Effectiveness of contact investigations for tuberculosis control in Arkansas

Technical Appendix

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E1. Model details

The model proposed in this study is based on a modification of a previously published one [E1]. For aspects that have been newly introduced in this study, we provide full details here. Where the model is unchanged with respect to the original version, we report modeling choices, and we redirect the reader to the reference study [E1] for details on their rationale.

E1.1 Socio-demographic structure and its evolution

The model reproduces the socio-demographic structure of Arkansas and its changes over time using individual based modeling [E2, E3]. A full validation of the socio-demographic model is reported in the reference study [E1].

Model population was initialized according to census data for Arkansas in year 2000 (2,673,400 individuals) and spatially distributed according to the estimated population density [E4] over 219 square cells covering the state territory. The spatial distribution of households, schools and workplaces was assumed proportional to the population density.

The composition of households is allocated in such a way to match marginal distributions of household size and population age structure from census data, and to maintain realistic age differences between generations (parents and children) within them. School sizes by type, school attendance rates by school type, as well as the distribution of workplace establishments by size and the age-specific probability of being employed were used to populate schools and workplaces, based on publicly available data [E1]. The assignment of students to schools / workers to workplaces was done in such a way that the probability density function of commuting distances complies with a power law (as proposed in [E2]) with parameters of the power law estimated for the US and Europe in [E3, E5].

The demography and the network of contacts among individuals are updated at the end of each year: individuals come to life, grow older, generate new households, procreate and die; the

processes of school enrolment (following the educational career), new employment, job loss and retirement are also modeled. The evolution of the socio-demographic structure was validated against Arkansas data and projections of the age structure in 2005 and 2030, and against the total number of births, deaths, marriages and divorces in 2001-2005 [E1].

E1.2 TB natural history

The compartmental structure of the model is displayed in Figure 1 in the main text. Individuals are born Uninfected and move to the Recent infection compartment upon contact with an infectious individual (either I_p, I_n or I_x). Recent infection is asymptomatic and progresses to either of the following epidemiological outcomes: i) the host heals completely, clearing the pathogen via immune response, with a probability χ (individual moved back to the Uninfected class); ii) the host progresses to TB disease within a few years from infection episode [E6] (termed "primary TB"), with an age-dependent probability p(a); iii) the host develops LTBI with a residual probability $1-\chi-p(a)$. Progression from the Recent infection class to any of the considered outcomes occurs with a rate *k*; the Recent infection compartment has the function to delay the emergence of TB, given that *Mycobacterium tuberculosis* are slow replicating bacteria and TB symptoms require up to several years to develop. Individuals with LTBI are asymptomatic and non-infectious, and are subject to an age-dependent risk $\rho(a)$ of developing Active TB via endogenous reactivation [E6], even several years or decades after the infection episode. Individuals with LTBI can be re-infected by contact with a TB infectious case (i.e. an individual moves to the Reinfection compartment, having the same meaning and characteristics of Recent infection). Re-infected individuals exit their compartment with a rate k, just like first-time exposed, and either develop active TB ("exogenous reinfection") within a few years or revert to the latent class. The probability of developing exogenous reinfection is lower than that of first-time exposed through an age-dependent coefficient $\sigma(a)$, representing the probability of protection from TB-specific immune memory arising after first

exposure to TB [E1, E6, E7].

Individuals with Active TB can develop infectious (pulmonary) or non-infectious (extrapulmonary) TB with a probability π. Individuals with infectious TB are assigned a differential infectiousness based on the age-specific proportion h(a) of being sputum smear positive, i.e. to have acid fast bacilli detected in their sputum, estimated from Arkansas surveillance data on TB sputum samples from 1997-2004 E[1]. Smear positive individuals are considered four times more infectious than smear negative ones based on estimates from literature [E8, E9]. Irrespectively of the site of TB and smear status, individuals with TB are passively diagnosed and cured with a rate γ, or die because of TB with a mortality rate μ_{TB}. Cured individuals move to the L compartment, given that it is not known whether TB treatment can completely clear the pathogen [E10, E11].

E1.3 Epidemiological risks

The functional forms of the age-specific risk of primary TB p(a) and the age-specific protection from previous infection $\sigma(a)$ were assumed to be piece-wise linear functions, following [E6]. More specifically, they are assumed to be constant from age 0 to a_1=10 years, linearly increasing from a_1 to a_2=20 years, and constant again from a_2 to 100. The slope of the curve in the linearly increasing segment is chosen in such a way that the function is continuous. The age-specific probability of smear-positive TB h(a) has the same general form[E6], but a_1 is set to 5 years and a_2 to 25 years based on available data from a molecular epidemiology study in Arkansas [E12]. The functional form of the reactivation risk $\rho(a)$ increases linearly from 0 to a value r_{50} until the age of 50 and quadratically from age 51 to 100. This accelerated growth in the reactivation risk for the elderly was previously shown to be necessary to fit the age-specific profile of TB incidence in Arkansas [E1], and is consistent with assumptions taken by modelers for the reactivation risk of other chronic infections (e.g. for Varicella Zoster Virus [E13, E14]).

E1.4 Contact investigation

The contact investigation procedure is a novelty of the present model. The procedure is implemented in such a way to mimic the process defined by the guidelines of the United States Centers for Disease Control (CDC) [E15], that we briefly summarize hereafter. According to the CDC, a contact investigation should be initiated for infectious, smear positive cases with highest priority, and should be extended to smear negative or non-infectious cases only if resources are available. However, in Arkansas contact investigation of smear negative cases is performed with the same frequency and effort as smear positive (unpublished data). Upon initiation of an investigation, a list of contacts is solicited through interviews with the index case. When a contact of a new culture-positive case is identified, a protein-purified derivative skin test (PPD, also called tuberculin skin test or TST) or a serological test (Interferon-gamma Release Assay, IGRA) is done. If the test is positive, even though the person is well and asymptomatic, chest x-ray and clinical evaluations are made. If the test is negative, but time elapsed since the last exposure to the index case is less than 8 weeks, a new test is repeated 8-10 weeks later [E15]. If the new test is positive, the contact can be evaluated for active TB. If active TB is excluded, the contact is considered infected with LTBI and offered treatment.

