day	1.3	2.2	
HIV positive		3.8	4.9	*0.003*
TB history		17.7	17.2	*0.52*
Cavitary disease		24.0	28.2	*<0.001*
Smear positive		63.4	71.0	*<0.001*
Culture positive		80.2	85.5	*<0.001*
Diagnostic delay	≥ 4 weeks	45.8	43.2	*0.007*
Season of diagnosis	Spring (Sep-Nov)	27.3	27.5	*<0.001*
	Summer (Dec-Feb)	24.8	28.5	
	Fall (Mar-May)	26.3	23.9	
	Winter (Jun-Aug)	21.7	20.1	
Symptom of coughing		85.4	87.8	*<0.001*

Table 1.1. (Continued)

Household characteristics				
Socioeconomic status	Low	32.9	38.9	*<0.001*
	Medium	46.4	38.3	
	High	20.7	22.8	
Crowding	> 4 people per room	19.6	29.9	*<0.001*
Type of Housing	House	12.2	26.7	*<0.001*
	Apartment	82.5	51.6	
	Other	5.3	21.8	
Household TB history		39.3	42.5	*0.001*
Contact characteristics				
Relationship between the contact and the index patient	Child of index patient	19.0	19.3	*0.11*
	Parent	15.0	14.1	
	Sibling	20.9	19.4	
	Spouse	7.6	8.1	
	Other	37.6	39.0	
Sex	Male	44.9	44.2	*0.48*
Age	*Median [IQR]*	23 [11, 41]	24 [10, 43]	*0.05*
	0-5	12.6	13.2	*<0.001*
	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*		30.5	29.7	*0.50*
Smoking*	None	90.2	88.6	*0.11*
	≤ 1 cigarette a day	5.1	5.9	
	> 1 cigarette a day	4.7	5.5	
Drinking*	None	58.6	61.3	*0.07*
	≤ 2 units per day	32.8	30.3	
	> 2 units per day	8.6	8.4	
Self-reported diabetes		1.5	2.4	*0.001*
HIV positive		0.4	0.5	*0.26*
Nutrition[§]	Normal	58.2	55.8	*0.02*
	Underweight	1.9	1.8	
	Overweight	39.9	42.4	
Body mass index*	*Mean (s.d.) (kg/m^2)*	26.7 (4.7)	27.0 (5.1)	*0.03*
TB history		7.5	8.1	*0.23*

Table 1.1. (Continued)

Number of BCG scars	0	13.5	14.9	*<0.001*
	1	63.1	66.0	
	2	18.4	16.1	
	≥ 3	5.0	2.9	
Cough	None	90.5	92.1	*0.007*
	1-7 days	3.1	2.8	
	8-14 days	0.5	0.5	
	15-30 days	5.1	3.7	
	More than 30 days	0.8	0.8	
Tuberculin skin test (TST)	TST contraindicated	12.1	19.9	*<0.001*
	< 5mm	42.4	34.4	
	5-9mm	12.1	9.9	
	10-14mm	21.7	20.9	
	≥ 15mm	11.6	14.9	
Endpoints				
Coprevalent TB		2.0	2.5	*0.08*
One-year incident TB		2.1	2.3	*0.38*
One-year incident TB*		1.8	2.1	*0.43*

P values were based on χ^2 tests for categorical variables, Wilcoxon rank-sum test for continuous variables with non-normal distributions (age of index patient, age of contact, and crowding), and t-test with equal variance for BMI.

† Training: We trained the models on the subset of contacts with index patients diagnosed in North Lima, East Lima and Rimac.

‡ Validation: 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 households than those represented by the training sample.

***** For adults (20+) only.

§ 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/m2. *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. Using weight for length may result in an underestimation in the prevalence of underweight for infants under 2 particularly in settings with high burden of stunting.

We developed two 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

(*co-prevalent TB*); the second model predicts a one-year incident TB diagnosis among contacts in whom TB had been ruled out at baseline (*incident TB*).

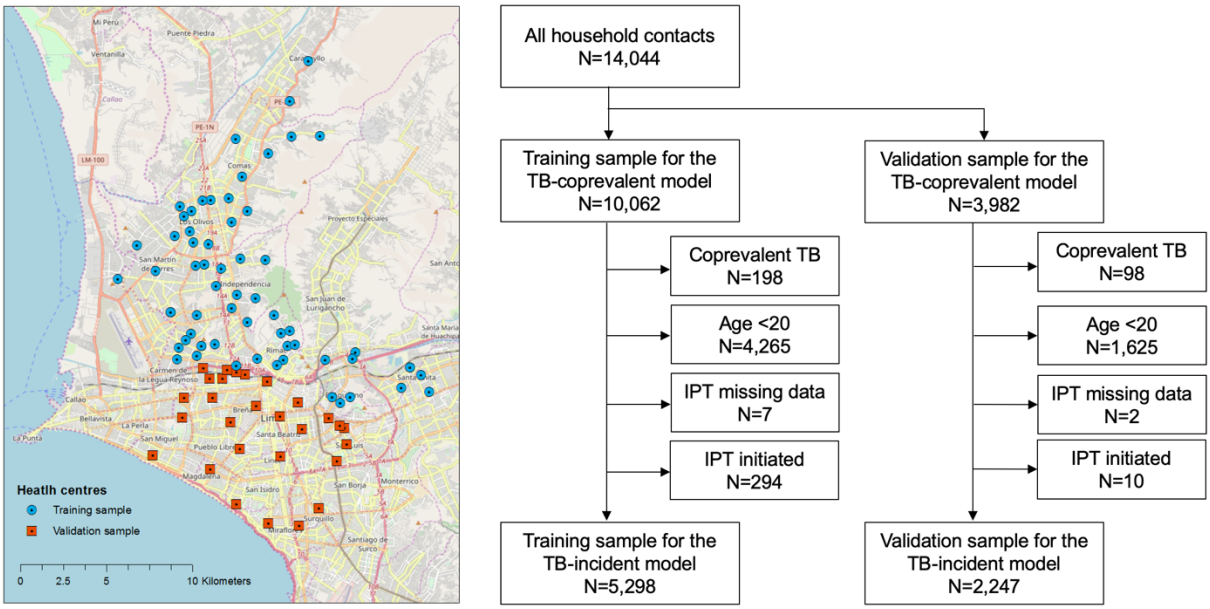

Figure 1.2. Flow diagram and map for participants included in the prediction models.

Training sample: contacts of adult pulmonary tuberculosis (TB) patients diagnosed in health centers in North Lima, East Lima and Rimac. For the TB-Coprevalent Model, n=10,062; for the TB-Incident Model (restricted to contacts ≥20 who did not receive preventive therapy), n= 5,298. *Validation sample*: contacts of adult pulmonary TB patients diagnosed in health centers in Central Lima (except Rimac). For the TB-Coprevalent Model, n=3,982, for the TB-Incident Model (restricted to contacts ≥20 who did not receive preventive therapy), n=2,247. 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.

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 1.2). We initially included 24 candidate predictors that had been previously associated with risk of TB (Table 1.2) [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 (e.g. $p<0.05$) indicate poor calibration. We used the coefficients from this final model to compute a risk score for co-prevalent 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 by comparing observed and predicted risks within three risk groups. We then estimated the score's sensitivity and specificity using plausible cut-offs indicated by its distribution. Finally, we validated the score among the subset of contacts diagnosed within Central Lima (*validation sample*, Figure 1.2). 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 non-normal 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 co-prevalent TB patient.

Using the same approach, we next developed a prediction model for one-year incident TB (*TB-Incident Model*) among contacts aged ≥20 years who did not have co-prevalent disease and had not received preventive therapy. (We note that Peru national TB policy specifies that preventive therapy is only offered to contacts <20 years and to individuals with specified co-morbidities [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, body mass index and diabetes mellitus, and the presence/number of visible scars from BCG immunization (Table 1.3). After obtaining a final Lasso logistic regression model in the training sample, we computed the risk score for one-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 one unit difference in BMI translates into one 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 one-year incident TB in our cohort. We classified contacts into three arbitrary risk groups based on their incident TB risks and calculated the net reclassification improvement (NRI) [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) LTBI 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*.

Table 1.2. TB-Coprevalent Model: Penalized Multivariate Logistic Regression Analysis Using Candidate Predictors for Coprevalent Tuberculosis, Training Cohort (n = 10 062)

		Univariate		Multivariate			Lasso model	
		OR*	*p value*	aOR†	(95% CI)	*p value*	OR‡	Score¶
Index TB patient characteristics								
Sex	Female	0.86	*0.4*	1.02	(0.65-1.49)	*0.9*		
Age	16-30	*ref*		*ref*				
	31-45	1.23	*0.4*	0.81	(0.48-1.37)	*0.4*		
	46-60	0.86	*0.7*	0.58	(0.27-1.23)	*0.2*	0.83	
	> 60	1.33	*0.4*	0.91	(0.45-1.83)	*0.8*		
HIV positive		0.62	*0.4*	0.54	(0.15-1.96)	*0.4*	0.77	**-1**
Cavitary disease		1.05	*0.8*	1.14	(0.72-1.81)	*0.6*	1.03	
TB history		1.44	*0.12*	1.59	(0.84-3.01)	*0.2*	1.17	
Smear positive		1.00	*0.98*	1.02	(0.66-1.60)	*0.9*		
Culture positive		0.94	*0.8*	0.83	(0.49-1.42)	*0.5*		
Smoking	None	*ref*		*ref*				
	≤ 1 cigarette a day	1.39	*0.7*	0.56	(0.11-2.90)	*0.5*	0.78	**-1**
	> 1 cigarette a day	3.01	*0.09*	2.14	(0.53-8.58)	*0.3*	1.58	**1**
Diagnostic delay	≥ 4 weeks	1.93	*<0.001*	2.27	(1.45-3.57)	*<0.001*	1.67	**1**
Season of diagnosis	Spring (Sep-Nov)	2.18	*<0.01*	1.96	(1.13-3.40)	*0.02*	1.45	**1**
	Summer (Dec-Feb)	1.28	*0.4*	1.36	(0.76-2.42)	*0.3*		
	Fall (Mar-May)	*ref*		*ref*				
	Winter (Jun-Aug)	1.13	*0.7*	1.33	(0.72-2.48)	*0.4*		
Symptom of coughing		1.39	*0.2*	0.86	(0.43-1.70)	*0.7*		
College education or higher		0.53	*<0.01*	0.59	(0.36-0.98)	*0.04*	0.72	**-1**
Household characteristics								
Crowding	> 4 people per room	1.52	*0.07*	1.41	(0.86-2.31)	*0.2*	1.19	

Table 1.2. (Continued)

Type of Housing	House	*ref*		*ref*				
	Apartment	0.84	*0.6*	0.96	(0.52-1.78)	*0.9*		
	Other	0.85	*0.7*	0.49	(0.20-1.25)	*0.1*	0.74	**-1**
Household TB history		1.47	*0.04*	0.76	(0.43-1.34)	*0.3*		
Contact characteristics collectible from index patients during TB diagnosis								
Relationship between the contact and the index patient	Child of index patient	1.24	*0.4*	2.00	(1.15-3.50)	*0.01*	1.35	**1**
	Parent	1.29	*0.3*	1.21	(0.63-2.32)	*0.6*		
	Sibling	1.09	*0.7*	1.11	(0.64-1.92)	*0.7*		
	Spouse	1.45	*0.2*	1.27	(0.61-2.65)	*0.5*		
	Other	*ref*		*ref*				
Sex	Male	1.29	*0.11*	1.40	(0.95-2.05)	*0.09*	1.15	
Age, coughing duration	≥ 20, ≤ 7 days	*ref*		*ref*				
	≥ 20, >7 days	95.9	*<0.001*	87.7	(49-157)	*<0.001*	47.8	**10**
	5-19, ≤ 7days	1.27	*0.4*	0.98	(0.50-1.90)	*0.9*		
	5-19, > 7 days	46.9	*<0.001*	33.92	(16-72)	*<0.001*	25.1	**8**
	< 5, ≤ 7 days	0.92	*0.9*	0.65	(0.25-1.71)	*0.4*	1.00	
	< 5, > 7days	7.85	*<0.001*	5.44	(1.70-17.4)	*<0.01*	4.71	**4**
Nutrition[§]	Normal	*ref*		*ref*				
	Underweight	2.63	*0.02*	1.54	(0.53-4.47)	*0.4*	1.30	**1**
	Overweight	0.86	*0.4*	0.69	(0.45-1.06)	*0.09*	0.82	**-1**
TB history		2.47	*<0.001*	1.68	(0.89-3.15)	*0.11*	1.53	**1**
Current smoker		0.93	*0.8*	0.57	(0.25-1.26)	*0.2*	0.81	**-1**
Drinks alcohol		1.30	*0.13*	1.04	(0.67-1.62)	*0.8*		
College education or higher		0.89	*0.6*	0.96	(0.55-1.68)	*0.9*		

Table 1.2. (Continued)

* Univariate OR: univariate odds ratio estimated using mixed-effect models with random intercept and fixed slope, accounting for clustering at household level.
† aOR, 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.
‡ 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 0.05 cut-offs: between contact age group and contact cough ($p<0.001$), relationship and contact age group ($p=0.6$), index case sex and relationship ($p=0.4$), and index case smear and index case cough ($p=0.12$).
¶ 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.
§ 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/m2. *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/m2. *Normal*: otherwise.

