1 Capturing heterogeneous infectiousness in transmission dynamic 2 models of tuberculosis: a compartmental modelling approach

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24Abstract

25Infectiousness heterogeneity among individuals with tuberculosis (TB) is substantial and is
26likely to have a significant impact on the long-term dynamics of TB and the effectiveness of
27interventions. However, there is a gap in capturing heterogeneous infectiousness and
28evaluating its impact on the effectiveness of interventions.

29Informed by observed distribution of secondary infections, we constructed a deterministic
30model of TB transmission using ordinary differential equations. The model incorporated
31assumption of heterogeneous infectiousness with three levels of infectivity, namely non-
32spreaders, low-spreaders and super-spreaders. We evaluated the effectiveness of dynamic
33transmission untargeted and targeted implementation of an intervention intended to represent
34active case finding with a point-of-care diagnostic tool. The simulated intervention detected
3520% of all TB patients who would otherwise have been missed by the health system during
36their disease episode and was compared across four epidemiological scenarios.

37Our model suggested that targeting the active case finding intervention towards super-
38spreaders was more effective than untargeted intervention in all setting scenarios, with more
39effectiveness in settings with low case detection and high transmission intensity. For instance,
40a targeted intervention achieved a 42.2% reduction in TB incidence, while the untargeted
41intervention achieved only a 20.7% reduction over 20 years, given the same number of
42people treated. Although the most marked impact on equilibrium TB incidence came from the
43rate of late reactivation, the proportion of super-spreaders and their relative infectiousness
44had shown substantial impact.

45Targeting active case-finding interventions to highly infectious cases likely to be particularly
46beneficial in settings where case detection is poor. Heterogeneity-related parameters had an

47equivalent effect to several other parameters that have been established as being very
48important to TB transmission dynamics.

49**Keywords:** heterogeneous infectiousness; *M. tuberculosis* transmission; mathematical model;

50Introduction

51Tuberculosis (TB) is the world's leading cause of death from a single infectious agent, in
522019, ranking above HIV/AIDS with an estimated 10.0 million cases and 1.2 million deaths
53worldwide [1]. The World Health Organization developed the new End TB Strategy for post-
542015 TB elimination activities, with the ambition of a 95% reduction in TB deaths and a 90%
55reduction in TB incidence by 2035 by comparison to 2015 rates [2]. However, the natural
56history of TB remains poorly understood, and consequently, the uncertain potential impact of
57control interventions limits confidence about the possibility of its elimination. The
58heterogeneous transmission of *Mycobacterium tuberculosis* (*Mtb*) within populations is well-
59established, but its epidemiological impact is poorly understood. Moreover, up to a third of
60TB cases are not diagnosed, so finding and treating infectious cases is key to achieving TB
61control, and finding and treating highly infectious people is the key to TB control in high
62transmission settings [3, 4].

63We define infectiousness heterogeneity as the variability in the capacity of infectious patients
64to produce secondary infections, which may be attributable to characteristics of the host, the
65agent and the environment [5-9]. Heterogeneity of infectious individuals in spreading *Mtb*
66infection is well-recognised, with a small group of highly infectious individuals producing a
67large proportion of secondary infections, while many others produce very few or none [10].
68Previous TB genomic epidemiology has identified TB super-spreading events by quantifying
69heterogeneity in the infectiousness of TB patients through fitting a standard statistical
70distribution (the negative binomial distribution, NBD) to the distribution of secondary cases

71produced by each infectious patient (the “offspring distribution”) [11]. More recently, data
 72from TB contacts in a low-transmission setting have allowed estimation of the proportion of
 73all TB patients that can be categorised as super-spreaders, finding it to be approximately 10%
 74[9]. In such studies, super-spreaders were typically defined as patients who produced a
 75number of secondary “infections/cases” greater than the 99th centile of a standard Poisson
 76offspring distribution, with distribution mean equal to the average number of secondary
 77infections per index [9, 12]. This heterogeneity is likely to have implications for both the
 78burden of disease and the effectiveness of control interventions. Thus, we propose that it is
 79necessary to capture this heterogeneity when modelling TB transmission dynamics.