We implemented the mentioned guidelines according to the diagram reproduced in Figure 2. Here we provide details on the workflow and on data sources for contact investigation parameters.

Case management procedure (Figure 2A in the main text). In the model, for each infectious index case (diagnosed either passively or through contact investigation), a contact investigation is initiated with a probability that, in general, depends on the index's smear status, estimated from the CDC Aggregate Reports on Program Evaluation (ARPE) [E16]. However, in the specific case of Arkansas, contact investigations are run with the same priority, independently of smear status: therefore, the same probability has been used. For non-infectious index cases, or if contact investigation has not been initiated, the case management routine is closed without further action. If

an investigation is initiated, all individuals in the same household of the index case are listed as contacts (however, if the current index case was diagnosed during a contact investigation in household, members of the household are not listed because they have already been screened during contact investigation of the source case). If the index case has changed household within the last year, members of the previous household are also listed as contacts. Members of the same workplace are all listed as contacts if the number of colleagues is 20 or less. For larger workplaces, contacts are sampled randomly from workplace members in number proportional to the workplace size, so that the minimum number of listed contacts is 20 and the maximum number never exceeds 200. This choice is based on the size distribution of a large contact investigation study in US workplaces [E17]. Individuals who have actually been infected by the index case have a high probability Z (set to 80% and subject to sensitivity analysis) of being named as contacts by the index case and thus are listed for enrollment in the program. This rule follows the assumption that infection is more likely for close contacts who share more time and space with the index case, and who are also more likely to be mentioned as contacts. If the index case has changed workplace within the last year, members of the previous workplace are also listed in the program following the same rules. If the index case was diagnosed during a contact investigation in the workplace, contacts in the same setting are not elicited. The procedure for school contacts is identical to that of workplace contacts. Finally, regarding contacts in the general population, only actually exposed contacts are enrolled in the program with probability Z.

Trace, test and treat procedure (Figure 2A in the main text). For various reasons, not all contacts listed can always be traced for TB screening; therefore, for a fraction of contacts in the list the procedure ends with no further action. If the contact is actually traced (the observed probability is taken from [E16]), the epidemiological status is tested and action is taken accordingly. If the contact is in the susceptible class (i.e., uninfected), the algorithm will end with no further action.

In a case of active disease, a traced individual has a high probability D_{Se} of being correctly

diagnosed and cured [E18]. In such a case, a traced individual is moved to the L class and a new case management procedure for elicitation of his contacts will be started. Although treatment for active TB is quite lengthy, symptoms (including cough, which is a main factor of infectiousness) generally disappear within the first few weeks after initiation of therapy. Therefore, we assume for simplicity that treatment is instantaneously effective.

If the contact was recently or remotely infected, his PPD test will come out positive depending on the test sensitivity, L_{Se}. In such a case, he can initiate and complete LTBI treatment with given probabilities. The contact is assumed to heal completely and moves to the susceptible compartment only if LTBI treatments are completed. Also in this case, cure is assumed to occur instantaneously, given that the few months of required LTBI therapy are a relatively short time span when compared to the decades long time scales of LTBI reactivation. In a case of a negative PPD test, a repetition of the test is performed in 8-10 weeks, during which time the individual's epidemiological status may have changed. If a second PPD test is negative, the procedure ends with no further action.

Parameters defining the performance of contact investigation strategies in Arkansas, reported in Table E1, were available from the Aggregate Reports on Tuberculosis Evaluation Programme [E16]. Parameters for the sensitivity of the PPD skin test and of clinical evaluation [E19] are reported in Table E2.

Year	Coverage (% of cases with elicited contacts)	% missed contacts	% LTBI treatments initiated	% LTBI treatments completed
2001	92.4*	34.8	48.1	53.2
2002	92.4*	18.0	45.9	69.7
2003	92.4†	15.5	69.6	55.8
2004	92.7†	31.9	80.8	64.8
2005	91.9†	15.1	87.9	57.0
2006	92.4†	18.4	53.4	57.1
2007	92.2†	10.2	82.4	58.8
2008	93.3‡	11.9	78.9	60.4
2009	94.4‡	15.6	76. 7	63.6
2010	95.6‡	6.7	83.2	69.2
2011	96.7	9.7	90.8	70.0
2015**	100	7.0	88.0	79.0

Table E1: parameters for the contact investigation program deployed in Arkansas (from [E16]).

* Assumed equal to data from 2003

† Data from [E18]

‡ Linearly interpolated between data from 2006 and from 2011

** CDC targets used in the 2015 targets scenario [E18]

Parameter	Symbol	Value	Reference
Senstitivity of TST test	L_{Se}	83%	[E19]
Sensitivity of TB diagnosis	D_{Se}	95%	[E19]
Fraction of exposed individuals who are listed as contacts	Z	80%	Assumption

Table E2: time-invariant parameters for contact investigation.