Table 1.3. TB-Incident Model: Penalized Multivariate Logistic Regression Analysis Using Candidate Predictors for 1-Year Incident Tuberculosis Among Adult Contacts, Training Cohort (n = 5298)

		Univariate		Multivariate			Lasso model	
		OR*	*p value*	aOR†	(95% CI)	*p value*	OR‡	Score¶
Index TB patient characteristics								**30 +**
Sex	Female	1.34	*0.2*	1.40	(0.91-2.15)	*0.13*	1.02	
Age	16-30	*ref*		*ref*				
	31-45	0.63	*0.2*	0.53	(0.27-1.02)	*0.06*		
	46-60	0.54	*0.14*	0.57	(0.23-1.41)	*0.2*	0.996	
	> 60	0.61	*0.2*	0.74	(0.29-1.88)	*0.5*		
HIV positive		1.22	*0.7*	1.32	(0.49-3.57)	*0.6*		
Cavitary disease		1.30	*0.3*	1.40	(0.87-2.24)	*0.2*		
TB history		1.38	*0.2*	1.84	(0.95-3.56)	*0.07*		
Smear positive		1.42	*0.14*	1.33	(0.82-2.17)	*0.2*	1.04	
Culture positive		1.34	*0.3*	1.12	(0.61-2.04)	*0.7*		
Smoking	None	*ref*		*ref*				
	≤ 1 cigarette a day	0.87	*0.9*	0.91	(0.12-6.93)	*0.9*		
	> 1 cigarette a day	2.97	*0.12*	2.47	(0.69-8.83)	*0.2*		
Diagnostic delay	≥ 4 weeks	1.05	*0.8*	1.02	(0.65-1.60)	*0.9*		
Season of diagnosis	Spring (Sep-Nov)	1.31	*0.4*	1.32	(0.73-2.39)	*0.3*		
	Summer (Dec-Feb)	1.27	*0.4*	1.38	(0.76-2.48)	*0.3*		
	Fall (Mar-May)	*ref*		*ref*				
	Winter (Jun-Aug)	1.25	*0.5*	1.38	(0.74-2.56)	*0.3*		
Symptom of coughing		1.16	*0.6*	0.93	(0.48-1.80)	*0.8*		
College education or higher		0.92	*0.7*	1.01	(0.62-1.64)	*0.96*		

Table 1.3. (Continued)

Household characteristics								
SES	Low	*ref*		*ref*				
	Medium	0.62	*0.05*	0.60	(0.37-0.95)	*0.03*		
	High	0.54	*0.05*	0.56	(0.30-1.04)	*0.07*		
Crowding	> 4 people per room	1.06	*0.84*	1.09	(0.62-1.90)	*0.8*		
Type of Housing	House	ref		ref				
	Apartment	1.13	*0.7*	1.00	(0.54-1.85)	*0.99*		
	Other	0.41	*0.2*	0.26	(0.06-1.14)	*0.07*	0.98	
Household TB history		1.15	*0.53*	0.59	(0.31-1.13)	*0.11*		
Contact characteristics								
Relationship between the contact and the index patient	Child of index patient	0.81	*0.7*	1.09	(0.36-3.24)	*0.9*		
	Parent	1.12	*0.7*	1.44	(0.70-2.96)	*0.3*		
	Sibling	1.59	*0.12*	1.35	(0.74-2.48)	*0.3*		
	Spouse	1.96	*0.04*	2.10	(1.09-4.05)	*0.03*	1.18	**2**
	Other	*ref*		*ref*				
Sex	Male	1.30	*0.2*	1.27	(0.81-1.99)	*0.3*		
Age	20-30	1.21	*0.6*	1.30	(0.56-3.03)	*0.5*	1.16	**2**
	31-45	0.60	*0.2*	0.83	(0.37-1.85)	*0.6*		
	46-60	0.60	*0.2*	0.73	(0.32-1.67)	*0.4*		
	> 60	*ref*		*ref*				
Body mass index		0.87	*<0.001*	0.88	(0.83-0.93)	*<0.001*	0.91	**-1**
TB history		2.07	*0.007*	2.06	(1.07-3.95)	*0.03*	1.31	**3**
Number of BCG scars	None	*ref*		*ref*				
	1	0.65	*0.2*	0.71	(0.38-1.34)	*0.3*		
	2	0.48	*0.04*	0.60	(0.29-1.22)	*0.16*		
	≥ 3	0.62	*0.3*	0.90	(0.35-2.31)	*0.8*		

Table 1.3. (Continued)

Diabetes		1.26	*0.7*	1.58	(0.46-5.36)	*0.5*		
Smoking	None	*ref*		*ref*				
	≤ 1 cigarette a day	0.79	*0.7*	1.04	(0.36-2.99)	*0.9*		
	> 1 cigarette a day	1.00	*1.0*	1.22	(0.46-3.28)	*0.7*		
Drinking	None	*ref*		*ref*				
	≤ 2 units per day	0.61	*0.05*	0.61	(0.37-1.02)	*0.06*	0.89	**-1**
	> 2 units per day	0.81	*0.6*	0.70	(0.31-1.57)	*0.4*		
College education or higher		0.54	*0.02*	0.55	(0.32-0.95)	*0.03*	0.73	**-3**
Coughing	None	*ref*		*ref*				
	1-14 days	0.39	*0.4*	0.40	(0.05-2.89)	*0.4*		
	> 14 days	3.24	*<0.001*	3.07	(1.61-5.87)	*<0.001*	2.16	**9**

* Univariate OR: univariate odds ratio estimated using mixed-effect models with random intercept and fixed slope, accounting for clustering at household level.

† aOR, 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.

‡ Lasso OR: 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 0.05 cut-offs: between index case smear and index case cough (p=0.06), BCG scar number and contact age group (p=0.4), and contact cough and contact age group (p=0.4).

¶ 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 BMI 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.

Table 1.4. 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	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 tuberculosis	≥6	65%	96%	22.4%	99.3%	6%	1.3%	0.7%
One-year incident tuberculosis	≥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.

Results

TB-Coprevalent Model risk score

The training sample for the *TB-Coprevalent Model* included 10,062 contacts of adult pulmonary TB patients (Figure 1.2), of which 2.0% (198) were found to have co-prevalent TB (Table 1.1). Of the 24 candidate predictors shown in Table 1.2, 17 remained in the best Lasso model which had an AUC of 0.86 (95% CI: 0.83 – 0.89) (Figure 1.3) and a Hosmer-Lemeshow test of p=0.72. The final risk score included the 12 predictors shown in Table 1.2. The risk scores were distributed bimodally (Figure 1.4 (b)): the majority of contacts (94%) had scores <6 and 0.7% of this group had co-prevalent TB, while 18.4% of those with scores between 6 and 10 and 36.5% of those with scores >10 had co-prevalent TB (Figure 1.4 (c)). We found no significant differences between predicted and observed prevalences (Supplemental Figure 1, Supplemental 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 co-prevalent disease, with a positive predictive value (PPV) of 22.4% and a negative predictive value (NPV) of 99.3% (Table 1.4).

Contacts in the validation sample (n=3,982) had a higher prevalence of co-prevalent TB (2.5%, n=98) than those in the training sample (2.0%, p=0.08) (Table 1.1). The validation AUC was 0.83 (0.78 – 0.88) (Figure 1.3) and the Hosmer-Lemeshow statistic was p=0.005. Calibration plots (Figure 1.4 (d), Supplemental Figure 1, Supplemental Table 1) indicate that the score tended to underestimate co-prevalent TB risks for contacts in the median risk category.

The relative utility of using the *TB-Coprevalent Model* to inform contact screening is substantially higher than the WHO recommendation (Figure 1.5) [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.

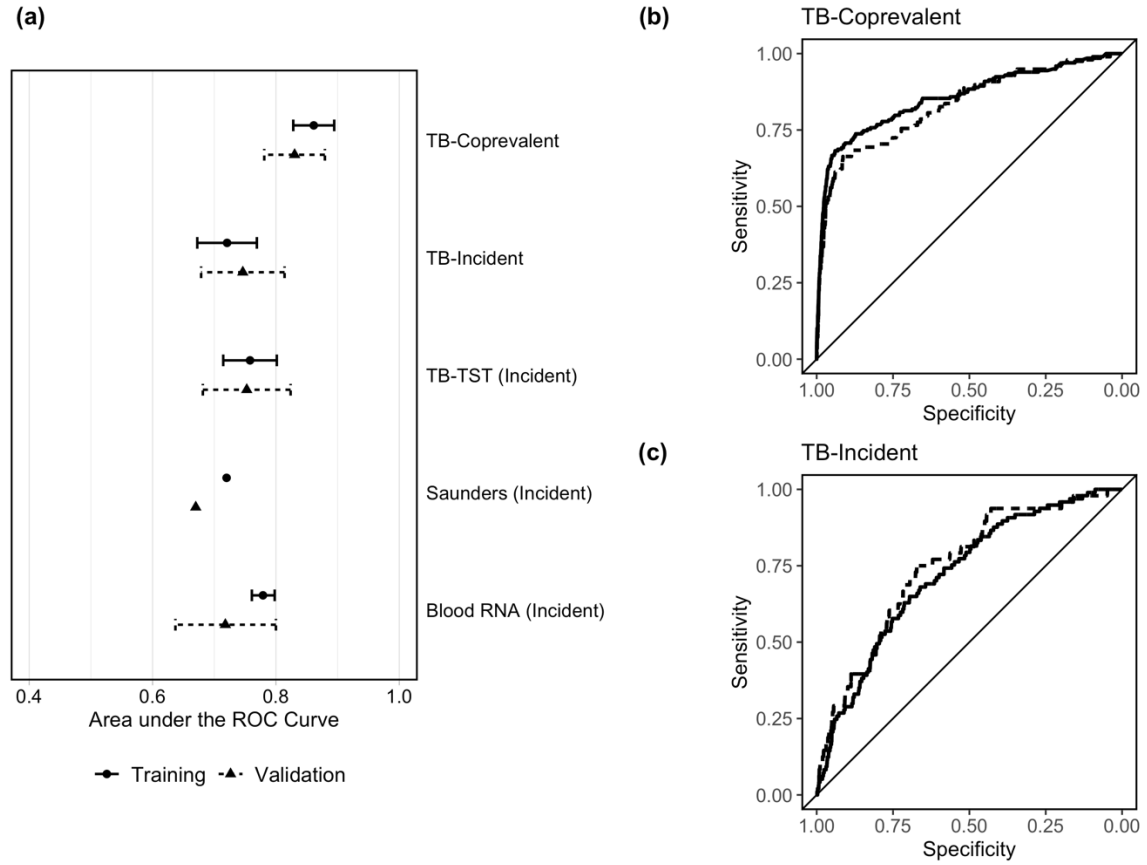

Figure 1.3. Receiver operating characteristic (ROC) curves for the Tuberculosis (TB)–Coprevalent Model and the TB-Incident Model, with area under the curve (AUC) statistics.

(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.

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

		Index patient score
Are you diagnosed with TB in the spring?	+1	
Have you ever tested positive for HIV?	-1	
If you smoke: do you smoke at most one cigarette a day?	-1	
If you smoke: do you smoke more than one 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 in 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 cigarette?	-1	
Has the contact had TB before?	+1	

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

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

Read the risk of co-prevalent TB using the calculated total score:

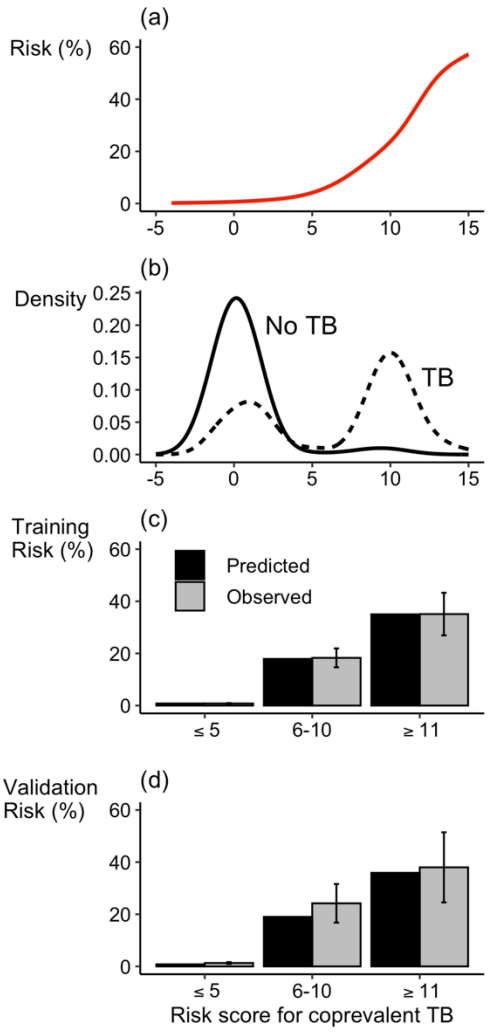

Figure 1.4. Distribution of Tuberculosis (TB)–Coprevalent Model risk scores and predicted coprevalent TB risk in the training and validation samples

(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.

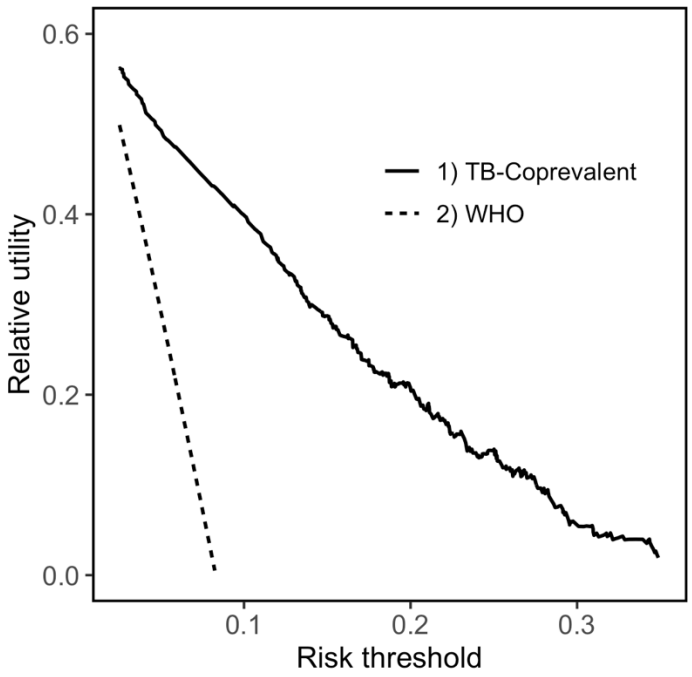

Figure 1.5. Relative utility curves comparing the Tuberculosis (TB)–Coprevalent Model vs the World Health Organization (WHO) recommendations for identifying high-risk household contacts for contact investigation

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.

