AN AGENT-BASED SIMULATION OF A TUBERCULOSIS EPIDEMIC: UNDERSTANDING THE TIMING OF TRANSMISSION

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ABSTRACT

Tuberculosis (TB) transmission is a key factor for disease-control policy, but the timing and distribution of transmission and the role of social contacts remain obscure. We develop an agent-based simulation of a TB epidemic in a single population, and consider a hierarchically structured contact network in three levels, typical of airborne diseases. The parameters are adopted from the literature, and the model is calibrated to a setting of high TB incidence. We model the dynamics of transmission at the individual level, and study the timing of secondary infections from a single source throughout the duration of the disease. We compare the patterns of transmission among different networks and discuss implications. Sensitivity analysis of outputs indicates the robustness of the results to variations in the parameter values.

1 INTRODUCTION

New and re-emerging infectious diseases pose an enormous burden on global health, and massive effort has been put into combating them. As an example, TB is a contagious bacterial infection responsible for 1.4 million deaths each year. About one third of the world's population is infected with TB, and close to 9 million new TB cases occur each year (CORE Group 2006). Despite the vast literature and ongoing research on disease evolution, however, our understanding of the transmission dynamics is incomplete, and many questions remain unanswered (Dowdy, Dye, and Cohen 2012).

TB is an airborne disease transmitted through infectious contact with an active case. TB transmission is one of the key determinants of epidemic severity, and has important implications for design, implementation, and scaling-up of control interventions (e.g., improved diagnosis, active case finding) that aim to reduce the rate of transmission. Unlike other airborne diseases such as influenza, however, TB transmission is not directly measurable, i.e., available diagnostic techniques cannot estimate the original timing of infection in diagnosed cases. TB also has a predilection for establishment of a latent state that is non-infectious and asymptomatic, but may progress to active, infectious disease at any time. As a result, one cannot reliably differentiate between primary infection with rapid progression to active disease, re-infection following a remote initial infection, or reactivation of a previous latent infection. Such limitations pose several challenges to the study of transmission dynamics across populations, including

the lack of informative data to trace the chain of transmission across various contact networks in retrospective studies. The prospective following a cohort population, on the other hand, are prohibitively expensive and restricted by the time and budget constraints. In such settings, the relationships between the duration of disease, symptom burden, contact networks, diagnosis/treatment, and patients' infectiousness remain obscure (Dowdy, Dye, and Cohen 2012).

We propose an *agent-based simulation* (ABS) to study TB transmission dynamics and the role of various contact networks. Our model simulates the course of a TB epidemic across a single population and uses a hierarchical network of contacts in three levels, typical to the transmission of airborne diseases (Mossong et al. 2005). Parameters are chosen from the literature, and the model is calibrated to a setting of high TB incidence. We use our model to study the transmission dynamics at an individual level with regard to the timing and distribution of secondary infections from a single source. The average time for disease diffusion to reach 50% of infections at an individual level is estimated, and the timing patterns are compared among different networks. We perform sensitivity analysis of results with regard to multiple parameter values, and discuss the implications for TB control policy.

2 BACKGROUND

Modeling TB dynamics has a long history, including mathematical models and analytical techniques to describe and predict disease prevalence at the population level (Waaler, Gese, and Anderson 1962; Porco and Blower 1998; Castillo-Chavez and Song 2004). Analytical studies, however, are usually restricted by their simplifying assumptions regarding the population heterogeneity, network structure, and parameters uncertainty, and do not provide a realistic representation of transmission dynamics.

Simulation modeling of TB epidemics in human populations, on the other hand, has a shorter history. One group of studies uses *system dynamics* to model disease prevalence at the population level (Brewer et al. 1996; Atun et al. 2007). Following a top-down approach, these studies divide the population into different health states, and use transition rates to describe the disease's natural history. A system of differential equations is used to model disease prevalence through time. In comparison to the analytical approach, such studies apply a semi-Markov system in which transition rates can change with time, and are able to capture output uncertainty.