80Some past compartmental models of TB transmission dynamics have attempted to capture
 81heterogeneity in patients’ infectiousness by stratifying the active TB compartment into
 82different levels of infectivity. Amongst the most typical approaches is stratification as either
 83infectious (usually representing pulmonary TB) or non-infectious (extrapulmonary TB) [13-
 8417]. This approach implies that all pulmonary TB patients are equally infectious, while all
 85extrapulmonary patients are entirely non-infectious, and so does not capture the heterogeneity
 86among pulmonary patients. Other TB models have considered sputum smear status as a factor
 87in stratifying patients’ levels of infectiousness, considering both smear-negative and smear-
 88positive pulmonary TB to be infectious, with the relative infectiousness of smear-negative
 89patients compared to smear-positive typically set between 15 and 25% [18-33]. While
 90stratifying pulmonary TB patients based on smear status captures an additional clinical
 91attribute that is important in determining infectiousness, even these models still do not
 92capture the full picture of TB patients’ infectiousness variation, since several behavioural and
 93demographic factors other than smear status can affect the level of infectiousness [5].

94An individual-based model simulated patterns of meetings and *Mtb* transmission between
 95three different types of contact to determine the effects of variation in infectiousness and

susceptibility on transmission location. The study defined super-spreading defined based on the number of secondary cases instead of secondary infections and suggested that the majority of disease resulted from infection by a small proportion of people with TB or super-spreaders [34]. However, as TB disease activation may take long time and also depend on mainly on the characteristics of contact person, the definition of super-spreading used in the study may not show true heterogeneity in *Mtb* transmission [35]. In the current study, we present a deterministic compartmental *Mtb* transmission model that incorporates three levels of TB patients' infectivity, namely non-spreaders, low-spreaders and super-spreaders. Using this framework, we analysed how infectiousness heterogeneity affects disease dynamics and evaluated the effectiveness of a hypothetical active case finding intervention and the impact of targeting super-spreaders.

Methods

Literature review

Before constructing our model, we systematically reviewed how previous TB models have approached heterogeneous infectiousness [36]. In the review, we found that TB models frequently stratified the active TB compartment according to one or more patient-related factors. We constructed a flexible model with three levels of infectiousness, without restricting to a given factor, and the ability to transition between these levels using empirical measures of heterogeneous infectiousness to parametrise the model.

Empiric data

Data from the VTP which are stored by the Victorian Department of Health and Human Services (DHHS) were used for the following analysis. Index patients were classified as confirmed cases of TB notified from 1 January 2005 to 31 December 2015 in residents of Victoria. The data set includes contact tracing information and results of testing for *Mtb*

infection, with cases of subsequent active TB disease linked to these contact episodes now extending to March 2017 (see [37] for earlier publication of linkage process). We constructed empirical offspring distributions from the detailed contact tracing data set of the VTP.

Ethical approval was obtained from Monash University, Human Research Ethics Committee (Project Number: 7776) and permission was given by the VTP and DHHS.

Model structure

Using ordinary differential equations (ODE), we constructed a deterministic model of *Mtb* transmission in a hypothetical high TB burden setting. To represent heterogeneous infectiousness and super-spreading in *Mtb* transmission, we stratified the active TB compartment into three sub-classes with different levels of infectiousness: non-spreaders (I_0), low-spreaders (I_1) and super-spreaders (I_2). We did not use any specific factor to discriminate I_0 , I_1 and I_2 a priori. Instead, we use the offspring data (number of secondary infections per index) and a Bayesian approach to find the most realistic parameterisation to implement heterogeneous infectiousness in our model.

Fig 1 presents the model structure. The model simulates a closed population, such that births (π) accrue into the fully susceptible compartment (S) to replace all deaths. Natural death occurs from all compartments at a constant rate (μ). Susceptible individuals are dynamically infected, with the force of infection (λ) contributed by super-spreaders and low-spreaders. Following infection, individuals enter a rapid-sojourn early latent compartment (L_A), from which they may progress to one of the three active TB compartments (I_0 , I_1 or I_2) at a total rate of ϵ or enter the low-risk late latent stage (L_B) at rate κ . From the late latent state they may progress more slowly to disease (total rate ν), also entering the active TB compartments (I_0 , I_1 or I_2). Re-infection may occur during late latency with a reduced force of infection λ_r ($\lambda_r = r \times \lambda$) and, if re-infection occurs, these individuals similarly enter the early latent compartment,

progressing to the disease at the same rates as for newly infected persons. Individuals with active disease may either die due to TB (rate μ_i) or background mortality (μ); or spontaneously recover and return to the late latent state (rate γ); or be detected and treated by the health system (rate δ) and return to the susceptible compartment (S).