TB-Incident Model risk score

Among 5,298 adult contacts included in the *TB-incidence model* (Figure 1.2), 1.8% (n=97) developed incident TB within one year of enrollment. Of 27 candidate predictors (Table 1.3), 11 remained in the best Lasso model which had an AUC of 0.72 (95% CI: 0.67 – 0.77) (Figure 1.3) and a Hosmer-Lemeshow test of p=0.65. The final risk score consisted of seven predictors after rounding model coefficients (Table 1.3). After we rounded model coefficients,

the score was normally distributed in the training sample (Figure 1.6 (b)), 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 1.6 (c)). Table 1.4 shows the sensitivity, specificity, PPV and NPV at several arbitrary cut-off points.

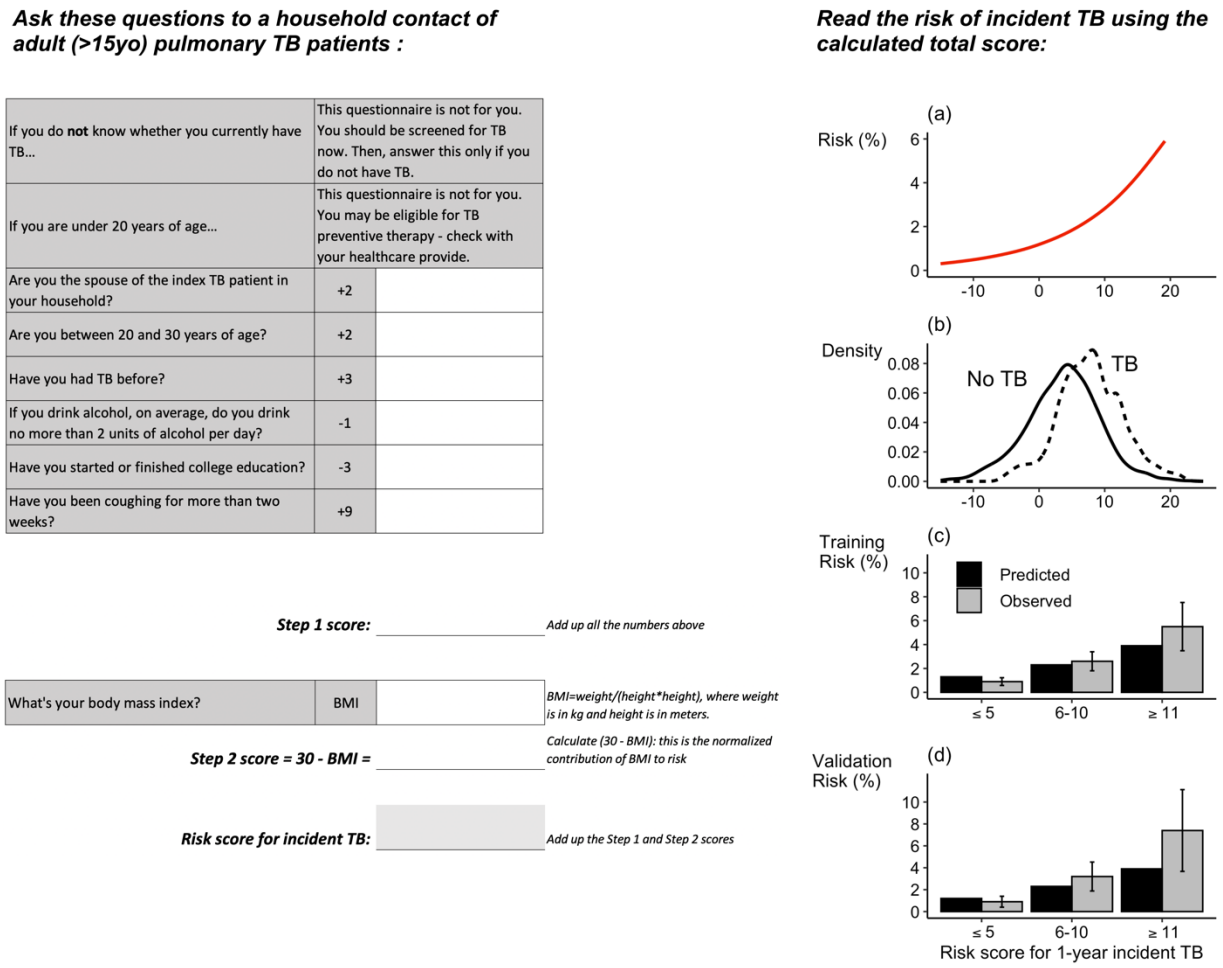

Figure 1.6. Distribution of Tuberculosis (TB)–Incident Model risk scores and predicted 1-year incident tuberculosis risk in the training and validation samples

(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.

Among 2,247 contacts in the validation sample (Figure 1.2), 2.1% (n=48) developed incident TB compared to 1.8% in the training sample (p=0.4). The AUC was 0.75 (0.68 – 0.81) (Figure 1.3) and the Hosmer-Lemeshow statistic was p=0.06. The calibration plots (Figure 1.6 (d), Supplemental Figure 2, Supplemental 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 Supplemental Table 3), the model improved only slightly with an AUC of 0.76 (0.71 – 0.80) in the training sample and 0.75 (0.68 – 0.82) in validation sample (Figure 1.3).

The Saunders' score [20] gave an AUC of 0.65 (0.60 – 0.69) in our cohort; it overestimated risk for the high and medium risk contacts and underestimated risk in the low risk group (Supplemental 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 1.5): the reclassification improvement [21] using the *TB-Incident Model* risk score is 13.1% for contacts who progressed to TB and 4.6% for contacts who did not progress, giving an NRI of 17.7%.

For risk thresholds between 1% and 5%, i.e. 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 1.7). 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 below 1%, different tests yielded similar utilities whilst for risk thresholds above 5%, test utilities were no better than treating no one in the population.

Table 1.5. 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 tuberculosis within one 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)*	*8*	*(33.3)*	16	(66.7)	24
Total	42		62		41		145
Contacts who did not develop incident tuberculosis within one year							
Low risk	3,621	(83.9)	**609**	**(14.1)**	**88**	**(2.0)**	4,318
Medium risk	*939*	*(38.7)*	1,211	(49.9)	**278**	**(11.4)**	2,428
High risk	*43*	*(6.6)*	*336*	*(51.4)*	275	(42.0)	654
Total	4,603		2,156		641		7,400

Data are presented as frequency (row %). **Boldface text** indicates positive reclassification; *italic text* indicates negative reclassification. Abbreviation: TB, tuberculosis.

Discussion

We developed two tools that are predictive of TB risks for household contacts of adult pulmonary TB patients 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 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 one 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 in reducing secondary TB cases than current practice.

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 co-prevalent disease among

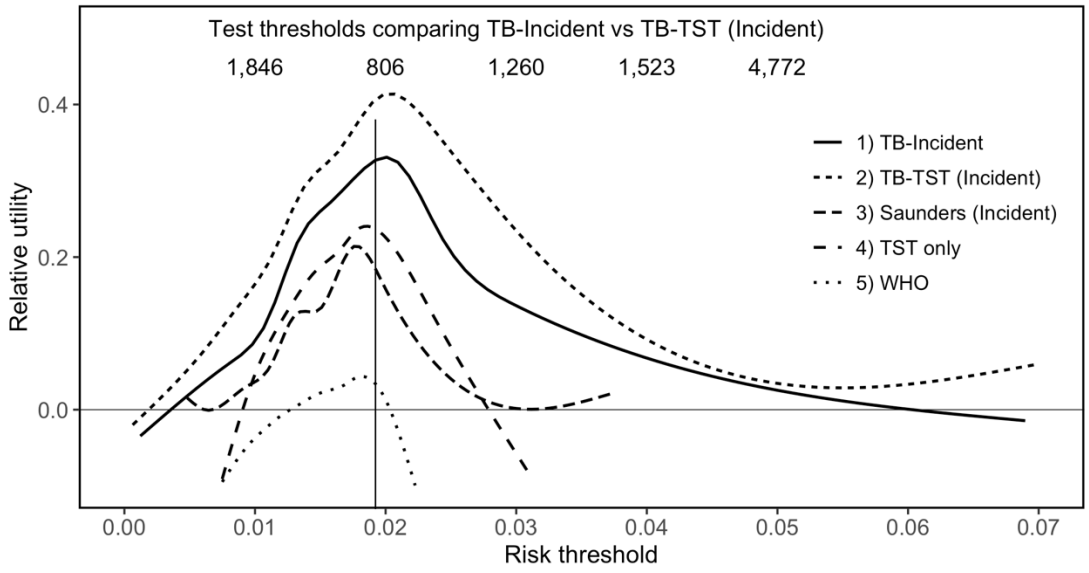

Figure 1.7. Relative utility curves comparing the Tuberculosis (TB)–Incident Model to other strategies for identifying high-risk household contacts for preventive treatment

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 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.

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], HIV-infected individuals [26,24], 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 health care system.

In contrast to screening for co-prevalent disease, the prediction of incident TB often involves both epidemiological risk factors and/or biomarkers such as TST, 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 ELISpot 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 one study, the addition of epidemiological indicators to the TST improved the prediction of TB disease among child contacts from an AUC of 0.80 to 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 post-enrollment [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 the previous model focuses on contacts of smear-positive

TB patients. 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 6 (b)). 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 [35,11], 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 was collected from the contacts during household visits. It is possible that index patients undergoing an initial diagnostic work-up 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 by an index patient, and we

classified our continuous BMI variable into three 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. Secondly, we assumed that index patients are aware of their HIV status. While TB patients are routinely tested for HIV if they don't 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 co-prevalent TB and does not impact the 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 higher HIV burden areas, 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 two 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.

Reference

1. World Health Organization. Global tuberculosis report 2018. 2018.

2. Sreeramareddy CT, Panduru KV, Menten J, Van den Ende J. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. BMC Infect Dis **2009**; 9:91.

3. World Health Organization. Recommendations for Investigating Contacts of Persons With Infectious Tuberculosis in Low- and Middle-income Countries. World Health Organization, 2012.

4. Systematic screening for active tuberculosis: principles and recommendations. Geneva, Switzerland: World Health Organization, 2013.

5. Rodriguez CA, Sasse S, Yuengling KA, Azzawi S, Becerra MC, Yuen CM. A systematic review of national policies for the management of persons exposed to tuberculosis. Int J Tuberc Lung Dis **2017**; 21:935–940.

6. Rutherford ME, Ruslami R, Anselmo M, et al. Management of children exposed to Mycobacterium tuberculosis: a public health evaluation in West Java, Indonesia. Bull World Health Organ **2013**; 91:932-941A.

7. Banu Rekha VV, Jagarajamma K, Wares F, Chandrasekaran V, Swaminathan S. Contact screening and chemoprophylaxis in India's Revised Tuberculosis Control Programme: a situational analysis. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis **2009**; 13:1507–1512.

8. Armstrong-Hough M, Turimumahoro P, Meyer AJ, et al. Drop-out from the tuberculosis contact investigation cascade in a routine public health setting in urban Uganda: A prospective, multi-center study. PLOS ONE **2017**; 12:e0187145.

9. World Health Organization. Latent TB Infection : Updated and consolidated guidelines for programmatic management. 2018. Available at: http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/. Accessed 1 March 2019.

10. Zachariah R, Spielmann MP, Harries AD, et al. Passive versus active tuberculosis case finding and isoniazid preventive therapy among household contacts in a rural district of Malawi. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis **2003**; 7:1033–1039.

11. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis **2016**; 16:1269–1278.

12. Fox GJ, Loan LP, Nhung NV, et al. Barriers to adherence with tuberculosis contact investigation in six provinces of Vietnam: a nested case–control study. BMC Infect Dis **2015**; 15:103.

13. Ayakaka I, Ackerman S, Ggita JM, et al. Identifying barriers to and facilitators of tuberculosis contact investigation in Kampala, Uganda: a behavioral approach. Implement Sci IS **2017**; 12:33.

14. Harvard University Faculty of Medicine, Harvard School of Public Health, Brigham Women's Hospital, Socios En Salud, National Institute of Allergy, Infectious Diseases. Epidemiology of MDR-TB in Peru. 2009. Available at: https://ClinicalTrials.gov/show/NCT00676754.

15. Becerra MC, Huang C-C, Lecca L, et al. Transmissibility and potential for disease progression of drug resistant Mycobacterium tuberculosis: prospective cohort study. BMJ **2019**; 367. Available at: https://www.bmj.com/content/367/bmj.l5894. Accessed 1 December 2019.

16. Murray M. The Epidemiology of Tuberculosis. In: Tuberculosis The Essentials. New York: Informa Healthcare, 2010.

17. Friedman JH, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. J Stat Softw **2010**; 33:1–22.

18. Baker SG, Cook NR, Vickers A, Kramer BS. Using relative utility curves to evaluate risk prediction. J R Stat Soc Ser Stat Soc **2009**; 172:729–748.

19. Ministerio de Salud, Dirección General de Salud de las Personas, Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis. Norma técnica de salud para la atención integral de las personas afectadas por tuberculosis. Lima: Ministerio de Salud, 2013.

20. Saunders MJ, Wingfield T, Tovar MA, et al. A score to predict and stratify risk of tuberculosis in adult contacts of tuberculosis index cases: a prospective derivation and external validation cohort study. Lancet Infect Dis **2017**; 17:1190–1199.

21. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med **2011**; 30:11–21.