Other researchers have developed *discrete-event simulation* (DES) models of TB to evaluate the impact of new diagnostic tools (Langley et al. 2012), or to study more complex structure as in the coinfection of HIV/TB (Hughes, Currie, and Corbett 2006; Mellor, Currie, and Corbett 2011). The DES studies use a schedule of events that are executed in chronological order, and model disease transmission using random generation of Poisson distributions in each mixing group. The aggregate (top-bottom) modeling nature of DES, however, offers low flexibility for direct modeling of contacts (and transmission events) at the individual level, and restricts application of such models to complex social networks.

ABS is an alternative approach that models the system at the individual level and offers high flexibility to incorporate various modeling assumptions. ABS models have wide application in the social sciences (Epstein 1999, Macal and North 2010), and the models have been applied to study various infectious diseases such as influenza (Chao et al. 2010), smallpox (Longini et al. 2006), and HIV/AIDS (Alam, Meyer, and Norling 2008). The literature on application of ABS models in the study of TB, however, is quite limited. Espindola et al. (2011) use an ABS approach to study the emergence of drug-resistant TB due to treatment with antibiotics. They assume a lattice structure for spatial presentation of their population and model TB transmission through local and global interactions across the lattice. The lattice structure, however, does not provide a realistic representation of social settings and cannot be used to study transmission dynamics at the individual level.

We consider a model of transmission involving three contact networks that represent the main social relationships in transmission of an airborne disease. Our model simulates the stochastic contact events at an individual level, and enables us to study patterns of transmission across different networks.

3 METHOD

Agents represent people in the population whose personal characteristics, social relationships, and health states are programmed at the individual level (Figure 1). The model initiates from an existing epidemic and is calibrated to a setting of high TB incidence. The model is developed using Anylogic (XJ Technologies 2012) and the extensions are coded in Java. A time step of one month is chosen to update the contact networks and model the transmission events, while the internal simulation time-step is very small (0.001 month) and the population dynamics are simulated on a closely continuous time-scale. Outputs are gathered at the end of each year, and the time horizon is 50 years. In this section, we briefly describe the model's population structure, contact network, and natural history of TB, and discuss our calibration procedure.
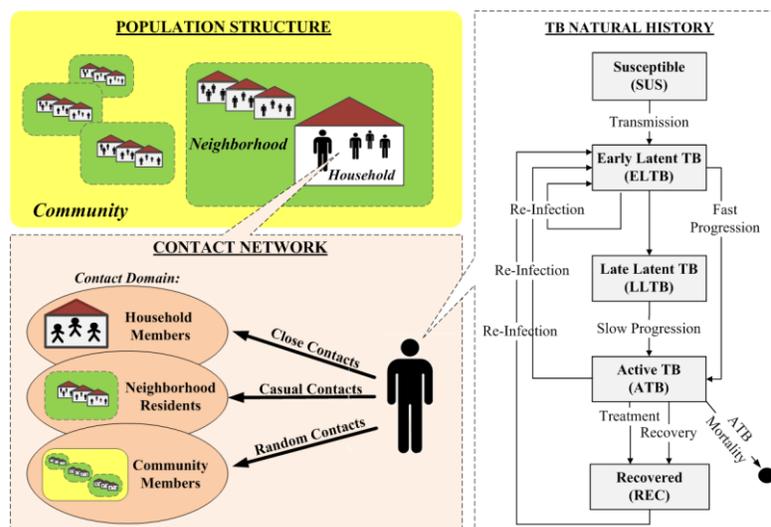

Figure 1: ABS model outline.

3.1 Population Structure

Following the literature on modeling of airborne infectious diseases (Raffalli, Sepkowitz, and Armstrong 1996) and using a similar approach to Chao et al. (2010), we consider a hierarchically structured population including households, neighborhoods (clusters of households) and communities (sets of neighborhoods). While the exact definition and size of these mixing groups are chosen arbitrarily, their inclusion in the model provides a realistic representation of the population structure, and enables us to model different transmission routes associated with each mixing group.