Fig 1: Transmission dynamic model of TB with heterogeneous infectiousness. Boxes represent compartments in the model and arrows represent flows. Not shown here but included in the model are natural mortality from each compartment and TB-related mortality from each active TB compartment (I_0 , I_1 and I_2). Red arrows represent transmission flows; black arrows represent disease progression processes; green arrows represent self-recovery, blue arrows represent detection and treatment cure.

Estimation of the infectiousness parameters using empiric evidence

The four model parameters that capture heterogeneous infectiousness in the model were the proportions of non-spreaders, low-spreaders and super-spreaders, and the relative infectiousness of super-spreaders compared to low-spreaders. In order to estimate these parameters, we first determined the statistical distribution of the number of secondary infections per index associated with the stochastic equivalent (continuous-time Markov) model of our ODE-based model. We obtained a mixture of three classic statistical distributions: two geometric distributions for low-spreaders and super-spreaders and one Dirac delta distribution for non-spreaders. A detailed demonstration of this result is provided in the **Supplementary Material**.

A Hamiltonian Monte Carlo (HMC) algorithm was used to generate 20,000 samples from the posterior distributions of the parameters. The 20,000 samples used for inference were obtained from 40,000 iterations of the HMC, burning the first 20,000 draws. Burn-in size and convergence were assessed by inspecting the trace plots of the estimated parameters. The

168 reported 95% credible intervals were obtained by computing the 2.5th and 97.5th percentiles of
169 the parameters' posterior distributions. The parameter estimates from the Bayesian process is
170 provided in **Supplementary fig.1**.

171 The resulting statistical distribution was then compared in a Bayesian context with empiric
172 data obtained from our previous analysis of TB contact tracing data in the Australian state of
173 Victoria [9]. A comparison between the distribution of the number of secondary infections
174 per index simulated by our calibrated model with the one observed empirically is presented in
175 Fig 2.

176 The parameter values other than those pertaining to infectiousness introduced above were
177 estimated from a review of relevant evidence, with the relevant sources presented in **Table 1**.

178 *Fig 2. Comparison of the effective modelled secondary infection distribution with empiric*
179 *data from Victoria, Australia (red points represent the modelled distribution while blue*
180 *points are observed empiric data).*

181 Model calibration

182 For the baseline equilibrium state, the ODE model was calibrated to a high TB burden
183 settings with an incidence rate of 200 per 100,000 population per year by adjusting the
184 transmission rate parameter for low-spreaders.

185 The model was programmed in R 3.4.0 (R Project for Statistical Computing), and we used a
186 package called 'deSolve', solver for initial value problems of ODE [38, 39]. The Bayesian
187 parameter estimation was done using the package 'rstan' (v.2.18.2) [40] and the source code
188 for the model is publicly available from https://github.com/Yayehirad/TB_heterogeneity

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191Table 1: Model parameter values

Corresponding model parameter	Symbol	Base model value	Uncertainty range	Source
Natural mortality rate, per year	μ	0.0154	0.0133 - 0.0182	[41]
Rate of early progression, per year	ε	0.401	0.307 - 0.548	[42]
Rate of progression to late latency after infection, per year	κ	3.599	3.452- 3.693	[42]
Rate of late progression, per year	ν	0.002	0.0009 - 0.004	[42]
Average duration of infectiousness, years	D	3	2-4	[43]
TB-related mortality among Super-spreaders, proportion	μ_{12}	0.534	0.327 - 0.78	[43, 44]
TB-case fatality among low-spreaders, proportion	μ_{11}	0.077	0.077 - 0.096	
TB-case fatality among non-spreaders, proportion	μ_{10}	0.077	0.077 - 0.096	
Conversion from non-infectious to low-spreaders, proportion	h	0.014	0 - 0.06	[32, 45]
Conversion from low-spreaders to super-spreaders, proportion	j	0.014	0 - 0.06	Assumed
Relative reduction in force of re-infection compared to new infection	r	0.21	0.15 - 0.4	[46]
Parameters calibrated from data				
Proportion of infectious among all TB		0.42	0.39 - 0.46	Estimated from data [9]
Proportion of in super-spreaders among infectious		0.18	0.1 - 0.29	Estimated from data [9]
Transmission rate per low-spreader per-year	β_1	12	10 - 15	Calibrated
Relative infectiousness of super-spreaders compared to low-spreaders	m	4.67	3.69 - 5.88	Estimated from data [9]
Intervention parameters				
Baseline case detection rate, proportion	CDR	0.65	0.5 - 0.75	Assumed
Intervention (proportion of missed cases detected)	q	0.2	0 - 0.4	Assumed
Proportion of intervention targeted to super-spreaders	d	0.5	0 - 1.0	Assumed

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193Sensitivity analysis

194We first performed a one-way sensitivity analysis on each parameter to understand the
195sensitivity of equilibrium incidence to parameter ranges in the absence of interventions. We
196then undertook multidimensional sensitivity analyses to assess the correlation between
197equilibrium incidence and each parameter by taking 1000 samples from each parameter
198ranges with Latin hypercube sampling (LHS) technique [47, 48].

