Supplementary Appendix

Contents

Supplementary Table 1: Population demographics and pulmonary TB rates for South Asian and Black African ethnic/social groups. The ethnic/social group population sizes, rates of birth and immigration are estimated from the latest Office for National Statistics (ONS) census data (2011). Birth rate is calculated from the number of 0- to 4-year-olds per ethnic/social group. The number of new arrivals in England and Wales is used to estimate the immigration rate. Baseline TB incidence and proportion of MDR-TB cases are from Enhanced TB Surveillance (ETS) data (2015).[1]

Ethnic/social group	Region of birth	Population size	Births per year	Immigrants per year	Annual active TB cases	Proportion of active TB cases that are MDR (%)
South Asian	England and Wales	1,461,439	70,163	-	185	1.0
	Foreign	1,258,561	-	49,142	808	0.3
Black African	England and Wales	320,615	27,259	-	64	1.1
	Foreign	607,566	-	27,977	411	1.1

Supplementary Table 2: Summary of uncertain parameters. The table shows the baseline values and plausible value ranges of the parameters considered in the sensitivity analysis.

Parameter	Baseline value (uncertainty range)	Unit	Source
Prevalence of LTBI among new South Asian migrants	20 (17-23)	%	[2]
Prevalence of LTBI among new Black African migrants	28 (22-34)	%	[2]
Relative infectivity of smear-negatives (vs. smear-positives)	0.25 (0.13-0.41)	Ratio	[3-5]
Proportion of contacts successfully screened with IGRA	73 (50-95)	%	[6]
Proportion of IGRA+ contacts successfully screened for active TB	76 (50-95)	%	[7]
Time to molecular test report	1.5 (1-3)	Days	[8]
Time to culture-positivity	13 (8-17)	Days	[9]
Time from culture-positivity to WGS report	8 (6-9)	Days	[10]
Time from culture-positivity to DST report	24 (20-33)	Days	[9,10]
Proportion assessed as being at risk of MDR TB	1.3 (1-1.7)	%	[1]
Duration of standard isolation (for DS TB)	14 (14-90)	Days	[8]
Duration of completed DS TB treatment	180 (180-270)	Days	[11]
Proportion accepting LTBI treatment	78 (50-95)	%	[12]
Proportion completing LTBI treatment	79 (50-95)	%	[12]
TB: Tuberculosis; MDR: Multi-drug resistant; DS: Drug sensitive; DST: Drug sensitivity testing; WGS: Whole-genome sequencing.			

Supplementary Table 3: Summary of breakdown of treatment and diagnosis costs for each strategy. The table shows a breakdown of discounted costs calculated over a 10-year horizon for each strategy. Values are £M and show the mean and 95% range. X, U: molecular testing options.

Strategy	DS TB treatment	MDR TB treatment	LTBI treatment	False-positive TB treatment	Diagnostics
Baseline	62.5 (38.8, 86.1)	18.3 (10.7, 25.8)	6.2 (3.5, 8.9)	1.5 (1.4, 1.5)	25.5 (25.3, 25.7)
WGS alone	62.2 (38.5, 85.8)	13.0 (9.0, 17.0)	6.2 (3.5, 8.9)	1.5 (1.4, 1.5)	23.9 (23.8, 24.0)
X + DST	61.2 (37.8, 84.5)	18.7 (16.9, 20.4)	6.1 (3.5, 8.7)	0.8 (0.8, 0.8)	27.1 (27.1, 27.2)
U + DST	60.9 (37.7, 84.1)	18.9 (17.3, 20.6)	6.0 (3.4, 8.6)	1.01 (1.01, 1.01)	27.0 (27.0, 27.1)
X + WGS	61.2 (37.8, 84.5)	14.5 (12.7, 16.2)	6.1 (3.5, 8.7)	0.8 (0.8, 0.8)	25.7 (25.6, 25.8)
U + WGS	60.9 (37.7, 84.1)	15.0 (13.1, 16.8)	6.0 (3.4, 8.6)	1.01 (1.01, 1.01)	25.7 (25.6, 25.7)

Supplementary Table 4: consistency of cost-effectiveness rank-order. The table shows the percentage of simulations that result in a given ranking by incremental net benefit over a 10-year horizon for each of the strategies. Rank 1 is the highest incremental net benefit (most cost-effective) and Rank 5 is the lowest Incremental net benefit (least cost-effective). X, U: molecular testing options.