E1.5 Initialization

A common assumption in mathematical models is that the disease is at epidemiological equilibrium at the beginning of simulations. For TB in low-burden countries, the steady-state assumption is clearly inaccurate, given that incidence has been declining for decades (with the exception of the HIV/AIDS epidemics). Recent research has shown that relaxing the equilibrium assumption in chronic infections may lead to dramatic consequences in epidemiological predictions [E20]. However, modeling non-equilibrium is often difficult, as it requires either of the two: implementing relevant sources of equilibrium perturbation over time, starting from a historical epoch where the equilibrium assumption is accurate (as in [E20]); or being able to accurately characterize the initial conditions, i.e. an epidemiological state of the system that can be used as a starting point. Here we follow the latter approach, exploiting available information from multiple empirical estimates to initialize model variables and reproduce the state of TB in Arkansas in 2000. Model simulations are run from this non-equilibrium state with no need for a burn-in period. The number of prevalent TB cases at the beginning of the simulation, corresponding to calendar year 2000, was established using the relative prevalence in US in 2000 ([E21]) multiplied by the Arkansas population in the same year. The age-specific distribution of TB prevalent cases in 2000 is unknown. Since these are cases not yet diagnosed, and given that the large majority of active TB is diagnosed within a year from onset, we used the age distribution of incidence in Arkansas in 1999 as a proxy for the age distribution of the initial TB prevalence [E22]. The initial age-specific LTBI prevalence was

assigned using data from a large-scale LTBI prevalence study in the US in 1999-2000 [E23], weighting the relative contribution of foreign-born and US-born individuals by corresponding age-specific subpopulation in Arkansas in 2000 from census data.

E1.6 Foreign-born subpopulation

Every individual initialized as latently infected is assigned a probability, estimated from data [E23] of being foreign-born. If a latently infected individual is initialized as foreign-born, all members of the same household are assumed to belong to the same group. For immigrants after 2001, the age-specific number of incoming individuals with latent TB infection was calculated combining the observed average yearly number of immigrants in Arkansas (about 6,000 per year between 2000 and 2010 [24]), the age distribution of new immigrants [24] and the corresponding age-specific prevalence of latently infected individuals in the foreign-born [E23]. Individuals sharing the same household with the newly arrived latently infected individual are also considered foreign-born. Immigrant individuals may be carriers of TB, with a probability estimated by combining information on the number of immigrants and the number of TB cases from foreign-born diagnosed within one year of arrival to the US in the period 2001-2010 [E22]. Due to lack of specific data, foreign-born households are assumed to have the same demographic characteristics as US-born. In addition, foreign-born individuals are assumed to mix homogeneously with the resident population in terms of schools, workplaces and community transmission. Finally, no difference in model disease parameters (namely, risks of primary TB and endogenous reactivation) is assumed between the US-born and foreign-born subpopulations.

E1.7 Data

The TB incidence in Arkansas for the period 2001-2011, both by year and by age groups [E22], was used to calibrate the model.

Extensive model validation was done by comparing model predictions against several independent data sets that were not used during calibration:

i) Proportion of clustered and non-clustered cases by age group, and size distribution of clusters from a recent molecular epidemiological study in Arkansas in 2004-2011 [E25]. Here, a cluster is defined as at least two cases diagnosed within a year from each other, caused by mycobacterial isolates sharing the same molecular typing, independently of known epidemiological links; clusters may include secondary cases and span across multiple years, however the temporal distance between diagnoses of any two cases with same genotype will be lower than one year. Clustered cases correspond roughly to recently transmitted cases, while non-clustered cases are assumed to represent non-circulating genotypes derived from reactivation of old infections.

ii) Proportion of TB cases in foreign-born individuals, over time (2001-2011) and by time of sojourn in the USA (2005-2011) [E22].

iii) Secondary rates of TB disease and LTBI prevalence in household and workplace contacts of index cases from two large-scale US based studies [E17, E26].

E2. Calibration

E2.1 Choices for fixed parameters

- μ_T (TB death rate): set to 0.133 yrs^{-1}, based on the ratio between the yearly TB deaths and the estimated prevalent cases [E21].
- π (probability of pulmonary TB), set to 87% from surveillance data for Arkansas in 2001-2011 [E22];
- χ (rate of clearance for recent TB infections), set to 68% from previous estimates [E1]
- σ_c and σ_a (protection from exogenous re-infection given by previous infection in children and adults respectively) set to 0 and 40% respectively from previous estimates [E1, E6]

E2.2 Choice of objective function for calibration

Model calibration is obtained by searching for the optimal value of an objective function *F* between model predictions and calibration data, defined on the domain of all possible combinations of parameter values θ. A standard choice for *F* would be the likelihood; however, such a choice was not effective to obtain a good fit in this study, for two main reasons. First, calibration data are two different aggregations (by calendar year and by age group) of the same notification incidence data, and a likelihood function is difficult to define rigorously in this case; second, TB cases are rare in the population and the likelihood assumes very low levels, which are extremely sensitive to stochastic noise. Therefore, we choose *F* as the mean root relative squared error between each data point and the corresponding model prediction:

$$F(\theta) = \frac{1}{N_y + N_z} \sqrt{\sum_{i=1}^{N_y} \left(\frac{Y_i - y_i(\theta)}{Y_i} \right)^2 + \sum_{j=1}^{N_z} \left(\frac{Z_j - z_j(\theta)}{Z_j} \right)^2}$$

where Y_i is the observed yearly incidence (i=2001:2011) and Z_j is the observed incidence for age group j, while $y_i(\theta)$ and $z_j(\theta)$ represent the equivalent quantity predicted by the model, which depends on the parameter set θ. Ny=11 and Nz=7 are the number of data points for respectively the yearly and age-group specific incidence. This choice for the error function is supported by the need to combine heterogeneous data sources for model fitting. In practice, F selects parameter sets having a small relative error on each data point, independently of its absolute value. Thus, F can be approximately interpreted as the average percentage error for each data point.

E2.3 Calibration procedure

In a low burden setting, TB cases in the population are relatively rare and therefore subject to broad

stochastic variability. In this context, one should not look for a single parameter set that perfectly matches calibration data, but rather expect to find a region of parameter values that sufficiently approximates the observed trends in data. Therefore, we apply a heuristic procedure that does not aim to find the global maximum of the 9-dimensional parameter space on which our model is defined, but rather to identify a region of parameter values that meets two conditions. First, that model predictions in the region correspond to independent observations not used for calibration (as shown in Figure 4 in the main text); and second, that model predictions are robust in the identified region of optimal parameter values. Under these premises, estimated parameter values should not be interpreted strictly in terms of their biological value but only as a general indication of the order of magnitude of the phenomenon that they represent.