199 Intervention simulations

200 We simulated an intervention intended to represent active case finding with a point-of-care
 201 diagnostic tool, accelerating successful diagnosis and treatment of individuals as early as
 202 possible before they start transmitting the infection. This could be conceptually considered as
 203 implemented by a highly sensitive point-of-care diagnostic technology following community
 204 awareness campaigns that target individuals with noticeable symptoms in order to increase
 205 their rate of presentation [49]. To target the intervention, clinical symptoms and behavioural
 206 characteristics can be used to identify those individuals who are more likely to be super-
 207 spreaders.

208 We implemented an intervention capable of finding q proportion of TB cases that would
 209 otherwise remain undetected by the passive case detection process:

210 i.e. $CDR_{intervention} = q \times (1 - CDR_{baseline}) + CDR_{baseline}$, where, CDR is the case detection rate,
 211 being the proportion of all cases detected during their disease episode and q is the proportion
 212 of cases detected under the intervention scenario that would otherwise be missed by the
 213 baseline CDR. We set the maximum attainable level of CDR in all intervention scenarios
 214 including targeting super-spreaders at 90%. In targeting the intervention towards super-
 215 spreaders, the maximum possible CDR targeted to super-spreaders under the intervention
 216 occurs when the CDR for non-spreaders and low-spreaders is kept at the baseline. With this
 217 restriction, we defined a single parameter (d) to represent the extent of intervention targeting
 218 relative to the maximum amount of targeting possible, which ranges from zero to one, with
 219 zero representing untargeted intervention and one representing 100% targeting. That is, the
 220 CDR targeted to super-spreaders under the intervention scenario was $CDR_{intervention}$ plus d
 221 multiplied by the difference between the maximum possible CDR and $CDR_{intervention}$. This

implementation ensures equivalent effort or the number of people treated for untargeted and targeted interventions; details of these calculations are given in the *Supplementary Material*. We then evaluated the effectiveness of targeting super-spreaders ($d > 0$) compared to untargeted intervention ($d = 0$) in four independent scenarios. These four scenarios were settings with high transmission and high case detection, high transmission and low case detection, low transmission and high case detection, and low transmission and low case detection. These four scenarios were simulated by calibrating the transmission parameter for low-spreaders and CDR. In addition, we evaluated the impact of levels of targeting (d) for different coverage levels of the intervention (q) in these four setting scenarios, while other model parameters were sampled from the same plausible ranges as in the baseline sensitivity analysis using LHS.

Results

Baseline sensitivity analyses

The sensitivity analyses show that the most marked impact on equilibrium incidence arose from the rate of late TB progression followed by the CDR (**Fig 3**). The proportion of super-spreaders among persons with infectious TB and the relative infectiousness of super-spreaders compared to low-spreaders also had a substantial impact. **Supplementary Fig 2** presents a multidimensional sensitivity analysis, using the LHS method to sample 1000 parameter sets, which was consistent with the results of the one-way sensitivity analysis.

Fig 3: One-way sensitivity analyses of equilibrium TB incidence to variation between extremes of plausible parameter values. Maximum and minimum parameter values are given in Table 1. Values on the x-axis represent the equilibrium TB incidence, and the vertical line indicates the equilibrium incidence obtained with the baseline parameter set.

245 Impact of targeted interventions

246 Targeting the active case finding intervention towards super-spreaders was more effective
 247 than mass intervention in all setting scenarios. However, its effectiveness was particularly
 248 marked in settings with low case detection, regardless of transmission rates. For example, in
 249 the first scenario of both high transmission and high CDR, a 20% untargeted active case
 250 finding intervention led to a 22.8% reduction in incidence over 20 years, while with an 80%
 251 targeting an equal active case finding intervention resulted in a 35.9% reduction in TB
 252 incidence over the same period. However, in the scenario of high transmission but low CDR,
 253 the targeted intervention is much more effective (achieving a 42.2% reduction) than the
 254 untargeted intervention, which only reduced incidence by 22.8% over 20 years, considering a
 255 20% active case finding and an 80% level of targeting. Interventions in settings of low
 256 transmission and high case detection rates had a relatively minor impact on the burden
 257 (*Supplementary Fig. 3*).