22. van't Hoog A, Langendam M, Mitchell E, et al. A systematic review of the sensitivity and specificity of symptom- and chest-radiography screening for active pulmonary tuberculosis in HIV-negative persons and persons with unknown HIV status. 2013.

23. van't Hoog AH, Onozaki I, Lonnroth K. Choosing algorithms for TB screening: a modelling study to compare yield, predictive value and diagnostic burden. BMC Infect Dis **2014**; 14:532.

24. Van Wyk SS, Lin HH, Claassens MM. A systematic review of prediction models for prevalent pulmonary tuberculosis in adults. Int J Tuberc Lung Dis **2017**; 21:405–411.

25. Gonçalves B das D, Passos SRL, Santos MAB dos, Andrade CAF de, Martins M de FM, Mello FC de Q. Systematic Review With Meta-Analyses and Critical Appraisal of Clinical Prediction Rules for Pulmonary Tuberculosis in Hospitals. Infect Control Hosp Epidemiol **2015**; 36:204–213.

26. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. PLoS Med **2011**; 8:e1000391.

27. Heffernan C, Doroshenko A, Egedahl ML, Barrie J, Senthilselvan A, Long R. Predicting pulmonary tuberculosis in immigrants: a retrospective cohort study. ERJ Open Res **2018**; 4:00170–02017.

28. Harris JB, Siyambango M, Levitan EB, et al. Derivation of a tuberculosis screening rule for sub-Saharan African prisons. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis **2014**; 18:774–780.

29. Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis **2012**; 12:45–55.

30. Zak DE, Penn-Nicholson A, Scriba TJ, et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. Lancet Lond Engl **2016**; 387:2312–2322.

31. Suliman S, Thompson EG, Sutherland J, et al. Four-Gene Pan-African Blood Signature Predicts Progression to Tuberculosis. Am J Respir Crit Care Med **2018**; 197:1198–1208.

32. Chan P-C, Shinn-Forng Peng S, Chiou M-Y, et al. Risk for tuberculosis in child contacts. Development and validation of a predictive score. Am J Respir Crit Care Med **2014**; 189:203–213.

33. Kik SV, Cobelens F, Moore D. Predicting tuberculosis risk. The Lancet **2016**; 388:2233.

34. Edwards A, Unigwe S, Elwyn G, Hood K. Effects of communicating individual risks in screening programmes: Cochrane systematic review. BMJ **2003**; 327:703–709.

35. Waisbord S. Behavioral barriers in tuberculosis control: A literature review. 2004.

Chapter 2: A method for incorporating underlying TB risks into subnational TB burden estimators

Ruoran Li[1], Francesco Nordio[2], Marc Lipsitch,[1] Megan B Murray[1,3]

[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, Massachusetts, United States

[2]TIMI Study Group, Brigham and Women's Hospital, 75 Francis St, Boston, Massachusetts, United States

[3]Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Avenue, Boston, Massachusetts, United States

Introduction

In order to rationally forecast, plan, and budget for tuberculosis (TB) control programs,[1] health officials need to know the number of new TB patients they can expect each year, and where these patients will be. In high-burden countries such as India, Indonesia, and Nigeria, understanding the sub-national distribution of TB patients is paramount due to their vast geographical scale of the countries and large social differences between sub-national regions.

Data sources and methods for estimating within-country distribution of TB patients commands increasing attention from global health practitioners.[2] Prevalence surveys are often considered to be the gold standard method to estimate TB burden because they systematically count both diagnosed and undiagnosed TB patients in a population at a point in time. However, the high cost of this labor-intensive approach means that national surveys are often under-powered. They do not allow a statistically rigorous comparison of TB prevalence at provincial and district levels. Notification of diagnosed TB patients provides an avenue for sub-national comparison of TB incidence, but reporting is often limited to patients diagnosed in the public sector and differs between sub-national regions. Drug sales data have recently been used to compare TB treatment volumes between sub-national regions.[3,4] However, sales of drugs such as rifampicin cannot reflect the burden of undiagnosed – thus untreated – TB in a population and are further dependent on treatment regimen prescribed for patients. The last source of data is surveys of self-reported TB, which have been used to estimated sub-national TB prevalence.[5] However, self-reports also cannot reflect undiagnosed TB in a population, and are additionally impacted by the stigmatization for TB in some populations[5] (Table 2.1).

In India, an estimated one million TB patients are missing in the TB notification system.[6] A large private health care sector that makes up >50% of the TB treatment volume[4] contributes

Table 2.1. Different sources of data for TB subnational burden estimation in India

Source	Pros	Cons	Publicly available data for India
TB notification (incidence)	• Notifiable disease • Trend over time	• Under-reporting (esp. from the private sector) • Misses undiagnosed TB	• Yearly at district-level in the RNTCP's annual report[13]
Prevalence survey (prevalence)	• "Gold standard" • Captures undiagnosed TB	• Costly • Snapshots in time • National survey not powered for subnational estimate • By design, excludes children and extrapulmonary TB	• One state + several districts, summarized in Chadha et al, 2019[7] • Planned national survey in 2019-20
Survey of self-reported TB (prevalence)	• Captures private diagnosis	• Differentially under-reporting due to stigma • Snapshots in time • Misses undiagnosed TB	• NFHS-4, appx. every 5-10 years, representative at district-level, presented in Mazumdar et al, 2019[5]
Drug sales (treatment prevalence)	• Reflects both private + public sector treatment volume • Trend over time	• Misses undiagnosed and untreated TB • Drug sales may not reflect local treatment	• State-level data, estimated by Arinaminpathy et al, Lancet ID 2016,[3] BMC ID 2019[4]
Risk index (underlying risk)	• Reflects long-term underlying TB risks	• Is not a measure of the number of TB cases • Poor understanding how different risk factors interacts	• NFHS-4, appx. every 5-10 years, representative at district-level, developed in this paper

substantially to the gap between notified and estimated incident cases. In addition to not reflecting the true burden of TB in India, the notification system has also been unreliable in reflecting the relative TB burden between regions within India.[7] Although there is a large increase in TB notification since it became mandatory in 2012[8] and following the launch of

NIKSHAY,[9] the web-based national TB notification portal for both the public and private sector,[10] notification from the private sector remains low.[11]

In this study, we developed a new estimate of relative sub-national TB burden in India that reflects the underlying TB risks in a population, using information from a large-scale population-based survey on the distribution of comorbidities and sociodemographic factors that increase TB infection and progression risks. We synthesized this new estimate with TB incident notification, treatment volume and self-reported prevalence.

Methods

TB risk score

We used data from the 2015-16 India National Family Health Survey (NFHS-4)[12] to extract information on the joint distribution of risk factors at the individual level for incident TB. the NFHS-4 collected data from 601,509 households in 640 districts in India; the sampling scheme was designed to assess major household indicators at the district level. All women aged 15-49 were asked to complete the Women's Questionnaire while men aged 15-54 from a random sample of 15% of households were asked to complete the Men's Questionnaires and the Biomarker Questionnaire that includes measurements of height and weight, random blood glucose, and laboratory testing for HIV.[12]

For each surveyed adult with non-missing risk factor information (Table 2.2), we computed a TB risk score based on previously reported relative risks of incident TB for a series of known determinants of TB progression. Mathematically, we define an *individual risk score* as the sum of risks from n risk factors, $\sum_{i=1}^{n} \widehat{\beta_i} x_i$, where $\widehat{\beta_i}$ is the natural logarithm of the causal

Table 2.2. Risk factors for incident pulmonary tuberculosis

TB risk factor	Causal effect size*	Source of effect size estimates*	Definitions using the NFHS-4 data
Prevalence of infectious cases			
Problem in accessing quality care	1.57 [1.16, 2.11]	Empirical	Proportion of women in the survey cluster reporting >1 big problem in accessing health care
Poor utilization/ quality of primary care	2.93 [1.83, 4.67]	Empirical	Proportion of under 5s in the survey stratum not receiving appropriate care for fever, diarrhea, or acute respiratory infections
Contact rate			
Living in urban slums	2.61 [0.85, 8.02]	Empirical	Household settlement type: slum designated by observation
Susceptibility			
HIV seropositive	12.6[§]	Dodd 2013[16], World Bank Group[17]	HIV testing results
Body mass index (kg/m^2)	0.862 [0.858-0.866]	Lönneroth 2010[18]	Per unit increase in BMI vs. a baseline of 25 kg/m^2, for men and non-pregnant women with measured weight and height
Diabetes mellitus	2.00 [1.78-2.24]	Al-Rifai 2017,[19] pooled estimates from all types of studies	Presence of self-reported diabetes, and/or a random blood glucose level of ≥200 mg/dL
Current smoking	2.01 [1.63-2.48]	Lin 2007,[20] estimates for pulmonary TB, current smoking vs non-smoker	Current cigarette or bidis smoking, with at least one smoked in previous 24 hours
Passive smoking	2.44 [1.27-4.67]	Lin 2007,[20] estimates for non-smoker adults	Individual is not a current smoker, and reported "Someone smoked in respondent's home or presence, in last 30 days"
Daily alcohol use	1.35 [1.09-1.68]	Imtiaz 2017,[21] alcohol use vs no alcohol use	Reported drink alcohol "Almost every day"

Table 2.2 (Continued)

Indoor air pollution	1.17 [0.83-1.65]	Lin 2014[22]	Cook indoors, no separate room used as a kitchen, and reporting biomass fuel use

* The causal effect sizes are the adjusted risk ratio (RR) of the risk factor on TB incidence. They are equivalent to the exponent of the contribution of the risk factor to the TB risk score. For risk factors with cited references, these are the risk ratios [95% CI] from meta-analysis of prospective studies (unless noted in the table). Empirical estimates of the causal effect sizes were estimated based on the odds ratio of the risk factors on self-reported TB in the NFHS-4 data using survey-weighted logistic regression, controlling for all other risk factors in this table.

§ The effect of HIV on TB risk depends on antiretroviral therapy (ART) status,[16] so we estimated an average effect of HIV assuming 43% HIV patients were on treatment in India based on a World Bank estimates that in India in 2015, of all adults aged 15 years and over living with HIV, 43% were on treatment.[17] For those not on ART, RR of HIV on TB ranges between 2.5 and 35; for those on ART, incident rate ratio=4.4 (2.5-17).[16] We further noted that 10% of HIV-positive people (newly enrolled in care) were on TB isoniazid preventive treatment (IPT) in 2017 in India (WHO 2017 TB country profile), and IPT added to ART has been shown to further reduce TB rates by a supplementary factor of around 0.31-0.63[16]. We assumed that all people living with HIV on IPT were on ART, and that IPT reduces TB risks among people living with HIV only if they are on ART.

effect of risk factor i on TB incidence, and x_i is the observed level of risk factor i for the individual. Assuming the effects of risk factors are additive on the natural logarithm scale, an individual's *risk score* is the natural logarithm of the relative risk of incident TB for that individual compared to a hypothetical person with none of these risk factors.

We selected the TB risk factors in Table 2.2 based on a theoretical framework of disease transmission and progression. Epidemic theory holds that the incidence of an infectious disease is correlated with the 1) the prevalence of infectious individuals in a population, 2) the contact rate, and 3) the risk of transmission given contact between an infectious and a susceptible individual and 4) the rate of disease progression among those who are infected. The relative risk of transmission given contact and the relative rate of disease progression among infected for a risk factor are usually co-estimated as a single relative risk representing a host's susceptibility to TB disease. We used variables in the NHFS-4 data to capture these contributors to TB incidence (Table 2.2). We assumed that the contact rate varied with the urbanicity of the household (urban

slums, urban non-slums, and rural areas based on NFHS-4), and that the risk of disease given contact was represented by biological, behavioral and social factors that increase the susceptibility to disease among TB contacts. We also assumed that the prevalence of infectious individuals is a function of the duration of untreated disease and that it would therefore vary with variables that captured poor access to and utilization of primary care.

We then estimated the effect sizes of these risk factor on TB incidence to be used to compute the risk score (Table 2.2). For variables representing a host's susceptibility to TB, we used estimates from meta-analyses of the adjusted effects of these individual risk factors on incident TB (Table 2.2). For poor access/utilization and urbanicity, we estimated the empirical odds ratio of these variables on self-reported TB in the NFHS-4 data using survey-weighted logistic regression, controlling for other risk factors.

Estimates of TB burden

We next summarized the individual-level TB risk scores in each Indian state into an area-level *risk index* and compared this new estimate with the area-level burden as estimated by three other methods: TB notifications, self-reported TB in the DHS and drug sales. Following Arinaminpathy et al,[4] we aggregated smaller states and union territories into larger area units.

TB risk index

We defined a sub-national *TB risk index* as the 90th percentile of the risk scores for all surveyed adults within a specified area. Because some of the risk factors for TB were only assessed in a sub-sample of the study population,[12] we developed a prediction rule for participants with missing data, using a linear regression model selected from candidate models using a ten-fold cross validation procedure to predict TB risk score. Candidate models were weighted by survey design and utilized available information as predictors such as sex, age,

wealth index, education, self-reported TB, TB knowledge, indoor air pollution, household crowding, insurance coverage, passive and active smoking, drinking, urbanicity, and state.

Self-reported TB

We used data from NFHS-4[12] to extract information on self-reported TB prevalence in 2015-16. An eligible woman respondent for each surveyed household was asked "*Does any usual resident of your household suffer from tuberculosis?*" in local languages, followed by listing the household members with TB and where they have sought treatment. Based on this question, we used survey-weighted methods similar to those described in a previous study[5] to estimate the prevalence of self-reported TB in 2015-16 for each area.

Drug sales

Following previous investigators,[3,4] we estimated both private and public treatment volumes for each area in India based on commercially available data on the sales of rifampicin-containing drugs by dividing the patient-months of private TB drug sales by the private market share.