A simplified version of the calibration procedure used in this study is shown in Figure E1 for a 2-dimensional parameter space. For graphical convenience, we show a case where we search for regions that maximize an objective function, rather than minimizing an error; however the two problems are equivalent up to the sign of the objective function (e.g., minimizing F is equivalent to maximizing -F). The calibration procedure follows the following steps, corresponding to panels in Figure E1.

A) The unknown objective function F, defined over all possible combinations of values for the *k* model parameters, is measured at *M* points (parameter configurations) over a broad dominion of possible values. This broad dominion was defined using literature estimates and preliminary model simulations (reported in Table E3). The M points are chosen through an efficient technique of parameter space exploration called Latin Hypercube Sampling (LHS) [E27].

B) A threshold is set on the M objective values obtained and the range of exploration is restricted to the hypercube (a rectangle, in two dimensions, shown at the bottom of the graph) enclosing parameter sets above this threshold (shown as darker points in Figure E1).

We set as threshold the w-th percentile of the distribution of errors.

C) A new batch of M points is sampled in the restricted region, corresponding values of the objective function are calculated and the same percentile threshold is set on the new distribution of value. The region of exploration is further restricted.

D) A third batch of M parameter configurations is sampled in the further restricted region; the highest 100 scoring parameter sets (across the three batches) are used throughout the main text (shown in green in Figure E1); a final restriction of the parameter space (green area in Figure E1) defines the best fitting hypercube, enclosing such highly scoring parameter sets.

Figure E1 shows that the procedure allows the identification of a region of the parameter space that is in the neighborhood of a maximum. At each step, the adopted threshold is defined as $w=10^{th}$ percentile of the M=10,000 values of the objective function obtained in the current batch of sampling. The value of F was calculated as the average for each parameter set over 10 stochastic simulations. The boundaries for the best-fitting hypercube are reported in Figure E4 and used as the interval of parameter variability in the main text and sensitivity analysis (section E4). All model results reported in the main text are based on 100 stochastic simulations, chosen on the basis that the average of all relevant epidemiological quantities stabilized completely after about 10-15 stochastic simulations. Thus, the stochastic variability of the model is sufficiently represented in the provided error intervals.