258 We evaluated the impact of intensifying active case finding (q) from zero to 40% detection
 259 and varying the proportion of this intervention targeting the super-spreaders (d). As shown in
 260 **Fig 4**, both these quantities are essential – i.e. the increase in CDR and the extent of targeting
 261 provided the increase in CDR is more than negligible. The most significant impact of
 262 targeting was in the setting of high transmission and low CDR at all coverage levels of the
 263 intervention. Targeting super-spreaders was more effective at all levels of relative CDR
 264 increases in settings with high transmission and low case detection (Panel B), while in
 265 settings with high transmission and high case detection, targeting super-spreaders has a
 266 significant effect if the relative increase in CDR is low (Panel A).

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Fig 4: Comparison of extent of active case finding and the proportion of targeting to super-spreaders on the 20-year projected relative reduction in TB incidence under the four scenarios. A) High transmission and high case detection setting; B) high transmission and low case detection; C) low transmission and high case detection; D) low transmission and low case detection.

Fig 5 presents the results of the one-way sensitivity analysis performed to observe the impact of high and low extremes of parameter values on the intervention's 20-year projected relative incidence reduction. The sensitivity analyses show that the most marked impact on intervention effectiveness arose from the rate of late progression, followed by the rate of early progression and the proportion of super-spreaders. Notably, while higher rates of late progression were correlated with lower effectiveness of the active case finding intervention, higher rates of early progression resulted in greater reductions in the incidence.

Supplementary fig 4 presents the results of the multidimensional sensitivity analyses assessing the impact of parameter ranges on intervention effectiveness (relative reduction in annual incidence with 20-years projections). This multidimensional analysis supports the results of the one-way sensitivity analysis: that the proportion of super-spreaders had a considerable impact on intervention effectiveness, and was the most important parameter after the disease progression parameters.

Fig 5: One-way sensitivity analyses of 20-year projected relative reduction in incidence to variation between extremes of plausible parameter values. The maximum and minimum parameter values are given in Table 1. Values on the x-axis represent the relative reduction in incidence following the implementation of a 20% active case finding intervention with 80% targeting. The vertical line indicates the relative reduction in incidence obtained with the baseline parameter set.

293 Discussion

294 Our model suggested that targeted active case finding interventions directed toward people
 295 likely to be super-spreaders could have a substantial impact on the TB burden, particularly in
 296 settings with high transmission but low case detection rates. This model also showed that
 297 parameters related to infectiousness heterogeneity such as the proportion of super-spreaders
 298 and their relative infectiousness compared to other low-spreaders were as crucial as other
 299 previously recognised epidemiological parameters, such as the latency progression
 300 parameters, in determining the burden of TB. The current model is also able to incorporate a
 301 range of commonly used approaches to capturing heterogeneous infectiousness of active TB
 302 cases. The choice of three infectiousness levels for active TB and the values assigned to each
 303 compartment was based on empirical data estimates, strengthening the validity of our
 304 findings.

305 Active case finding has been described as “turning off the tap” in TB control intervention
 306 strategies since it represents a method of identifying individuals with TB and promptly
 307 initiating treatment to avoid further onward transmissions [50]. Previous TB modelling has
 308 suggested that active case finding with highly sensitive diagnostic tools can reduce delay to
 309 treatment and so significantly reduce TB transmission [51]. The use of point-of-care
 310 diagnostic technologies with high sensitivity to detect persons with TB soon after they begin
 311 to transmit, such as GeneXpert Omni [49], could enable the implementation of active case
 312 finding interventions similar to that considered in this study. In fact, any TB active case
 313 finding intervention necessarily incorporates some level of targeting towards the highly
 314 infectious individuals, because highly infectious patients’ disease characteristics (such as
 315 higher sputum-bacilli concentration and lung-cavitation) make them more easily detectable
 316 with existing microbiological and radiological diagnostic tools. This means that
 317 implementing more sensitive diagnostics may paradoxically decrease targeting of super-

318 spreaders – whereas traditional smear-based interventions might ensure that resources are
319 targeted to the most infectious.. In agreement with previous modelling [52], our model
320 suggested that active case finding interventions are particularly valuable in high transmission
321 and low case detection settings to limit onward transmission. In the implementation of the
322 intervention, although we did not perform cost-effectiveness analyses, our study shows that
323 finding super-spreaders (less than 10% of all TB cases) is equally as effective
324 epidemiologically as finding 40% of general TB population. In addition, the cost of
325 identifying and treating super-spreaders that only comprises less than 10% of total TB cases
326 can be compared with the cost of treating all active TB cases in a population. Our findings
327 concerning the effectiveness of interventions can provide broad directions to future TB
328 modellers and policymakers, although predictions from our model are not intended to provide
329 location-specific estimates.