Rank	Strategy				
	WGS alone	X + DST	U + DST	X + WGS	U + WGS
1	0	0	0	0	100
2	0	0	0	100	0
3	0	8.3	91.7	0	0
4	28.4	71.6	0	0	0
5	71.6	20.1	8.3	0	0

Description of the process of identification and treatment of TB

The baseline clinical pathway for active-TB diagnosis uses chest X-ray as an initial rule-out test for pulmonary TB.[13] An abnormal chest X-ray prompts collection of sputum samples for smear microscopy and culture, with positive cultures followed by culture-based DST.

Patients diagnosed with active TB (usually based on sputum-smear microscopy or culture) are given drug treatment. Typically, treatment is initiated prior to DST results becoming available, so the choice of regimen is based on a risk assessment for drug resistant infection, based previous TB treatment history, contact with a known MDR-TB case, or birth or residence in a country where ≥5% of new TB cases are MDR-TB.[13] Treatment can be modified if necessary when DST results become available.

We divide TB in into drug-sensitive (DS) and MDR-TB because NICE recommends that mono-resistant infection that is not rifampicin resistant be treated the same as fully drug-sensitive with only slight modifications (extended duration of treatment),[13] whilst rifampicin-resistant infection be treated as MDR-TB. This simplifying assumption may result in an underestimation of DS-TB treatment costs, which we address in sensitivity analysis by varying the treatment duration between 6 and 9 months (the recommended duration for DS-TB and isoniazid or pyrazinamide single drug resistance respectively).[13]

Close contacts of people with pulmonary TB are investigated for infection using Interferon-gamma release assay (IGRA).[13] Contacts with positive IGRA results have a chest X-ray to detect active TB. Those with an abnormal X-ray are managed as suspected active-TB patients. Individuals with a positive IGRA result and a normal chest X-ray are

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offered LTBI treatment of 3 months of isoniazid, pyridoxine and rifampicin, if the index case has DS TB. (Where the index case has MDR TB, LTBI treatment is not offered to contacts in case their infection is MDR, which would make LTBI treatment ineffective; however, contacts with active TB are treated, as their MDR status is determined in the diagnostic process.)

Studies in London and Birmingham estimated that about 86% and 60%, respectively, of pulmonary TB contacts are investigated.[6, 14] We consider a midpoint baseline value of 73% and perform sensitivity analysis varying the value between 50-95%. It is also uncertain what proportion of patients accept and complete LTBI treatment. A recent study in London estimated that 78% of contacts with LTBI start treatment and 79% go on to successfully complete it.[12] We use these estimates as baseline values and perform sensitivity analysis, varying both values between 50% and 95%.

Isolation of infectious patients is recommended:[13]

(i) At least 2 weeks standard isolation of smear-positive presumed DS-TB cases, to be extended if there is delayed smear conversion.

(ii) For cases with suspected or confirmed MDR-TB, admission to a negative-pressure room until 3 consecutive weeks of negative sputum-smear results or a negative culture result.