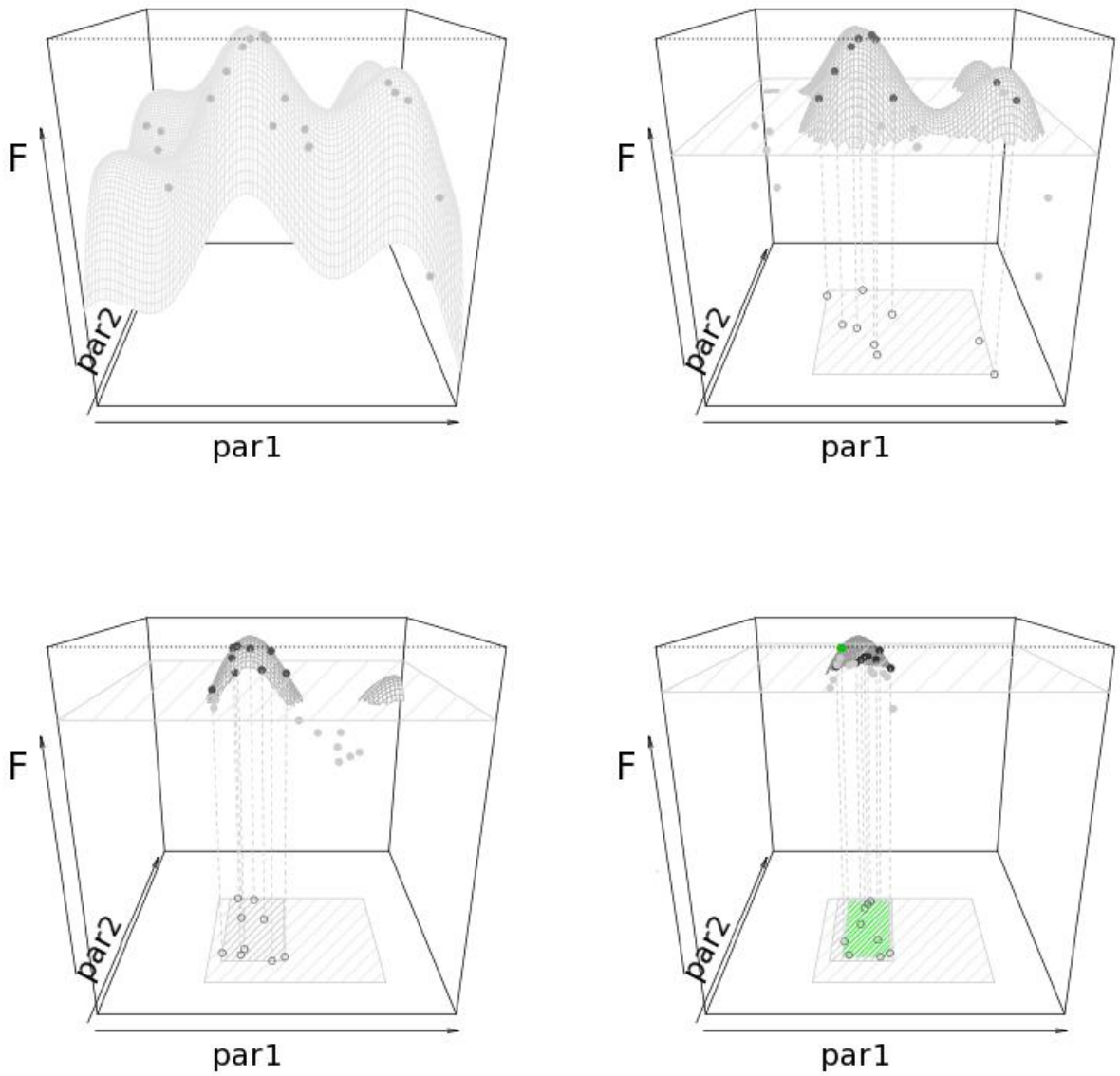

Figure E1. Simplified stochastic realization of the calibration procedure on a 2-dimensional parameter set. A) Objective function and initial exploration over the whole dominion of plausible parameter values; B) first selection of best-fitting parameters and corresponding sub-region of the parameter space; C) Sampling of the selected sub-region, second selection of best-fitting parameters and corresponding sub-region of the parameter space; D) Sampling of the newly selected sub-region and final selection of the best-fitting parameter sets.

	Description	Unit	Min	Max	Reference
k	Rate of progression to outcome	yrs^{-1}	0.2	3	[E1]
γ	Passive detection and treatment rate	yrs^{-1}	1	2	[E22]
p_c	Probability of primary TB in children (<10 yo)	%	1	20	[E6]
p_a	Probability of primary TB in adults (>20 yo)	%	6	20	[E6]
r	Mean reactivation rate	yrs^{-1}	$5 \cdot 10^{-4}$	$2.0 \cdot 10^{-3}$	[E28]
r_m	Slope of reactivation rate for <50 yo	yrs^{-2}	$5 \cdot 10^{-5}$	$2.0 \cdot 10^{-3}$	[E1]
β_H	Transmissibility (households)	yrs^{-1}	1	30	Preliminary runs
β_P	Transmissibility (schools and workplaces)	yrs^{-1}	1	30	Preliminary runs
β_R	Transmissibility (casual contacts)	yrs^{-1}	1	30	Preliminary runs

Table E3: initial ranges for the exploration of free model parameters.

E3. Interpretation of parameter estimates

Figure E2 shows the boxplots of the 100 best-fitting parameter values, normalized in such a way to represent a percentage of the original range of exploration specified in Table E3. Below and above the boxplots are reported the minimum and maximum values selected. Some parameters (γ, k, r and r_m) are estimated with a relative precision, whereas those relative to transmission and, even more, primary TB (β_H, β_P, β_R, p_a, p_c) have a wider range of variability. This is likely due to the positively correlated effects of transmission rates and probability of primary TB, so that an increase of the former can be compensated by a decrease of the latter.

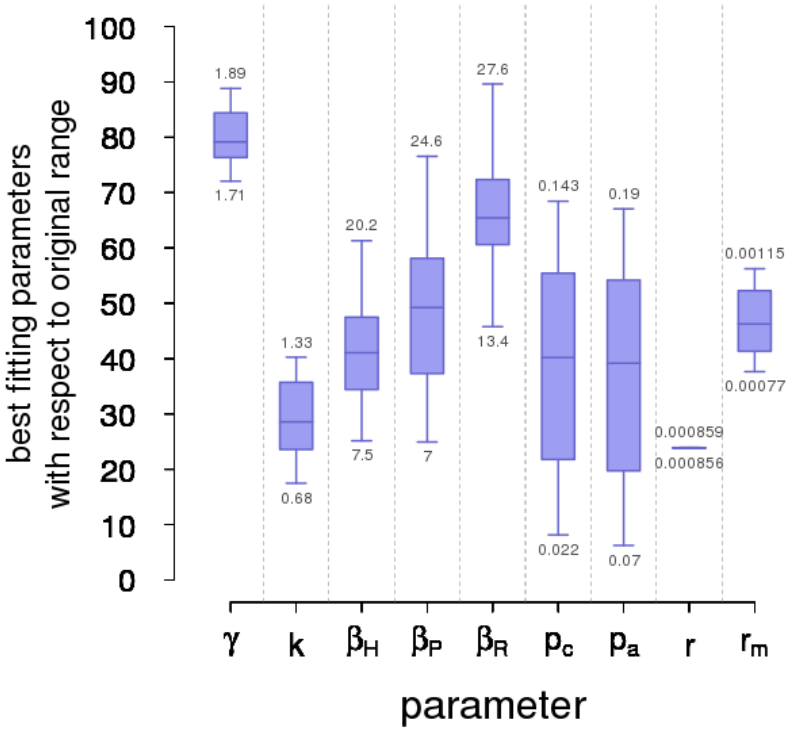

Figure E2. Boxplots representing the distribution of best fitting parameters, normalized with respect to the original range of exploration: on the vertical axis, 0 corresponds to the minimum, 100 to the maximum. Numbers reported at each end of each boxplot represent the minimum and maximum parameter value estimated by the model.

Hereafter we provide an intuitive interpretation to the values of free model parameters in Figure E2. Once again, we note that these values should not be considered strictly as model predictions, given the high stochastic noise in data.

- **k** defines the exponential rate at which an exposed individual exits the E0 compartment (representing the acute phase after the transmission episode where the clinical outcome is not yet determined). There is a 50% probability that the individual has become susceptible, latently infected, or infectious after a time $t = \log(2)/k = 6.2\text{-}12.2$ months from the infection episode. This is consistent with timings of the immune response according to immunological models [E7, E29] that estimate a time of about 200 days before the infection outcome is

defined. It is also consistent with the notion that the majority of TB cases occur within 1 year from infection, but that a significant proportion occur within two or more years [E6].