TB notification

We extracted area-specific 2016 TB notification rates for both the private and public sectors from the Revised National Tuberculosis Control Program's (RNTCP) Annual Status Report in 2017[13]. TB was made a notifiable disease in 2012, and notification of all diagnoses and treatment initiations is required by law. Since then, the TB notification rate has steadily increased as more patients from the private sector have been reported.

Statistical analysis

We described the distribution of the individual risk scores by sex, age group, urbanicity, and wealth index using survey-weighted linear regression models.

We estimated the Spearman correlation coefficient between each pair of TB burden measures at the area level. We used principal component analysis (PCA) to further summarize all four measures by estimating the proportion of variances explained by the first two principal components (PCs) and ranked each area according to the first two PCs.

Results

Of the 601,509 households sampled in NFHS-4, complete information on all TB risk factors was collected from 105,112 men and 110,096 women. After we accounted for survey design, TB risk score exhibited a normal distribution, with a mean of 1.40 (95% CI: 1.39–1.41). Men had an 8% higher TB risk score than women, and participants aged 15-29 had a >25% higher risk than older adults (Table 2.3). People living in urban slums have 58% higher risk score than those living in rural areas, while those living in non-slum urban areas have 40% *lower* risk than those living in rural areas. Table 2.3 shows that there is a linear dose-response relationship between wealth quintile and risk score: the average risk score increases by 0.25 point for each quintile decrease in wealth, translating to 28% increase in risk score for each quintile decrease in wealth.

The prediction model that we designed to estimate the risk scores of participants with incomplete data on TB risk factors (n=596,600) had a root mean square error of 0.59 and R^2 of 0.504. The district-level risk indices ranged from 1.24 for South Andaman in Andaman and Nicobar Islands to 2.90 for Zunheboto in Nagaland (Figure 2.1). For states, the risk index ranges from 1.50 for Kerala to 2.60 in Bihar.

Table 2.3. Distribution of TB risk score by socioeconomic and demographic factors, India, NFHS-4 (2015–2016)

	Proportion	Risk score (95% CI)	Difference[§]	(S.E.)	% change in TB risk[†]
Sex					
Female	50.8%	1.36 (1.35, 1.37)	ref		
Male	49.2%	1.44 (1.43, 1.45)	0.079*	(0.004)	8%
Age, y					
15-29	48.8%	1.57 (1.56, 1.58)	ref		
30-44	37.1%	1.23 (1.22, 1.24)	-0.339*	(0.005)	-29%
45+	14.0%	1.26 (1.25, 1.28)	-0.307*	(0.007)	-26%
Urbanicity					
Rural	65.1%	1.57 (1.56, 1.58)	ref		
Urban	34.1%	1.06 (1.05, 1.08)	-0.505*	(0.009)	-40%
Urban slum	0.8%	2.03 (1.88, 2.17)	0.460*	(0.074)	58%
Wealth Index			*Per one quintile decrease in wealth*		
Wealthiest	22.3%	1.90 (1.89, 1.91)	0.254*	(0.003)	29%
Wealthier	21.2%	1.71 (1.70, 1.72)			
Middle	20.8%	1.47 (1.45, 1.48)			
Poorer	19.6%	1.21 (1.20, 1.23)			
Poorest	16.0%	0.89 (0.87, 0.91)			

[§] Difference between groups is the coefficient of the survey-weighted univariate linear regression models.
***** Statistically significant at p<.001 with survey-weighted linear regression models.
[†] The percentage change in TB risk comparing two population subgroups is calculated by taking the exponential of the difference in risk scores (this is the relative risk), minus 1, and then multiplied by 100%.

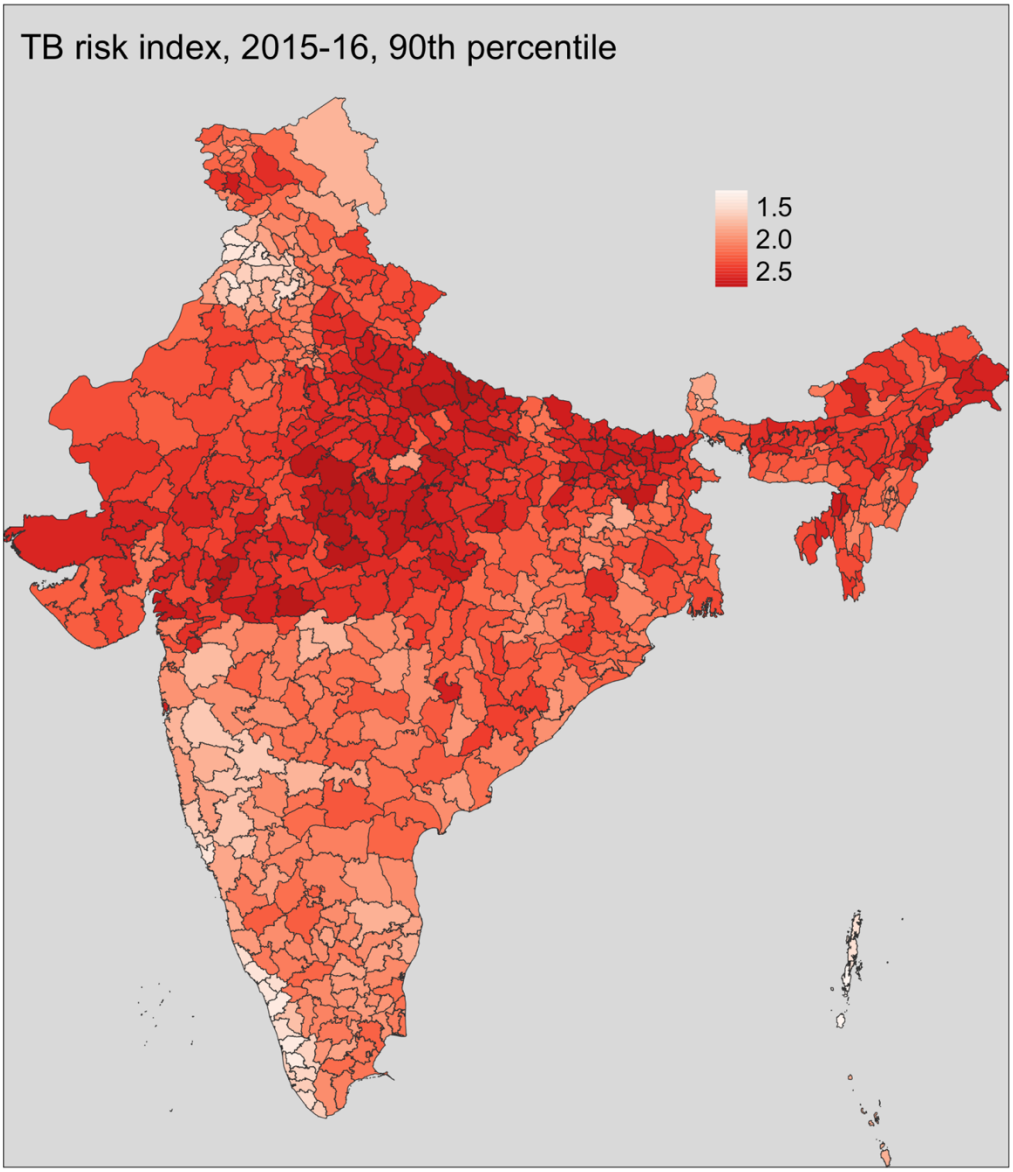

Figure 2.1. TB risk index across districts in India, 2015-16

The TB risk index is the 90th percentile of the risk scores for all surveyed adults within a district. An individual's risk score is estimated as the natural logarithm of the relative risk of incident TB for that individual compared to a hypothetical person with none of the included risk factors (problem in accessing quality care, poor utilization/quality of primary care, living in urban slums, HIV seropositive, low body mass index, diabetes mellitus, current smoking, passive smoking, daily alcohol use, and indoor air pollution). The higher the risk index in a district, the higher the underlying TB risk in that district.

Figure 2.2 shows the four measures of TB burden in states in India: risk index in 2015-16 (Figure 2.2 (a)), self-reported TB prevalence in 2015-16 (Figure 2.2 (b)), private and public sector drug sales in 2016 (Figure 2.2 (c)), private and public notification of incident TB cases in 2016 (Figure 2.2 (d)). Notification and drug sales were strongly positively correlated (spearman's r=0.69, p<0.001) while self-reported TB was negatively correlated with both notification and drug sales data (spearman's r for self-report with notification: -0.50, p=0.014, with drug sales: -0.17, p=0.4). The risk index was modestly associated with both self-reported TB (r=0.25, p=0.2) and drug sales (r=0.37, p=0.08), but not with notification.

The first two principal components explained 84% of the variance in the four burden measures (Figure 2.3). The first component placed most weight on notification (loading=0.68) and drug sales (0.63), and a small negative weight on self-report (-0.36); this principal component reflected the current TB notification and drug sales volume in a state (*official burden statistics*). The second principal component placed most weight on the risk index (0.75), followed by self-report (0.59), and drug sales (0.30): it was most likely a reflection of the underlying risk and burden for TB that was uncorrelated with current notifications (*underlying burden statistics*). Some areas had similar estimates of burden for both PCs. For example, Delhi, Gujarat, Madhya Pradesh, Uttarakhand, Rajasthan and Uttar Pradesh all ranked in the top ten while Kerala, Jammu & Kashmir, Tamil Nadu, and Andhra Pradesh ranked low by both measures. Others (Bihar, West Bengal, Odisha, and North East) ranked low on PC1 but high on PC2, or high in PC1 but low in PC2, (Himachal Pradesh, Maharashtra, Punjab, and Goa.)

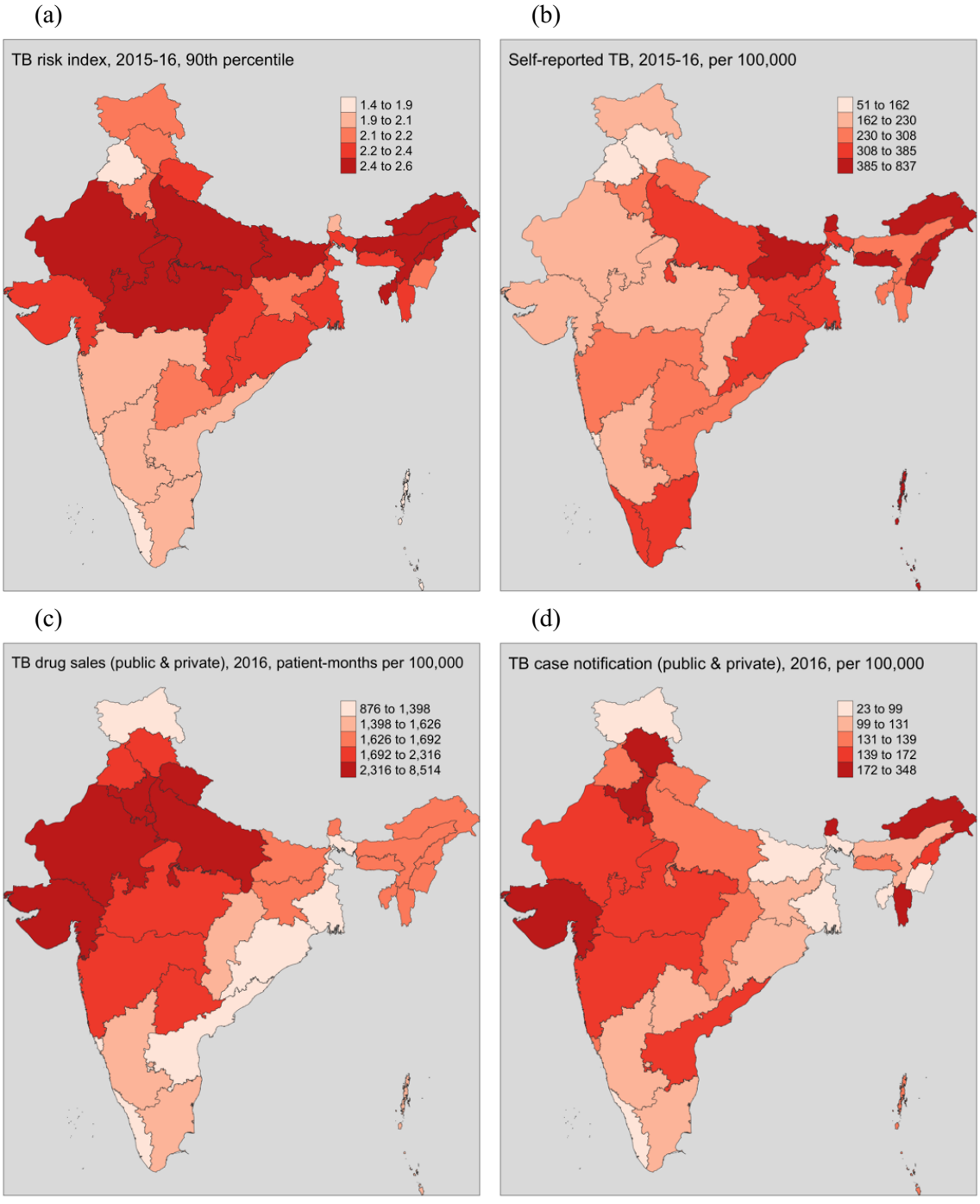

Figure 2.2. State-level TB burden estimates, India, 2015-16.