In the model patients are not able to transmit TB while in isolation. The duration of isolation recommended by NICE is a minimum of 2 weeks.[13] However, a recent study in Germany estimated the time from treatment initiation to smear conversion, for DS-TB, to be 19 (10–32) days.[15] We perform sensitivity analysis varying this parameter over a range of 10–32 days with a baseline value of 14 days. Smear-positive MDR-TB cases are admitted to negative-pressure isolation rooms for 89 days[8, 16] whilst smear-negative MDR-TB cases are admitted to negative isolation rooms for 23 days followed by a further 23 days as a non-isolation inpatient.[8]

Detailed model description

The model considers TB transmission within each Black African and South Asian ethnic/social groups, with homogeneous mixing of UK-born and foreign-born individuals within those groups. The model makes the simplifying assumption that there is negligible transmission between Black African and South Asian groups, which is supported by both epidemiological evidence and sociological evidence. A UK study using molecular typing and cluster investigation found that 85% of transmissions were between individuals with the same country of birth, and there were no instances of transmission detected between South Asian and Black African groups[17] and the 2011 census found that <0.56% of South Asians are in relationships with Black Africans and <1.62% of Black Africans are in relationships South Asians.[18]

The population is divided into compartments representing infection and treatment status (i.e. naive, latent infection, active disease, on treatment, recovered, etc). Individuals flow between the compartments depending on per-capita rates and the number of individuals in the relevant compartment. The model structure is the same structure for DS and MDR TB, and there are separate sets of compartments for Black African (UK-born), Black African (foreign-born), South Asian (UK-born), and South Asian (foreign-born) groups.

Flows between compartments are described by a set of ordinary differential equations (see below), in which each compartment has a state variable indicating the number of individuals in that compartment at a point in time; these are listed in Supplementary Table 5. The differential equations specify the rate of change in the number in each compartment with respect to time, e.g. dS/dt is the rate of change in the number Susceptible (S) with respect to time (t).

Individuals enter the model population through birth or immigration and exit through death or emigration. The rate of entry is τ, which corresponds to births for UK-born individuals and the immigration rate for foreign-born individuals. The proportion of new entrants who have latent TB infection is p_e: in the case of UK-born entrants, who

are newborns, this has the value 0: for new entrants who are migrants its value corresponds to the LTBI prevalence estimated by Pareek et al.[2] Thus the rate of entry into the TB naïve compartment (S) is $(1-p_e)\tau$. Exit from all compartments occurs at rate μ due to emigration and death due to non-TB related causes.

Heterogeneity in rates of progression from LTBI to active TB is represented by dividing individuals with LTBI into slow-progressors (Ls) or fast-progressors (Lf). The ratio of new immigrants who are slow-progressors to fast-progressors, p_m, is estimated by model fitting (explained below). (For UK-born individuals this parameter is irrelevant.) The flow rates of new entrants into to Lf and Ls compartments are $p_e\tau/(p_m+1)$ and $p_e\tau p_m/(p_m+1)$, respectively. The proportion of TB infection in new arrivals that is drug sensitive is p_{d1} and the proportion that is MDR is p_{d2}, where $p_{d1} = (1-p_{d2})$.

Interaction between uninfected individuals and those with active TB can result in TB transmission. TB-naïve individuals are infected at rate λ, whilst those who have recovered have partial protection and are infected at rate $b_R\lambda$. Newly-infected individuals have latent TB infection (LTBI) which is asymptomatic and non-infectious. A proportion p_s have slow-progressing LTBI with a progression rate ϕ_S. The remaining individuals $(1 - p_s)$ have fast-progressing LTBI with a progression rate ϕ_F. Individuals with LTBI can have their infection diagnosed via contact tracing and be treated at rate θ_L. Details of how θ_L is calculated are provided below.

Individuals who progress to develop active TB, which is symptomatic and infectious, are either sputum smear-positive TB (USp) or sputum smear-negative TB (USn), with the former being more infectious. The proportion of nascent disease that is smear-positive is p_{Sp}. Smear-negative individuals can convert to smear-positive, at rate σ. The infectiousness of smear-negative relative to smear-positive individuals is b_N. Depending on the clinical pathway considered (Figure 2), individuals seeking care due to symptoms are diagnosed and end-up in either DS-TB or MDR-TB treatment compartments at rate θ_P. Additional active TB cases are identified by contact tracing (θ_C) as explained below. Untreated active-TB cases can naturally revert to the slow-progressing latent state at rate π. Untreated active TB causes mortality at rate μ_U.