- γ defines the exponential rate at which an individual is passively diagnosed and cured. With current estimates, there is a 50% probability that the individual has been passively diagnosed within a time $t = \log(2)/\gamma = 4.4\text{-}4.85$ months from the onset of disease.
- $\mathbf{p_c}$ and $\mathbf{p_a}$ are the proportion of infections that result in primary (i.e. recently transmitted, as opposed to reactivated) TB. Between 2.2% and 14.3%of infections result in TB in children below 10 years, and between 7.1% and 19.1% in adults above 20 years. For ages between 10 and 20 years, intermediate values are taken. Vynnycky and Fine [E6], give an estimate of respectively 4.6% in children and 14.8% in adults for UK.
- **r** is the average risk of reactivation for individuals with LTBI; if an individual is infected with LTBI at birth and lives up to 100 years, his lifetime risk of developing TB by endogenous reactivation is between 8.56% and 8.59%. This is close to estimates by Horsburgh et al. [E28], who measure this risk at about 8.7% for the US born population. According to the same study, the risk of reactivation is not distributed uniformly across ages, but is about 3.8 times higher at ages above 50 years with respect to ages below 50 [E28]. In this model, we assume that the risk increases slowly until 50 years, and then with a higher pace after 50. $\mathbf{r_m}$ defines how quickly the risk increases in younger ages, and since the average over all ages is fixed by r, it also defines how quickly the risk must increase at older ages in order to give an average value equal to r. The predicted ratio of the average reactivation risks in individuals aged 50-80 years against that in <50 years is about 3.92, very close to estimates by Horsburgh and colleagues. With current best estimates, we obtain the curves for the reactivation risk by age shown in Figure E3. The figure also shows the described effect of increasing values for r_m.

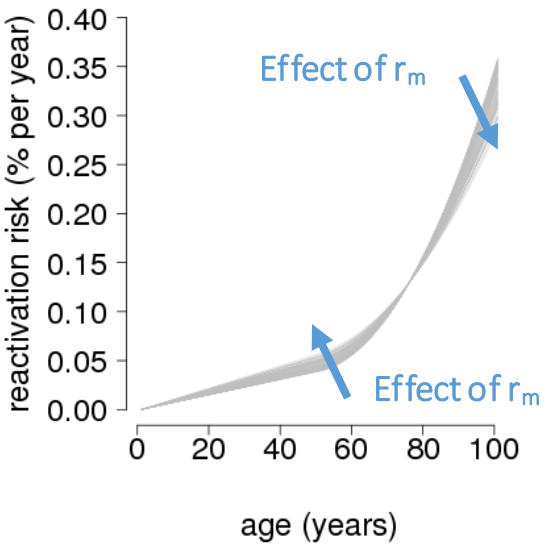

Figure E3. Estimates of the age-specific risk of endogenous reactivation in individuals with LTBI, and the effect of increasing values of the shape parameter r_m for fixed values of r (average of the risk over all ages).

- β_H, β_P and β_R define the potential of transmission of infectious individuals in the different settings (H: households; P: schools and workplaces; R: casual contacts). Current estimates result in a 15.6-47.5% probability per week that exactly one member of the same household of a smear-positive TB case will be exposed, a 14.4-60.6% probability per week that exactly one member of the same workplace or school will be exposed, and a 29.5-70.3% probability that exactly one member the same geographic cell will be exposed through casual contacts. For contacts of smear negative TB cases, these probabilities become 3.7-10.2%, 3.4-12.6% and 6.7-14.2% respectively. These figures derive from index cases that encounter on average many more random individuals than those that they encounter at home. Therefore, while the average individual probability of being infected is lower for random contacts than for household contacts, the model estimates more individuals exposed in the general population rather than within household. About 13.6% (95-percentile interval 9.1-19.6%) of recently

transmitted TB cases are predicted to be due household transmission, 23.2% (13.1-35.1%) to school or workplace transmission, and 64.1% (47.3-84.7%) to transmission from other contacts.

E4. Sensitivity analysis with respect to model calibration

Figures E4-E6 report the outputs of individual model simulations for 100 stochastic simulations of the best 100 parameter sets. In each figure, data points are arranged in a sort of Manhattan graph, in such a way that outputs corresponding to different stochastic realizations of a given parameter set are arranged on a vertical line (shown as light blue dots). The average output for each parameter set is reported with a blue dot within the Manhattan graph. On the side of each block, we report the average model output with corresponding 95-percentile interval, along with observed values where appropriate. Differently from figures in the main text, the 95-percentile interval for model output is calculated only on parameter-specific average output, so to represent inter-parameter variability decoupled from stochastic variability (included in the main text figures). The figures show that the stochastic variability is consistently more important than inter-parameter variability for most calibration and validation variables, but not for the main model predictions relative to the effectiveness of contact investigation, where the two effects are comparable.

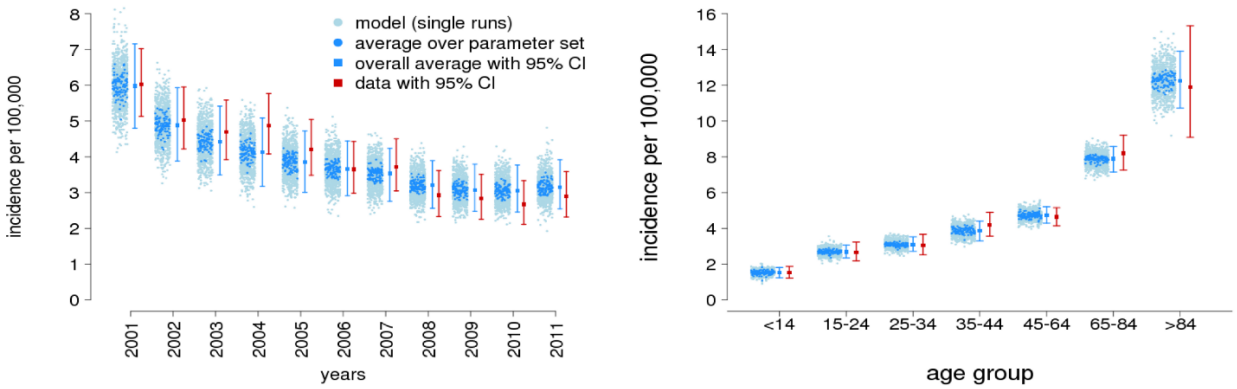

Figure E4. A) TB incidence over time (2001-2011) in Arkansas comparing model and data. B) TB incidence by age groups in Arkansas, average 2001-2011.