A household is the smallest and most intimate mixing group for transmission of airborne diseases (Verver et al. 2004; Chao et al. 2010). We assume that household size follows a triangular distribution, ranging from 1 to 10 with a mode of 5 people per family, which corresponds to low socioeconomic status typical of the high-incidence TB settings in India and Brazil. The natural mortality rate is defined at the individual level, and corresponds to a life expectancy of 73 years (Google 2010). We define the probability of child bearing for each family as a decreasing function of the family size such that the average population size remains constant, and the initial household-size distribution keeps its shape through the simulation (see Appendix A).

3.2 TB Natural History

We model TB natural history at the individual level using the five main TB health states (Figure 1). A person is assumed born in full health and susceptible to TB. Upon a successful transmission of the dis-

ease, the person enters the *early latent TB* (ELTB) state for a period of five years, during which he endures a high chance of active TB development (*fast progression rate*). At the end of this period, the individual enters the *late latent TB* (LLTB) state, which can last for many years, and is associated with a much lower chance of symptom development (*slow progression rate*). Symptomatic patients with *active TB* (ATB) are infectious and subject to an increased mortality rate. The ATB patients' infectiousness is modeled as a linear function of time, increasing during the first nine months of the disease from zero to a maximum infectiousness of I_{max}, and staying unchanged for the rest of the disease. The I_{max} value is subsequently calibrated to the overall incidence rate (Section 3.4).

Active cases become recovered through spontaneous recovery or upon diagnosis and treatment. Recovered and latently infected individuals are subject to multiple re-infections, upon which they return to the ELTB state. Table 1 shows the disease parameters and their values.

Table 1: Parameters and Values

Parameter	Value	Source/ Justification
Population structure:		
Number of neighborhoods (Number of families per neighborhood)	50 (40)	Calibrated to provide the mean number of contacts in each group (Appendix B)
Initial household-size distribution	Triangular (1,5,10)	(United Nations Data System 2013)
Life expectancy	73 years	(Google 2010)
Disease Natural History:		
ATB mortality rate	0.12 per year	(Tiemersma et al. 2011)
Early latency duration	5 years	(Dowdy et al. 2012)
Fast progression rate	0.03 per year	(Vynnycky and Fine 1997)
Slow progression rate	0.005 per year	(Horsburgh 2004)
Recovery rate	0.12 per year	(Tiemersma et al. 2011)
Diagnosis &treatment rate	0.74 per year	Calibrated to provide disease duration of 11 months (WHO 2012)
Latent immunity toward re-infection	0.8	(Andrews et al. 2012)

3.3 Contact Network

We define a three-layer contact network in association with our hierarchical population structure, referred to as *close*, *casual*, and *random* contacts. This is only an abstract representation of real social settings, but the lack of data on TB transmission restricts our ability to use a more sophisticated network. Nevertheless, the three-layer mixing structure enables us to represent the important routes of transmission detected in past TB breakouts (Raffalli, Sepkowitz, and Armstrong 1996; Classen et al. 1999), and contrast the dynamics of transmission over each network.

The three contact types represent the social relationships of any individual with the rest of the population (Figure 1). Each type is defined over a specific domain and among a sub-group of the population (e.g. household members). The individual's probability of engaging in a contact and the contact domain's size are calibrated to the average number of contacts in each network (Mossong et al. 2005). The contact duration (time delay between network updates representing the persistency of the social bounds) is chosen with regard to the definition of each category (e.g. close contacts are the most persistent type). Contact types are further differentiated by the effectiveness of contacts in transmission of the TB pathogen. The effectiveness parameters are calibrated to provide the given ratios of infections through each network (see Section 3.4). The infectious contacts are modeled at each time step, and the probability of disease transmission is computed with regard to the individual's infectiousness, immunity, and effectiveness of contact type.

Close contacts, at the first level, represent the most frequent contact type among household members. On the second level, casual contacts model social relationships such as those among friends at a bar, neighbors at a store, or children at school. These contacts are less frequent and intimate than close contacts, and restricted to a specific network of related individuals including friends, coworkers, etc. (Raffalli, Sepkowitz, and Armstrong 1996; Classen et al. 1999). We restrict the domain of casual contacts to each neighborhood's residents, and assume a limited period of one year for the duration of contacts (Appendix B). Finally, random contacts are used to model encounters of people at places such as bus stops, museums, etc. Such contacts have the shortest duration (one month), and account for potential risk of transmission among non-related people in the whole community.