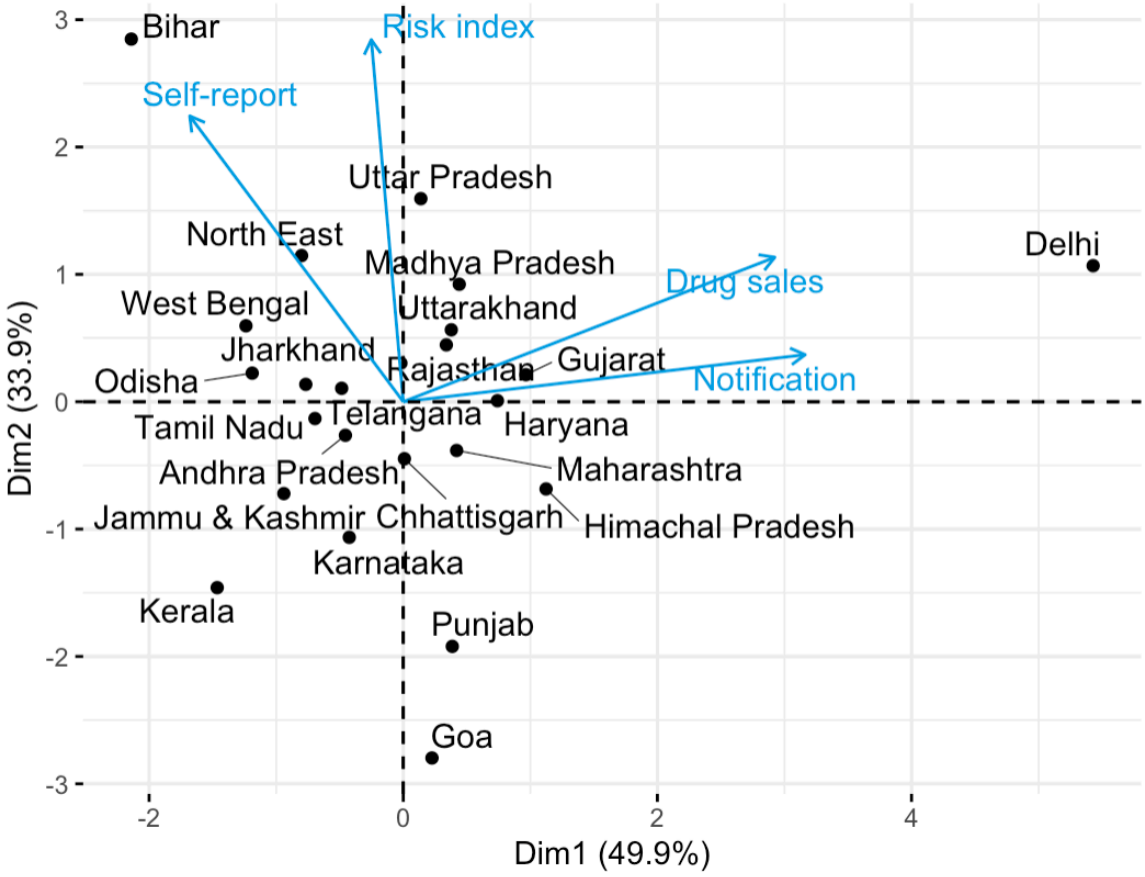

Figure 2.3. Two principal components of tuberculosis burden estimations in Indian States, 2015-16.

Smaller states and union territories are aggregated based on Arinaminpathy et al 2019.[4] Visualizing states on the two-dimensional plane defined by these two principal components (Dim1, *official burden statistics*, and Dim2, *underlying burden statistics*), we can identify states in the first quadrant (top right, e.g. Delhi) as having high notified incidence, drug sales volume and high TB risk, but comparatively low number of self-reported cases, while states in the second quadrant (top left, e.g. Bihar) have a similarly high underlying TB risk, but a high number of self-reported TB cases with a low notified incidence and drug sales volume. States in the third quadrant (bottom left, e.g. Kerala) had overall relatively low TB burden based on all measures (except with high number of self-reported cases), while states in the fourth quadrant (bottom right, e.g. Himachal Pradesh) had relatively lower TB risks and lower number of self-reported cases, but had high notified incidence and drug sales volume.

Discussion

In this paper, we developed a measure that designed to capture the underlying risk for TB in a community and compared it with three existing measures of sub-national TB disease burdens in India (Table 2.1). We observed no obvious agreement on the rankings of the highest burden states among these approaches, suggesting that the true subnational burdens across Indian states are still unknown. However, by focusing on the first two principal components of these measures, we were able to identify states that were consistently ranked as among the highest and lowest burden areas.

For areas that ranked high in *underlying burden* (PC2) but low in *official burden statistics* (PC1), such as Bihar, West Bengal, Odisha, and North East, local TB control programs would need to assess the scale of under-reporting in the notification system and to re-evaluate the resources needed for TB control based on true TB burden in the community.

Even after TB became notifiable for both public and private sectors in India, under-reporting from the private sector could still explain most of the current inaccuracies in the notification system. For example, between 2015 and 2017, a large private hospital in Karnataka state notified only 23% TB patients; patients with smear-negative disease and children were least likely to be notified.[11] Under-reporting could also be an issue with data from self-reports: adults with higher education levels were more likely to keep TB diagnosis of family members a secret.[5] More broadly, TB patients need to be diagnosed first before they can be recorded in the TB notification system, self-report as having TB, or purchase TB drugs. Without accounting for the magnitude of under-diagnosis for each state, these measures may not reflect the true TB burden difference across Indian states.[14] Prevalence surveys are often treated as the gold standard for estimating true TB burden because they can capture patients who do not otherwise have access to

adequate TB diagnosis and treatment. However, the planned TB national prevalence survey in 2019-20 in India, although will shed light on the absolute scale of under-reporting and under-diagnosis, is not powered for comparing the relative disease burden across states.

Although investigators have recently developed methods to overcome the issue of under-reporting and under-diagnosis for sub-national burden comparisons,[2,15] to our knowledge, the TB risk index is the first method that does not require prevalence survey data. One type of method uses small area estimation models with data points from surveyed clusters in national prevalence surveys,[2] so it relies on data from a recent national survey and a validity of prediction outside of observed clusters. Another type of method requires the existence of regional-level prevalence surveys to inform the weighting of demographic variables that can be used for district-level prediction.[15] By using data exclusively from existing population-based surveys that are updated every 5-10 years (the NFHS), the state- and district-level TB risk index could be a cost effective way to estimate the underlying TB burden within sub-national regions in India.

However, we acknowledge that the TB risk index is not meant to replace other sub-national estimates of TB prevalence or incidence. By constructing the risk index as the 90th percentile of TB risk scores of all adults within a region, we focus on comparing the risk of the region's highest-risk individuals, who we believe are most likely to drive the local TB endemics. The risk index is thus a reflection of underlying potential for TB transmission and disease, but not necessarily of actual number of TB cases. If a region's TB control program actively identifies and treats all patients and latent infections promptly, it is plausible that it may have a low TB burden, despite having a high underlying risk for TB. Therefore, we compared and summarized at all available estimates of TB burden and risk in India to triage the extent of under-diagnosis and under-reporting in each sub-national region.

We note several limitations to our study. First, ideally, the risk score would be more context appropriate if we had known the effect size of each risk factor on TB incidence for each Indian state. In the absence of this data, we used global estimates of effect sizes from meta-analysis as a best approximate to local effect sizes, assuming there is no multiplicative interaction between TB risk factors on TB transmission and progression rates. Secondly, for those variables for which we did not have previous estimates of the relative risk of TB, we estimated effect sizes based on self-reported TB in the NFHS, which is likely to be misclassified. However, no other data sources are available to quantify the effect of urbanicity and access/utilization of health care on TB risk. (what happens if we leave these out?) Thirdly, for those with incomplete information, the R^2 value for our prediction model was relatively low because risk score places substantial weight on HIV and BMI, which were not measured for all individuals and thus hard to predict with high accuracy. Different prediction methods yield similar results (results not shown). Fourthly, TB notification data was changing rapidly during the study period due to efforts in improving private care notification. This analysis can be updated after new NFHS-5 is completed in 2021. Lastly, we had not taken uncertainties into account in the correlation analyses. Spearman correlations are less sensitive to absolute values, so by using ranking of states, our conclusion is minimally affected. Furthermore, the errors should be independent so the net effect would be underestimating the variabilities in correlation coefficient.

In summary, we developed a measure that reflects the underlying TB risk across districts and states in India. It may prove a useful tool to supplement existing subnational burden estimation.

Reference

1. Dowdy DW, Grant AD, Dheda K, Nardell E, Fielding K, Moore DAJ. Designing and Evaluating Interventions to Halt the Transmission of Tuberculosis. J Infect Dis 2017;216(suppl_6):S654–S661.

2. Glaziou P, Floyd K. Latest developments in WHO estimates of TB disease burden: WHO Global Task Force on TB Impact Measurement meeting. 2018 [cited 2020 Jan 27]; https://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/tf7_background_4a_burden_estimates.pdf

3. Arinaminpathy N, Batra D, Khaparde S, et al. The number of privately treated tuberculosis cases in India: an estimation from drug sales data. Lancet Infect Dis 2016;16(11):1255–60.

4. Arinaminpathy N, Batra D, Maheshwari N, et al. Tuberculosis treatment in the private healthcare sector in India: an analysis of recent trends and volumes using drug sales data. BMC Infect Dis 2019;19(1).

5. Mazumdar S, Satyanarayana S, Pai M. Self-reported tuberculosis in India: evidence from NFHS-4. BMJ Glob Health 2019;4(3):e001371.

6. World Health Organization. Global tuberculosis report 2019. 2019.

7. Chadha VK, Anjinappa SM, Dave P, et al. Sub-national TB prevalence surveys in India, 2006-2012: Results of uniformly conducted data analysis. PLOS ONE 2019;14(2):e0212264.

8. National Health Portal Of India. Revised National Tuberculosis Control Programme [Internet]. 2018 [cited 2020 Jan 18]; https://www.nhp.gov.in/revised-national-tuberculosis-control-programme_pg

9. Nikshay [Internet]. [cited 2020 Jan 17]; https://nikshay.in/Home/AboutUs

10. Uplekar M, Atre S, Wells WA, et al. Mandatory tuberculosis case notification in high tuberculosis-incidence countries: policy and practice. Eur Respir J 2016;48(6):1571–81.

11. Siddaiah A, Ahmed MN, Kumar AMV, et al. Tuberculosis notification in a private tertiary care teaching hospital in South India: a mixed-methods study. BMJ Open 2019;9(2).

12. International Institute for Population Sciences (IIPS), ICF. National Family Health Survey (NFHS-4), 2015-16: India. Mumbai: IIPS; 2017.

13. Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare. TB India 2017: Revised National Tuberculosis Control Programme Annual Status Report [Internet]. 2017 [cited 2019 Mar 27]. https://www.tbfacts.org/wp-content/uploads/2017/12/TB-India-2017.pdf

14. Subbaraman R, Nathavitharana RR, Satyanarayana S, et al. The Tuberculosis Cascade of Care in India's Public Sector: A Systematic Review and Meta-analysis. PLOS Med 2016;13(10):e1002149.

15. Parwati C, Farid M, Suryani H, Basri C, Gebhard A, Houben R. Generation and interpretation of subnational Tuberculosis burden estimates in a high burden setting - a model for Indonesia [Internet]. [cited 2020 Feb 11]; https://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/tf7_p31_Indonesia_subnational_estimates.pdf

16. Dodd PJ, Knight GM, Lawn SD, Corbett EL, White RG. Predicting the long-term impact of antiretroviral therapy scale-up on population incidence of tuberculosis. PloS one 2013;8(9).

17. The World Bank Group. Antiretroviral therapy coverage (% of people living with HIV) [Internet]. World Bank Open Data. [cited 2019 Sep 5]; https://data.worldbank.org/indicator/SH.HIV.ARTC.ZS

18. Lönnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol 2010;39(1):149–155.

19. Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ. Association between diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. PLoS One 2017;12(11):e0187967.

20. Lin H-H, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLoS Med 2007;4(1):e20.

21. Imtiaz S, Shield KD, Roerecke M, Samokhvalov AV, Lönnroth K, Rehm J. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. European Respiratory Journal 2017;50(1).

22. Lin H-H, Suk C-W, Lo H-L, Huang R-Y, Enarson DA, Chiang C-Y. Indoor air pollution from solid fuel and tuberculosis: a systematic review and meta-analysis. Int J Tuberc Lung Dis 2014;18(5):613–621.

Chapter 3: Estimated Demand for US Hospital Inpatient and Intensive Care Unit Beds for Patients With COVID-19 Based on Comparisons With Wuhan and Guangzhou, China

Ruoran Li M.Phil.[1], Caitlin Rivers Ph.D.[2], Qi Tan M.D. Ph.D.[3,4], Megan B Murray D.PH. M.D.[3], Eric Toner M.D.[2], Marc Lipsitch D.Phil.[1]

1. Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

2. Johns Hopkins Center for Health Security and the Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

3. Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, USA

4. Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing Medical University, Nanjing, China

Abstract

Importance

Sustained spread of severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) has happened in major US cities. Capacity needs in cities in China could inform the planning of local health care resources.

Objectives

To describe and compare the intensive care unit (ICU) and inpatient bed needs for patients with coronavirus disease 2019 (COVID-19) in 2 cities in China to estimate the peak ICU bed needs in US cities if an outbreak equivalent to that in Wuhan occurs.

Design, setting, and participants

This comparative effectiveness study analyzed the confirmed cases of COVID-19 in Wuhan and Guangzhou, China, from January 10 to February 29, 2020.

Exposure

Timing of disease control measures relative to timing of SARS-CoV-2 community spread.

Main outcomes and measures

Number of critical and severe patient–days and peak number of patients with critical and severe illness during the study period.

Results

In Wuhan, strict disease control measures were implemented 6 weeks after sustained local transmission of SARS-CoV-2. Between January 10 and February 29, 2020, patients with COVID-19 accounted for a median (interquartile range) of 429 (25-1143) patients in the ICU and 1521 (111-7202) inpatients with serious illness each day. During the epidemic peak, 19 425

patients (24.5 per 10 000 adults) were hospitalized, 9689 (12.2 per 10 000 adults) were considered in serious condition, and 2087 patients (2.6 per 10 000 adults) needed critical care per day. In Guangzhou, strict disease control measures were implemented within 1 week of case importation. Between January 24 and February 29, COVID-19 accounted for a median (interquartile range) of 9 (7-12) patients in the ICU and 17 (15-26) inpatients with serious illness each day. During the epidemic peak, 15 patients were in critical condition and 38 were classified as having serious illness. The projected number of prevalent critically ill patients at the peak of a Wuhan-like outbreak in US cities was estimated to range from 2.2 to 4.4 per 10 000 adults, depending on differences in age distribution and comorbidity (ie, hypertension) prevalence.