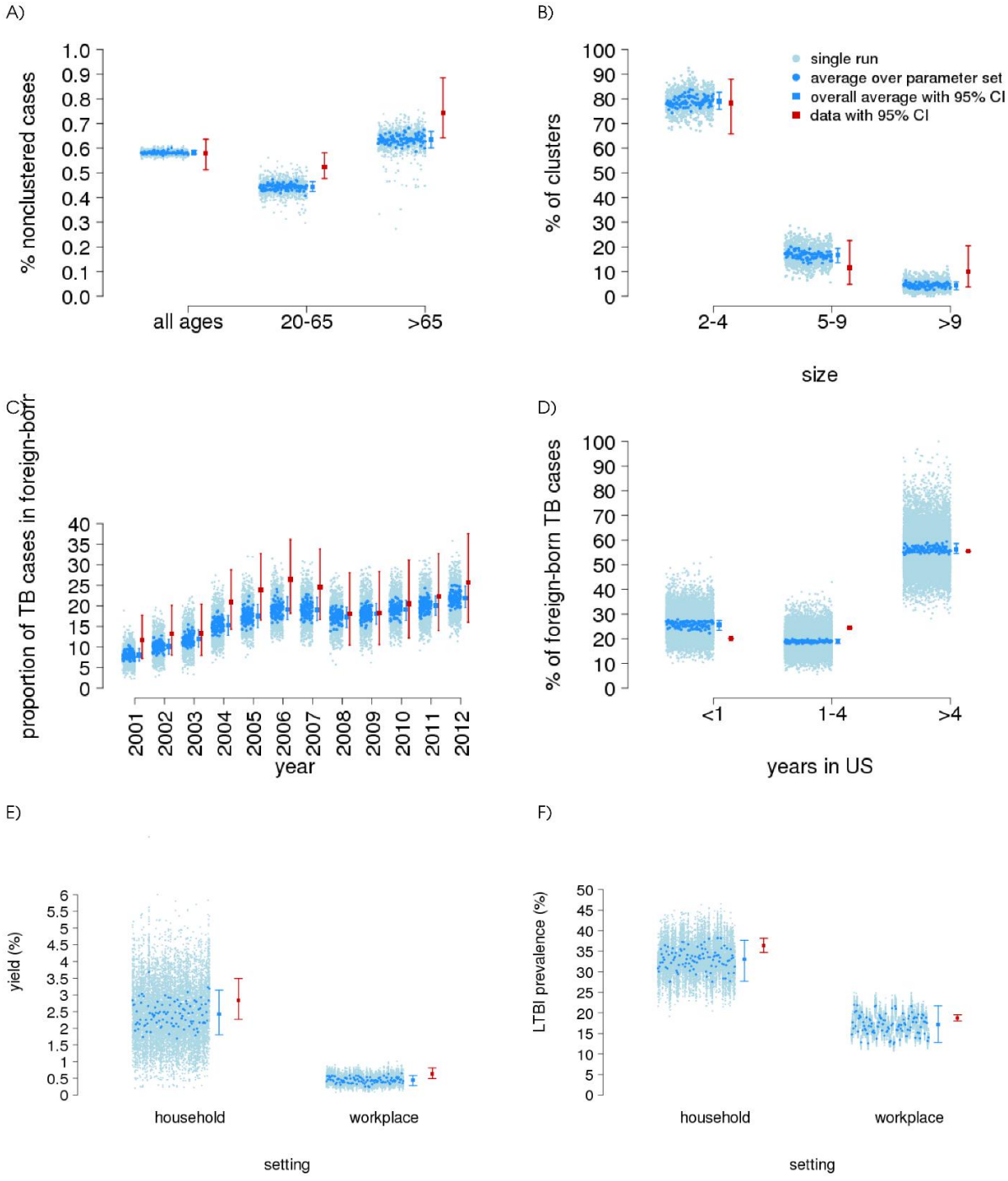

Figure E5. A) fraction of clustered TB over total of cases for the whole population and restricted by age group; B) distribution of cluster sizes; C) proportion of TB in foreign-born individuals over time; D) proportion of TB in foreign-born individuals by time of sojourn in the US for years 2005-2011; E) prevalence of secondary TB cases in household and workplace contacts of smear positive

index cases; F) prevalence of LTBI in household and workplace contacts of smear positive index cases.

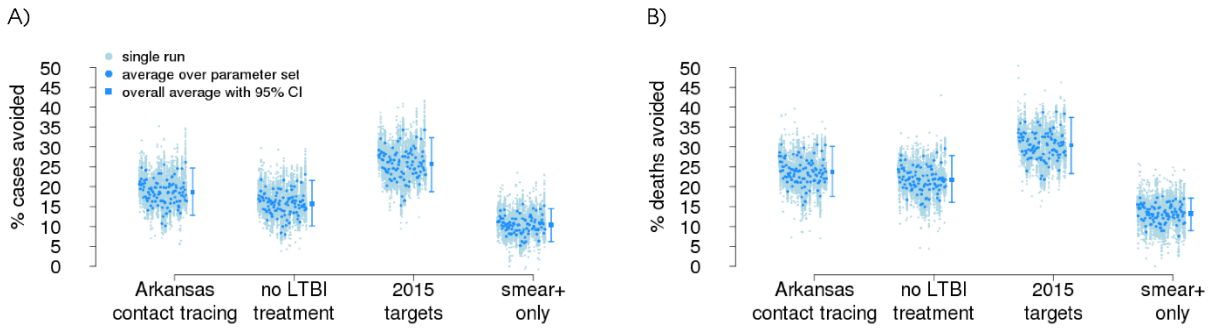

Figure E6. Percentage of avoided TB cases (A) and deaths (B) with respect to a passive diagnosis program by different contact tracing programs.