Individuals can be treated for LTBI, DS TB or MDR TB. Treatment may be completed successfully or patients may be lost to follow-up; to account for the different corresponding durations there are separate compartments for those who will complete treatment successfully and those who will not. The proportion of successfully-treated LTBI is p_{TsL} and the proportion of successfully-treated active TB is p_{TsAi}. The durations of successful and unsuccessful LTBI treatment are $1/d_{TsL}$ and $1/d_{TuL}$, respectively. The durations of successful and unsuccessful active TB treatment are $1/d_{TsAi}$ and $1/d_{TuA}$, respectively. Successfully-treated individuals enter the Recovered state, whilst unsuccessfully-treated individuals return to their prior infection state. Those being unsuccessfully treated for active disease are subject to the additional TB-associated mortality rate, μ_{Tu}.

Individuals in the Recovered state have a reduced susceptibility (b_R) to acquisition of TB infection compared to TB naïve individuals.

For each active TB case that is diagnosed, an average number (c) of contacts are successfully traced and IGRA-tested for TB infection, with IGRA-positives being investigated by chest X-ray to detect active TB: a normal X-ray indicates LTBI. The proportion of traced individuals that have LTBI, q_L, depends on the population prevalence of LTBI thus: $q_L = (Ls+Lf)/N + p_L$, where $(Ls+Lf)/N$ is the population prevalence of LTBI and p_L is the differential between the population prevalence of LTBI and the proportion of contacts that have LTBI. The value of p_L is the difference between the proportion of contacts with latent TB infection as estimated by Fox et al.[19] and the initial population prevalence of LTBI in the model. The proportion of contact-traced LTBI cases accepting LTBI treatment is a_L, so the rate of LTBI treatment is $\theta_L = c\, q_L\, a_L\, \theta_P$. Although they are traced, contacts of MDR TB index cases who are diagnosed with LTBI are not treated. However, another proportion (q_A) of successfully traced contacts are IGRA-positive and have an abnormal chest X-ray. These individuals enter the same treatment pathway (described above) as other active cases

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in the clinical pathways. The proportion of contact traced active TB cases going onto TB treatment is therefore given by $\theta_C = c\, q_A\, \theta_P$.

Supplementary Table 5: symbols for model variables and parameters. The variables correspond to model compartments (Figure 1) except N, λ, q_L, q_A, θ_L, and θ_C. Parameters specify rates of entry into and exit from compartments as described in the text and specified in the differential equations.