330 Our sensitivity analyses showed that a higher late reactivation rate had a negative impact on
331 the effectiveness of active case finding interventions, while higher rates of early progression
332 increased the impact on the 20-year projected reduction of incidence following the
333 intervention. This suggests that active case finding interventions are more effective if the TB
334 epidemic is more dependent on early progression and intense recent transmission than late
335 TB reactivation since the intervention would have a more significant effect on rapidly
336 reducing transmission. A recent study showed that variation in the latency progression
337 parameters had important impacts on model predictions around the effectiveness of
338 preventive therapy interventions [53], while our analysis complements this finding by
339 showing that these parameter variations also have indispensable effects on predictions
340 regarding the effectiveness of case-finding interventions.

341 In our analyses, the rate of conversion from low-spreader to super-spreader had little
342 significance, and impact of the rate of conversion from non-infectious to low-spreaders was

negligible. It is known that active TB cases' ability to spread *Mtb* may increase as they progress clinically to more severe disease, e.g. from smear-negative to smear-positive or from non-cavitary to cavitary-TB [54]. In previous TB models, spontaneous conversion from less infectious to more infectious states such as smear-negative to smear-positive was included with rates around 1.5% per year [18, 25, 32, 45, 55-57]. These parameters do not affect model outputs substantially, such that they can be omitted for model simplicity if the actual values are consistent with what has previously been assumed. Nevertheless, the exact values of these quantities remain uncertain, and future research to refine these quantities may modify this conclusion.

The current model structure enhances flexibility around the assumption of infectiousness heterogeneity that allowed for reflection of a broad range of factors that can alter active TB cases infectivity level [5, 58]. Thus, the model is able to incorporate many previous compartmental modelling structural approaches, including those that stratified active TB cases' infectivity into two levels, as non-infectious and infectious [13-17], or model structures that incorporate three levels of infectivity, as non-infectious, smear-negative infectious and smear-positive infectious [30, 31, 59]. However, in the application of this model to a particular epidemiological setting, data to estimate the proportion of super-spreaders is essential, since this information has a particularly marked impact on both baseline disease burden and intervention effectiveness.

We used empirical data to parameterise our model, but a noteworthy limitation is that these results may not be generalizable to other settings. However, we are not aware of any past work that has used empiric data to inform model parameters on the proportions of infectious TB and super-spreaders at all. As with any model-based analyses, our study has limitations that arise from its assumptions. In addition to those introduced above, our model is not intended to represent a specific setting, and as such does not incorporate stratification by age,

HIV or multidrug-resistant TB. The other limitation is that we used a very simplified implementation of an active case finding intervention with a theoretical point-of-care diagnostic tool, without considering all the complexities in TB diagnosis and treatment implementation.

Conclusions

The approaches we used to inform model parameters related to infectiousness heterogeneity from the observed distribution of secondary infections can be useful for future modelling studies of TB, in particular, and other infectious diseases, in general. The principles of implementation could be used in future TB modelling studies that represent specific epidemiological settings, especially when TB contact investigation data are available to estimate the proportion of super-spreaders. In the usage of advanced point-of-care technologies, targeting active case-finding interventions to super-spreaders is likely to be especially beneficial in low CDR settings.

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Availability of data and materials

The R-code used to analyse this model is publicly available.

Authors' contributions

390YAM, RR and JMT conceived the study. YAM developed structure and ODE of the model,
391which was reviewed by JMT and RR. ESM, ACA, JMT conceived the strategy of the
392intervention in the model. YAM coded the model in R that RR and JMT reviewed and
393evaluated. YAM drafted the manuscript, and all authors provided input into revisions and
394approved the final draft for submission.

395Ethics approval and consent to participate

396Not applicable

397Consent for publication

398Not applicable

399Competing interests

400The authors declare that they have no competing interests.

401Supplementary material

402Supplementary Material. doc

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Fig 1: Transmission dynamic model of TB with heterogeneous in

Fig 2: Comparison of the effective modelled secondary infe

Fig 3: One-way sensitivity analyses of equilibrium TB incidence to

Fig 4: Comparison of extent of active case finding a

Fig 5: One-way sensitivity analyses of 20-year projected relative