Figure E7 shows the values of the Partial Rank Correlation Coefficients (PRCCs) [E27] calculated between parameter values and relevant model predictions (proportion of avoided cases and proportion of avoided deaths for the Arkansas contact tracing program). Model parameters are sorted by the absolute value of their PRCCs with respect to the considered output. The figure shows the robustness of predictions with respect to uncertainty of parameter values in the best-fitting region, certified by the low, statistically non-significant (p-values > 0.05) values, for all parameters.

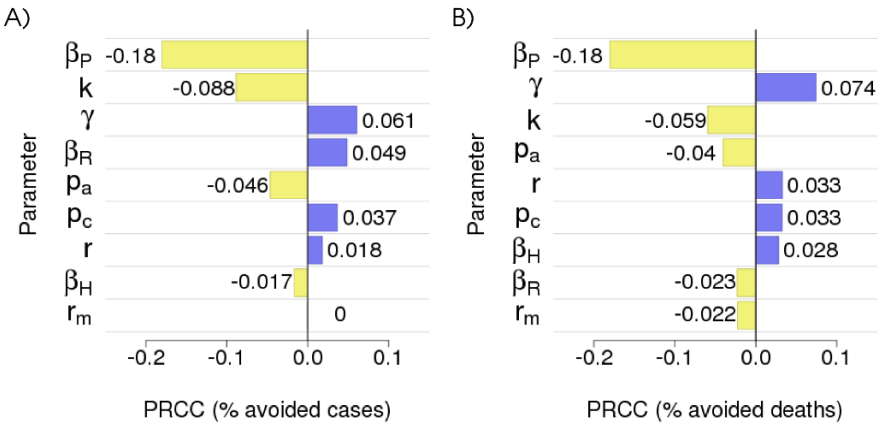

Figure E7. Partial Rank Correlation Coefficients between free model parameters and relevant

model outputs.

E5 Sensitivity analysis with respect to contact tracing parameter values

A sensitivity analysis was also performed to evaluate model robustness with respect to uncertainty in contact investigation parameters. In particular, we run the model by fixing free parameter values to the best-scoring parameter set, and used N=1,000 sets of values for parameters reported in Table E2, chosen uniformly over ranges reported in Table E4.

Symbol	Min	Max	Reference
L_{Se}	70%	90%	E17
D_{Se}	90%	100%	E17
Z	50%	100%	Assumption

Table E4. Range of variability of contact tracing parameter values used for sensitivity analysis.

Figure E8 shows that the estimated effectiveness of the contact investigation actually implemented by the Arkansas Department of Health is about as sensitive on these parameters as it is on free model parameters.

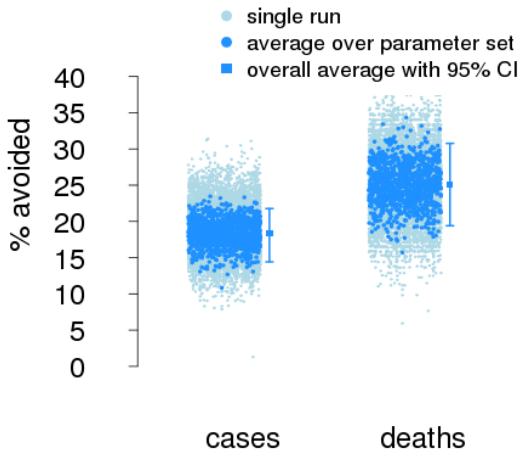

Figure E8. Sensitivity of the estimated percentage of avoided TB cases and deaths in the Arkansas

contact investigation program with respect to uncertainty in values of program parameters.

Figure E9 shows the PRCCs between contact tracing parameter values and corresponding prediction. In this case, parameter Z is most strongly correlated with the output. Given that Z represents the efficiency in identification of "random" contacts, this is not surprising as the majority of transmitted cases is suggested by the model to occur in the general community. A lower, but statistically significant, PRCC value is assigned also to the diagnostic sensitivity of TB screening. This is consistent with the notion that missed diagnoses will bring to increased opportunities for continuing the TB transmission chain.

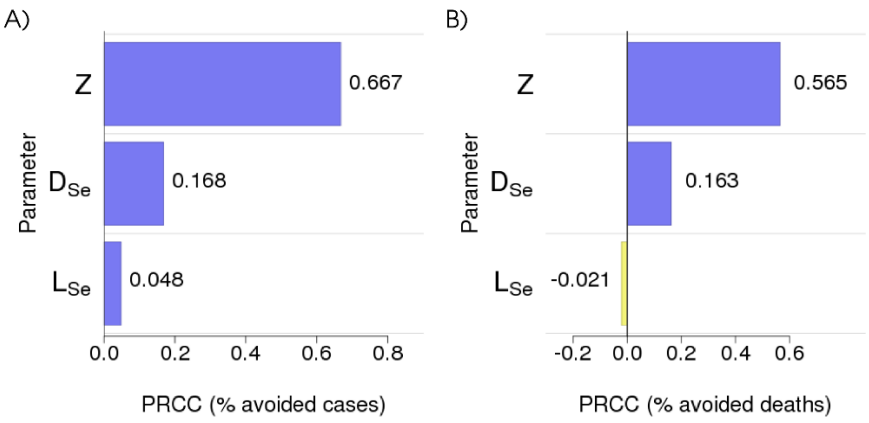

Figure E9. Partial Rank Correlation Coefficients between parameters of contact tracing and relevant model outputs.

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