Symbol	Description
Variables	
S	Susceptible (naive) individuals
Ls	Individuals with slow-progressing latent infection
Lf	Individuals with fast-progressing latent infection
USn	Individuals with untreated smear-negative active TB disease
USp	Individuals with untreated smear-positive active TB disease
TsLs	Individuals with slow-progressing latent TB infection on treatment which will be successful
TuLs	Individuals with slow-progressing latent TB infection on treatment which will not be completed successfully
TsLf	Individuals with fast-progressing latent TB infection on treatment which will be successful
TuLf	Individuals with fast-progressing latent TB infection on treatment which will not be completed successfully
TsSn	Individuals with smear-negative TB disease on treatment which will be successful
TuSn	Individuals with smear-negative TB disease on treatment which will not be completed successfully
TsSp	Individuals with smear-positive TB disease on treatment which will be successful
TuSp	Individuals with smear-positive TB disease on treatment which will not be completed successfully
R	Individuals who have recovered from TB infection
N	Total sub-population size
λ	Force of infection: per-Susceptible rate of infection per unit time
c	Average number of contacts of active-TB cases who are successfully traced
q_L	Proportion of traced contacts of active-TB cases that have LTBI
q_A	Proportion of traced contacts of active-TB cases that have active TB
a_L	Proportion of contact-traced LTBI cases accepting LTBI treatment
θ_L	Rate at which individuals with LTBI are diagnosed and treated due to contact tracing
θ_C	Rate at which individuals with active TB are diagnosed and treated through contact tracing
Parameters	
β_P	Transmission coefficient of smear-positive TB
b_N	Relative infectiousness of smear-negative individuals compared with smear-positive
b_{Tu}	Relative infectiousness of individuals being unsuccessfully treated for active TB compared with untreated active TB
b_M	Relative infectivity of MDR TB compared to non-MDR TB
b_R	Relative susceptibility of Recovered individuals
τ	Rate of entrance into population sub-group: births for UK-born, immigration for foreign-born
p_e	LTBI prevalence among population entrants: prevalence in immigrants was estimated by Pareek et al.; prevalence in newborns is zero
p_m	Ratio of latent slow progressors to latent fast progressors in new arrivals
p_{d1}	Proportion of TB infection in new arrivals that is drug-sensitive
p_{d2}	Proportion of TB infection in new arrivals that is drug-sensitive
μ	Rate of exit from population due to emigration + background mortality (i.e. death due to non-TB causes)
p_s	Proportion of incident infections that are slow-progressing
p_{TsL}	Proportion of LTBI treatment that is successful
$1/d_{TsL}$	Duration of successful LTBI treatment
$1/d_{TuL}$	Duration of unsuccessful LTBI treatment
ϕ_S	Rate of slow-progression from latent infection
ϕ_F	Rate of fast-progression from latent infection
p_{Sp}	Proportion of nascent active TB that is smear-positive

σ	Rate of conversion from smear-negative to smear-positive
π	Rate of reversion from active TB to LTBI
μ_U	Additional mortality rate due to Untreated active TB
p_{TsA}	Proportion of active-TB treatment that is successful
$1/d_{TsA}$	Duration of successful active-TB treatment
$1/d_{TuA}$	Duration of unsuccessful active-TB treatment
μ_{Tu}	Additional mortality rate in patients being treated unsuccessfully for active TB
p_L	Differential between the population prevalence of LTBI and the proportion of contacts that have LTBI
θ_P	Rate at which individuals with active TB are diagnosed and treated passively (i.e. through individuals seeking care)

Model equations

With the exception of S and R (which are uninfected), the model compartments denote infection with DS TB or MDR TB, which is distinguished in the equations below using the subscript i, where i=1: DS TB; i=2: MDR TB.

$$dS/dt = (1 - p_e)\,\tau - (\Sigma_i\lambda_i + \mu)\,S$$

$$dLs_i/dt = \lambda_i\, p_s\, (S + b_R\, R) + p_e\, p_{di}\, \tau\, p_m/(p_m+1) + \pi\, (USn_i + USp_i) + d_{TuL}\, TuLs_i - (\theta_L + \phi_S + \mu)\, Ls_i$$

$$dLf_i/dt = \lambda_i\, (1 - p_s)\, (S + b_R\, R) + p_e\, p_{di}\, \tau/(p_m+1) + d_{TuL} TuLf_i - (\theta_L + \phi_F + \mu)\, Lf_i$$

$$dUSn_i/dt = (1 - p_{Sp})\, (\phi_S\, Ls_i + \phi_F\, Lf_i) + d_{TuA}\, TuSn_i - [\sigma + \pi + (\theta_P + \theta_C) + (\mu + \mu_U)]\, USn_i$$

$$dUSp_i/dt = p_{Sp}\, (\phi_S\, Ls_i + \phi_F\, Lf_i) + \sigma\, USn_i + d_{TuA}\, TuSp_i - [\pi + (\theta_P + \theta_C) + (\mu + \mu_U)]\, USp_i$$