Conclusions and relevance

Even after the lock down of Wuhan on January 23, the number of patients with serious COVID-19 illness continued to rise, exceeding local hospitalization and ICU capacities for at least a month. Plans are urgently needed to mitigate the consequences of COVID-19 outbreaks on the local health care systems in US cities.

Introduction

In the 2 months after the first report of 4 cases of atypical pneumonia in Wuhan, China, on December 27, 2019,[1] the cumulative number of confirmed cases of coronavirus disease 2019 (COVID-19) in the city rose to 49 122, with 2195 deaths by the end of February 2020.[2] On January 23, Wuhan city shut down in response to the quickly evolving epidemic. All public transportation within, to, and from the city was suspended, and residents were barred from leaving. An estimated 9 million people remained in the city after the lock down.[3] Strict social distancing measures were also implemented, including the compulsory wearing of face masks in public.

During the early phase of the response in Wuhan, the number of patients overwhelmed local fever clinics and hospitals designated to receive patients with COVID-19. The media reported a significant shortage of hospital beds, intensive care unit (ICU) beds, and other healthcare resources. By February 12, more than 18 000 health care workers had been sent to Wuhan from other parts of China to help with the coronavirus response.[4] A total of 48 hospitals (including 2 new hospitals built specifically for patients with COVID-19) and more than 26,000 inpatient beds were designated for the isolation and treatment of patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Quarantine centers with more than 13 000 total beds were also established to isolate confirmed patients with milder illness. By the end of February, the local government reported that “finally patients don’t need to wait for beds. Now the beds are waiting for patients.”[5]

With human-to-human transmission now established in other countries, mitigating the potential consequences of COVID-19 on local healthcare systems is a top priority. A clinical study from China[1] reported that 81% of patients in whom SARS-CoV-2 is detected experience

mild disease, 14% experience severe disease, and 5% experience critical disease. However, questions still remain regarding the proportion of asymptomatic patients and the clinical course of the disease, preventing accurate prediction of hospitalization and ICU needs with transmission models.

Here, we describe the ICU and hospitalization needs for COVID-19 in 2 cities in China, Wuhan, the epicenter of China's outbreak, and Guangzhou, a metropolis that experienced an early importation of cases. As in all cities in China, Guangzhou implemented strict social distancing measures and contact tracing and quarantine protocols were implemented in late January, which resulted in a much smaller outbreak size than in Wuhan. Describing and comparing the resource needs in both cities may create benchmarks to help other large metropolises prepare for potential outbreaks.

Methods

We extracted and estimated confirmed COVID-19 case counts for severe and critical cases from Wuhan and Guangzhou from situation updates from Chinese national and local health commissions. We extracted the number of designated COVID-19 beds and hospitalizations from the Wuhan Municipal Health Commission website.

A confirmed COVID-19 case was considered severe if the patient experienced at least 1 of the following: dyspnea, respiratory frequency ≥30/minute, blood oxygen saturation ≤93%, arterial blood oxygen partial pressure (PaO_2) to oxygen concentration (FiO_2) ratio <300mmHg, and/or a patient with pneumonia showing significant progression of lesions infiltrating >50% of the lung field on chest imaging within 24 to 48 hours. A confirmed patient was considered critical if they experienced respiratory failure demanding invasive and/or noninvasive ventilation

for respiratory support, septic shock, and/or had multiple organ dysfunction or failure demanding intensive care.[6,7] These definitions have been more detailed with revisions of the Chinese diagnostic and treatment guidelines. In this study, we used the term *patient with serious illness* to describe patients with severe and critical illness collectively. We estimated the number of prevalent severe and critical cases cross-sectionally per day, allowing for the fact that patients could move in and out of these categories during the course of their disease.

We extracted Wuhan city and Hubei province COVID-19 data between January 10 and February 29, including the numbers of confirmed cases, new cures, new deaths, severe cases, critical cases, serious cases (a sum of severe and critical cases), cumulative cures, cumulative deaths, cumulative confirmed cases, and currently confirmed cases (cumulative confirmed cases - deaths - cures). If official sources did not have data for variables on some dates, we calculated the number of cases based on the relationships between variables. Because Wuhan did not systematically report the number of severe and critical cases, we estimated these numbers by assuming that the proportions of serious and critical cases out of all currently confirmed cases was the same in Wuhan as in the rest of Hubei. For dates when it was not possible to estimate the severe and critical case counts using these methods (January 18, 25, and 27), we assumed the number of severe and critical cases were the same as what was reported the previous day.
For Guangzhou, we extracted the city's case count on the number of confirmed, severe, clinical, and cured cases and deaths for each day between January 24 and February 29.

All data were extracted from publicly available sources with deidentified information. IRB review and informed consent were not required for this study due to non-human subject research determination. We adhered to the ISPOR guidelines for comparative effectiveness research[8] in the design and reporting of this study.

Statistical analysis

We summed the total patient-days under critical and/or severe condition to estimate the total ICU-days and serious-inpatient-days. We plotted the raw number of patients in critical and severe condition and patients hospitalized on each day for Wuhan and Guangzhou and estimated the proportion of hospitalizations and ICU admissions per 10,000 adults based on the assumption that there were 9 million people present in Wuhan during the lockdown,[3] of whom 88.16% were aged 15 years or older,[9] and 14.9 million people present in Guangzhou of whom 82.82% were aged 15 years or over.[10]

We then projected the number of patients who would have severe and critical COVID-19 at the peak of a Wuhan-like outbreak in the 30 most populous US cities by assuming that the association of age and comorbidity with patient outcomes would be the same as their associations with COVID-19 mortality, as derived from case reports from China until February 11.[11] Specifically, we estimated the stratum-specific critical care rate in Wuhan by assuming that the risk factor for being in critical care was the same as that for death (age and comorbidities, such as hypertension).[11] We estimated the probability of being in critical condition at the peak of the epidemic in each age and hypertension stratum using the COVID-19 mortality rate ratios for age and hypertension[11] and the proportion of the Wuhan population in each stratum. The hypertension prevalence in adults in Wuhan was estimated as 25.7%,[12] and the proportion of the population aged 65 years or older was estimated as 14.1%.[13] We applied these stratum-specific critical care rates to population structures in US cities based on crude hypertension prevalence in adults in 2017[14] and the proportion of the adult population aged 65 years and older in these cities.[15] We used *Wuhan-like outbreak* to describe an outbreak in a large metropolis where

minimal disease control measures were implemented during the first 2 months of community spread of SARS-CoV-2, followed by city-level lock-down measures to suppress transmission.

Results

In Wuhan, COVID-19 accounted for a total of 32 486 ICU-days and 176 136 serious-inpatient-days between January 10 and February 29 (Figure 3.1 (a) and Figure 3.1 (b)), an average of 637 ICU patients and 3454 serious inpatients on each day during that 51-day period. During the peak of the epidemic from mid to late February, a maximum of 19 425 patients (24.5 per 10,000 adults) were hospitalized, 9689 patients (12.2 per 10,000 adults) were considered in serious condition, and 2,087 patients (2.6 per 10,000 adults) needed critical care per day.

In Guangzhou, COVID-19 accounted for a total of 318 ICU-days and 724 inpatient-days between January 24 and February 29 (Figure 3.1 (c) and Figure 3.1 (d)), an average of 9 ICU patients and 20 inpatients during that 37-day period. During the peak of the epidemic (early February), 15 patients were in critical condition, while 38 were hospitalized and classified as serious. Unlike Wuhan, where patients with mild COVID-19 disease were isolated in quarantine centers and not in designated hospitals, all confirmed patients in Guangzhou were hospitalized until cure. The maximum number of hospitalizations in Guangzhou on any day was 271 patients.

At the peak of the epidemic, the critical care risk among adults younger than 65 years was 1.2 patients per 10,000 adults, among adults aged 65 years or older, it was 8.0 patients per 10,000 adults, among adults without hypertension, it was 1.3 patients per 10,000 adults, and among adults with hypertension, it was 9.5 patients per 10,000 persons.

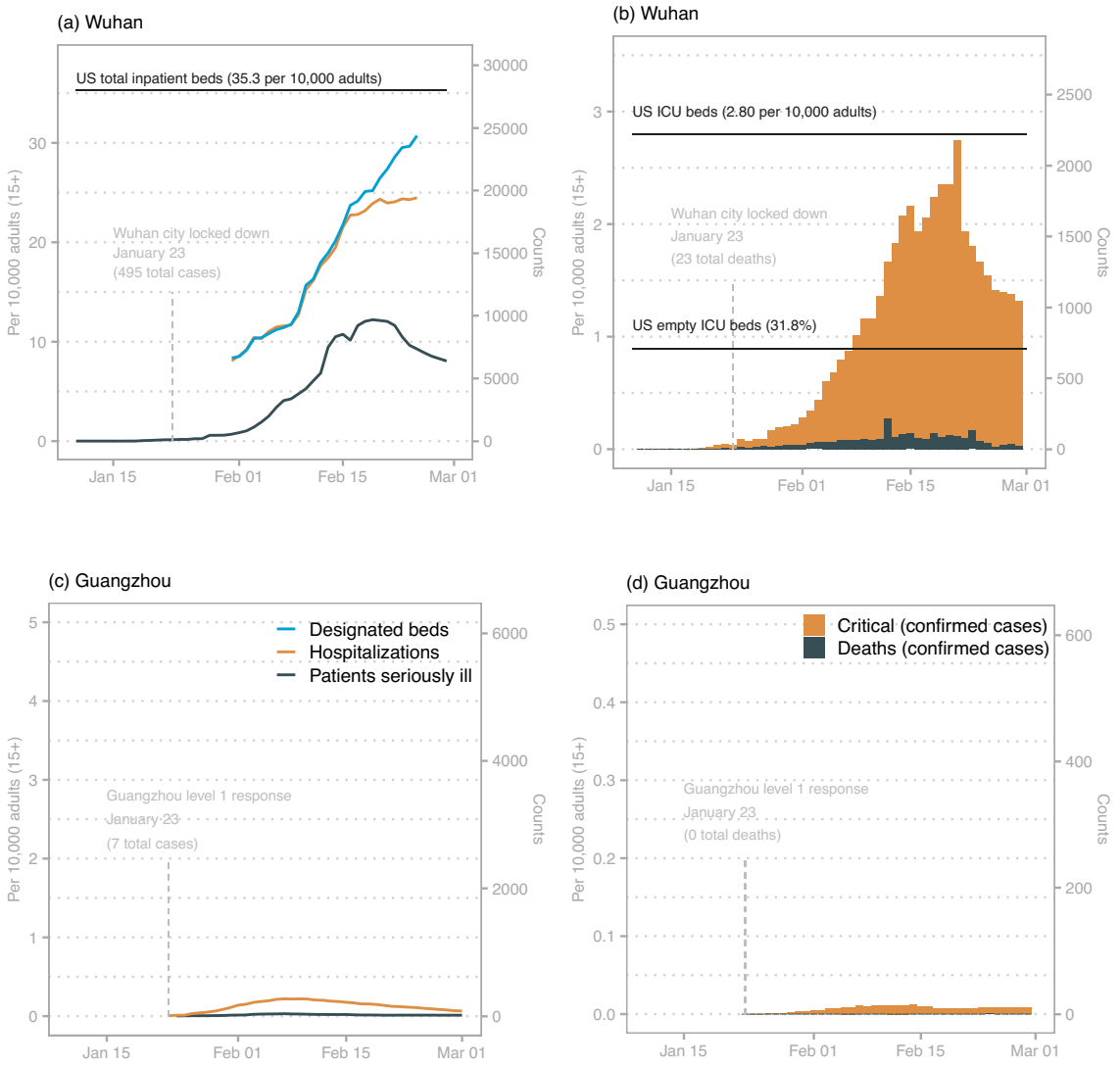

Figure 3.1. Burden of serious COVID-19 disease in Wuhan and Guangzhou, China

(a) Daily counts of hospitalizations, designated beds, and seriously ill patients in Wuhan, superimposed by US inpatient beds capacity; (b) Daily counts of deaths and critically ill patients in Wuhan, superimposed by US ICU beds capacity; (c) Daily counts of hospitalizations and seriously ill patients in Guangzhou, where all confirmed patients were hospitalized; (d) Daily counts of deaths and critically ill patients in Guangzhou. Wuhan city locked down on January 23 with a cumulative 495 confirmed cases and 23 deaths from COVID-19 patients. Guangzhou initiated level 1 public health response on the same date (January 23), with a cumulative 7 confirmed cases and 0 deaths. US data sources: US ICU beds;[16] US empty ICU beds;[17] US inpatient beds;[18] US population structure[19] was used to estimate the inpatient beds capacity per 10,000 adults.

Among the 30 most populous cities in the US, 11.0% to 22.5% adults are aged 65 years or older[15], and the crude hypertension prevalence ranged from 22.0% to 46.9%.[14] The projected number of prevalent critically ill patients at the peak of a Wuhan-like outbreak in US cities ranged from 2.2 to 3.2 patients per 10,000 adults, when the difference in age distribution was taken into account (Figure 3.2 (a)), and from 2.8 to 4.4 patients per 10,000 adults when the differences in hypertension prevalence was taken into account (Figure 3.2 (b)).