$$dTsLs_i/dt = \theta_L\, p_{TsL}\, Ls_i - d_{TsL}\, TsLs_i - \mu\, TsLs_i$$

$$dTuLs_i/dt = \theta_L\, (1 - p_{TsL})\, Ls_i - (d_{TuL} + \mu)\, TuLs_i$$

$$dTsLf_i/dt = \theta_L\, p_{TsL}\, Lf_i - (d_{TsL} + \mu)\, TsLf_i$$

$$dTuLf_i/dt = \theta_L\, (1 - p_{TsL})\, Lf_i - (d_{TuL} + \mu)\, TuLf_i$$

$$dTsSn_i/dt = (\theta_P + \theta_C)\, p_{TsAi}\, USn_i - (d_{TsAi} + \mu)\, TsSn_i$$

$$dTuSn_i/dt = (\theta_P + \theta_C)\, (1 - p_{TsAi})\, USn_i - (d_{TuA} + \mu + \mu_{Tu})\, TuSn_i$$

$$dTsSp_i/dt = (\theta_P + \theta_C)\, p_{TsAi}\, USp_i - (d_{TsAi} + \mu)\, TsSp_i$$

$$dTuSp_i/dt = (\theta_P + \theta_C)\, (1 - p_{TsAi})\, USp_i - (d_{TuA} + \mu + \mu_{Tu})\, TuSp_i$$

$$dR/dt = d_{TsL}\, (TsLs_1 + TsLf_1) + \Sigma_i d_{TsAi}\, (TsSn_i + TsSp_i) - [b_R\, (\Sigma_i\lambda_i) + \mu]\, R$$

The total population of each of the 4 sub-groups, N, is

$N = S + \Sigma_i(Ls_i + Lf_i + USn_i + USp_i + TsLf_i + TuLf_i + TsLs_i + TuLs_i + TsSn_i + TuSn_i + TsSp_i + TuSp_i) + R$

where Σ_i denotes summation over the compartments representing infection with DS TB and MDR TB.

The force of infection (per-Susceptible rate of infection per unit time) terms, for DS TB (λ_1) and MDR TB (λ_2), are

$\lambda_1 = \Sigma\beta_P\, [b_N\, USn_1 + USp_1 + b_{Tu}\, (b_N\, TuSn_1 + TuSp_1)] / \Sigma N$

$\lambda_2 = \Sigma b_M\, \beta_P\, [b_N\, USn_2 + USp_2 + b_{Tu}\, (b_N\, TuSn_2 + TuSp_2)] / \Sigma N$

where Σ denotes summation over the UK-born and foreign-born members of the relevant ethnic/social group.

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Model calibration and fitting

The model is implemented in Python 3 and solved using a forward Euler method. Fitting uses the Levenberg-Marquardt algorithm, which minimizes the sum squared residuals (difference between the data and the fitted model output).

Initial conditions are determined by fitting the model to the observed diagnoses in Black Africans and South Asians by varying the UK transmission rate, the ratio of latent slow-progressors to latent fast-progressors in new arrivals, the percentage of MDR TB cases among new arrivals and the relative transmissibility of MDR TB compared to non-MDR TB. Fitted parameter values are in Supplementary Table 6.

In the main analysis the population rates of birth, death due to non-TB causes, immigration and emigration are assumed to be constant over the 10-year time-horizon, and in sensitivity analysis the immigration rate is halved and doubled.

Supplementary Table 6: Summary of estimated parameter means and 95% ranges from 1,000 simulations.

Parameter	Black Africans	South Asians
Transmission rate of smear-positive DS TB (per person per year), β_P	11.86 (11.34, 12.35)	8.14 (7.78, 8.47)
Ratio of latent slow-progressors to latent fast-progressors in new arrivals, p_m	0.979 (0.978, 0.981)	0.974 (0.972, 0.978)
Percentage of TB infection in new arrivals that is MDR	0.715 (0.714, 0.718)	0.738 (0.735, 0.740)
Relative infectivity of MDR TB compared to DS TB	0.627 (0.624, 0.631)	0.209 (0.208, 0.210)

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