Discussion

Even after the lockdown of Wuhan on January 23, the number of patients with serious COVID-19 illness continued to rise, exceeding local hospitalization and ICU capacities for at least a month. During the peak of the Wuhan epidemic in February, nearly 20 000 patients with COVID-19 were hospitalized simultaneously, with 10 000 in severe or critical condition. If a Wuhan-like outbreak were to take place in a US city, even with strong social distancing and contact tracing protocols as strict as the Wuhan lockdown, hospitalization and ICU needs from COVID-19 patients alone may exceed current capacity. The need for healthcare resources may be higher in some US cities where there is a higher prevalence of vulnerable populations (i.e. older age and comorbidity) than in Wuhan.

Exceeding healthcare capacity may increase the community spread of SARS-CoV-2. In Wuhan, home isolation and quarantine were used in the early phase of the epidemic to alleviate the demand for healthcare resources. However, because of the exponential increase in the number of patients who developed serious illness but could not be hospitalized owing to capped capacity, secondary transmission in the community continued as patients and their household contacts moved between hospitals seeking care.

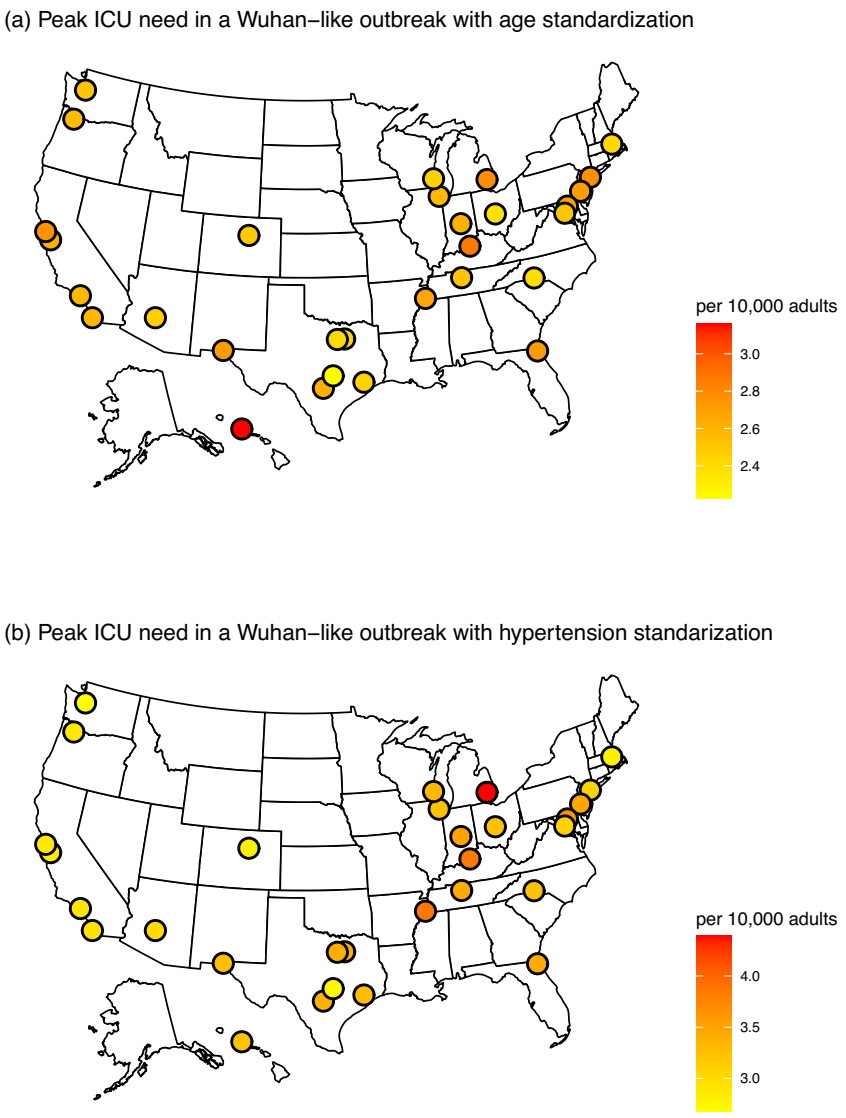

Figure 3.2. Estimate number of critically ill patients at the peak of a Wuhan-like outbreak in cities in the US, per 10,000 adults

(a): accounting for the proportion of population over 65 years of age. (b): accounting for the proportion of population with hypertension. Wuhan: 2.6 per 10,000 adults were critically ill at the peak of the COVID-19 epidemic, with a crude hypertension prevalence of 25.7% among adults (rate ratio for critical illness=6.9), and 15.9% adults over 64 years of age (rate ratio for critical illness=7.2).

Exceeding healthcare capacity may also lead to decreased quality of care, such as not being able to access a ventilator, which would lead to an increased case fatality ratio. By the end of February, Wuhan's case-fatality ratio was 4.5%, it was 3.2% for the rest of Hubei province, and 0.8% for the rest of China, where healthcare capacity was not exceeded because of strong social distancing and contact quarantine measures in the early phase of the epidemic (such as Guangzhou).[20] A contributing factor to the lower case-fatality ratio in the rest of China may be higher case ascertainment than Wuhan during the early phase of the epidemic.

In both Wuhan and Guangzhou, the lockdowns did not lead to immediate downturns in demand for hospitalization or the number of serious cases; rather, the peak in these measures occurred approximately a month after the lockdown in Wuhan and 2 weeks after the lockdown in Guangzhou. This delay reflects the potentially long time from infection to severe and critical conditions as many patients with COVID-19 who eventually require ICU care present initially with only mild symptoms,[21] and an even longer time to discharge or death,[22] resulting in the accumulation of hospitalized cases long after downturns in community spread. In Wuhan, the longer delay may also reflect ongoing transmission after the lockdown, as described earlier, which itself resulted from overloading the healthcare system.

This study has several limitations. We relied on officially reported statistics, which may not represent the change of actual case counts over time but rather reflect the capacity of testing and hospitalization. Thus, the number of serious cases and hospitalizations in Wuhan is not reflective of actual need but rather of the maximum capacity of the system of diagnosis and treatment. Therefore, we are more confident regarding the hospitalization and serious case counts in Wuhan after mid-February and in Guangzhou, where capacities in diagnosis and treatment were not exceeded according to both official and unofficial sources. Furthermore, we have only

accounted for the differences in age and hypertension distribution between Wuhan and US cities, but we did not accounted for other potential risk factors, such as diabetes, cardiovascular diseases, and chronic respiratory diseases.[11] Because no mutually adjusted associations of these risk factors with COVID-19 serious illness or death were available at the time of our analysis and because cardiometabolic risk factors likely coexist in the same population, we used hypertension adjustment as a proxy for adjusting other known comorbidities.

In addition, our projection of the ICU bed needs in US cities does not consider scenarios in which local transmission differs from that of Wuhan. The contact rate in Wuhan during the early phase of the epidemic may have been much higher than what we expect to occur in US cities because of the increased number of social contacts that occurred in Wuhan because of the Lunar New Year celebrations. If social distancing measures are effectively implemented early in US cities, the growth of the epidemic may be delayed. But it is also possible that US cities may not be able to implement the extreme social distancing measures that were put in place later in Wuhan. We further assumed that both settings had an equal (age- or hypertension-specific) incidence rate of severe and critical COVID-19 cases, but we did not account for differences in contact patterns in vulnerable populations, such as in nursing homes. Therefore, the actual number of hospital and ICU beds that will be needed during the course of a COVID-19 outbreak in a US city is impossible to estimate precisely. Our estimated capacity needs based on a Wuhan-like outbreak could be a benchmark for what healthcare systems would expect to see during the first 3 months of a local COVID-19 epidemic if the same outbreak control measures were implemented as in Wuhan.

Historical evidence has shown that in 1918, the US cities that imposed nonpharmaceutical interventions early in the influenza epidemic course and maintained these

interventions during a long period had lower peaks and fewer total cases than those that waited.[23,24] Although it included only 2 cities, our comparison of Wuhan with Guangzhou dramatically illustrates the same association of early intervention with lower epidemic sizes and peaks. Of course, the future course of these epidemics and others around the world depends on the ability to maintain burdensome control measures over an extended period.

In several locations with high-performing healthcare systems where SARS-CoV-2 transmission has been established earlier (such as Hong Kong, Singapore, and Japan), both supplies of personal protective equipment in hospitals and the availability of services has been problematic for COVID-19 care, and in all locations, ICU bed capacity is limited.[25] Combined with other evidence about the consequences of early and intense interventions to control viral spread,[23,24,26] the comparison with the Guangzhou situation dramatically illustrates that early intervention leads to lower epidemic sizes and peaks and that plans are urgently needed to mitigate the consequences of COVID-19 outbreaks on the healthcare systems of US cities.

Reference

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;(February). doi:10.1001/jama.2020.2648

2. Wuhan Municipal Health Commission. Wuhan COVID-19 situation report February 29, 2020. Accessed March 7, 2020. http://wjw.wuhan.gov.cn/front/web/showDetail/2020030109892

3. China News Network. Wuhan Mayor: new coronavirus pneumonia cases may increase another 1000. Published January 27, 2020. Accessed April 14, 2020. https://m.chinanews.com/wap/detail/zwsp/gn/2020/01-27/ 9070530.shtml

4. Hubei Daily. Twelve new medical teams with 1485 healthcare workers sent to help Hubei. Published February 13, 2020. Accessed April 14, 2020. http://hbrbshare.hubeidaily.net/hbshare/news/detail_index.html?contentType=5&contentId=649546&cId=0

5. Changjiang Daily. Three steps for Wuhan to achieve "beds waiting for patients." Published March 3, 2020. Accessed March 7, 2020. http://www.wh.gov.cn/2019_web/whyw/202003/t20200303_305956.html

6. WHO-China Joint Mission. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Accessed April 14, 2020. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on- covid-19-final-report.pdf

7. National Health Commission of the PRC. COVID-19 treatment and diagnosis guideline (7th version, trial). Accessed March 9, 2020. http://www.gov.cn/zhengce/zhengceku/2020-03/04/content_5486705.htm

8. Berger ML, Mamdani M, Atkins D, Johnson ML. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part I. *Value Health*. 2009;12(8):1044-1052. doi:10.1111/j.1524-4733.2009.00600.x

9. China Statistics Press. Tabulation on the 2010 population census of the People's Republic of China: table1-7a. Accessed April 15, 2020. http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm

10. Guangzhou Municipal Bureau of Statistics. Guangzhou population size and distribution in 2018. Accessed April 15, 2020. http://tjj.gz.gov.cn/tjgb/qtgb/content/post_2788687.html

11. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020; 41(2):145-151. doi:10.3760/cma.j.issn.0254-6450.2020.02.003

12. Dai J, Gong J, Yang N, Zhao Y, Yan Y. The epidemiologic characteristics of hypertension and diabetes and knowledge of risk factors for chronic diseases among residents in Wuhan municipality. *Zhongguo Manxingbing Yufang Yu Kongzhi*. 2019;27(9):663-671. Accessed April 15, 2020. http://kns.cnki.net/kcms/detail/Detail.aspx?dbname=CJFDTEMP&filename=ZMXB201909006&v=

13. Wuhan Municipal Health Commission. 2018 Analysis on the trend of aging population in Wuhan. Accessed April 14, 2020. http://wjw.wuhan.gov.cn/upload/file/20190301/1551431274814033488.pdf

14. Centers for Disease Control and Prevention. 500 Cities project: local data for better health. Updated December 5, 2019. Accessed March 8, 2020.https://www.cdc.gov/500cities/index.htm

15. US Census Bureau Quick Facts. Quick Facts: United States. Accessed March 8, 2020. https://www.census.gov/ quickfacts/fact/table/US/PST045219

16. Carr BG, Addyson DK, Kahn JM. Variation in critical care beds per capita in the United States: implications for pandemic and disaster planning. *JAMA*. 2010;303(14):1371-1372. doi:10.1001/jama.2010.394

17. Wunsch H, Wagner J, Herlim M, Chong DH, Kramer AA, Halpern SD. ICU occupancy and mechanical ventilator use in the United States. *Crit Care Med*. 2013;41(12):2712-2719. doi:10.1097/CCM.0b013e318298a139

18. American Hospital Association. Fast facts on U.S. hospitals. Accessed March 8, 2020. https://www.aha.org/ statistics/fast-facts-us-hospitals

19. US Census Bureau. Age and sex composition in the United States: 2018. Accessed March 8, 2020. https://www. census.gov/data/tables/2018/demo/age-and-sex/2018-age-sex-composition.html

20. China COVID-19 situation report by February 29. National Health Commission of the People's Republic of China. Accessed March 7, 2020. http://www.nhc.gov.cn/xcs/yqtb/202003/9d462194284840ad96ce75eb8e4c8039.shtml

21. Bouadma L, Lescure FX, Lucet JC, Yazdanpanah Y, Timsit JF. Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists. *Intensive Care Med*. 2020;46(4):579-582. doi:10.1007/ s00134-020-05967-x

22. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. The novel coronavirus, 2019-nCoV, is highly contagious and more infectious than initially estimated. medRxiv. 2020. doi:10.1101/2020.02.07.20021154

23. Hatchett RJ, Mecher CE, Lipsitch M. Public health interventions and epidemic intensity during the 1918 influenza pandemic. *Proc Natl Acad Sci U S A*. 2007;104(18):7582-7587. doi:10.1073/pnas.0610941104

24. Markel H, Lipman HB, Navarro JA, et al. Nonpharmaceutical interventions implemented by US cities during the 1918-1919 influenza pandemic. *JAMA*. 2007;298(6):644-654. doi:10.1001/jama.298.6.644

25. Legido-Quigley H, Asgari N, Teo YY, et al. Are high-performing health systems resilient against the COVID-19

epidemic? *Lancet*. 2020;395(10227):848-850. doi:10.1016/S0140-6736(20)30551-1

26. Kraemer MUG, Yang CH, Gutierrez B, et al; Open COVID-19 Data Working Group. The effect of human mobility and control measures on the COVID-19 epidemic in China. *Science*. 2020;eabb4218. doi:10.1126/science.abb4218