The suggested network structure can be further extended to a more detailed network (involving additional mixing groups such as schools, work places, etc.) so that it provides a more realistic view of social settings. The trade-off for developing such models, however, is lack of suitable data for calibration, as well as the computational expense of more extensive simulation runs.

3.4   Calibration

We model a community of 2000 households in 50 neighborhoods. The community size and its composition is tuned to provide the average number of contacts in each mixing group as described in Appendix B. Individuals are subject to a mortality rate so that some families may eventually die out from the model. We tune the probability of child bearing for each family such that the average population size remains constant (10200 people), and the initial family-size distribution keeps a stable shape through time (see Appendix A). The model is initiated from an existing epidemic, and is calibrated to provide an incidence rate of 120 per 100,000 people/year, representative of the current global TB incidence rate (WHO 2012).

In order to ensure the fidelity of the ABS model, we use a simplified instance of the simulation model with homogenous mixing structure as a benchmark, and align this model against a corresponding deterministic model of TB (Appendix C). Except for the subtle variation of simulation outputs due to stochasticity, the timing pattern and estimated values of compartment sizes at steady state are similar. Consequently, we extend the verified homogenous model to incorporate the heterogeneous network structure, and continue our analysis with this model.

Figure 2 shows the main ABS outputs over 150 years. The *external infection ratio* represents the proportion of disease incidence due to reactivation or progression among individuals who were latently infected at time zero (as a part of the existing epidemic). Since such infections did not originate within the simulation period, they cannot be used for the analysis of transmission. Moreover, due to the stochastic nature of the simulation model and disease dynamics, the annual incidence rate shows a non-stationary pattern during the first decades. We choose the simulation transient period such that the external infection ratio is less than 5%, and the incidence rate has a stationary mean. We test the external infection ratio mean using a one-tailed t-test, and test the stationarity using multiple comparison tests of the incidence mean in consecutive 5-year periods after the transient time (using Bonferroni-adjusted paired t-tests). Consequently, we choose a transient period of 100 years for the simulation model, and start our analysis of the output in year 101.
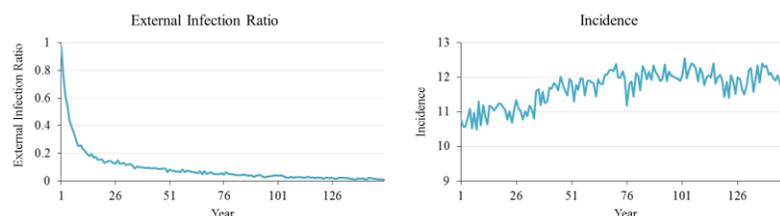

Figure 2: ABS output patterns.

Furthermore, we follow the literature on the proportion of TB transmissions in different social settings, and let close contacts account for 20% of transmissions (Verver et al. 2004) while casual contacts account for 60% of transmission corresponding to 75% of non-household infections (Classen et al. 1999). The effectiveness parameters for each contact type are subsequently calibrated to provide the specified transmission ratios (Table 1).The main outputs of the simulation model including the disease progression measures are provided in Appendix D.

4   RESULTS

We use the calibrated ABS model to study the dynamics of transmission at the individual level and estimate the timing of secondary infections from a single source during the course of the disease. Figure 3a shows the average frequency of infections from a single individual with active TB throughout the course of infectiousness (i.e., from onset of infectiousness, defined as time zero, to treatment or death, the timing of which varies across individuals). The three curves are stratified by the type of contact, and show a similar general pattern: increasing during the initial months as the infectiousness increases, and then decreasing as the infectiousness period ends (e.g., due to recovery). In these figures, the maximum frequency of infections reflects the proportion of transmission due to each type of contact (e.g., higher peak for casual contacts reflects our model assumption that these contacts are responsible for more transmission events than close or random contacts). The different shapes of these curves, however, demonstrate that transmission due to close contact occurs earlier in the course of infection and declines more rapidly over time such that, among individuals with very long periods of infectiousness, random contacts actually become more important sources of transmission than close (household) contacts.

Figure 3b shows the cumulative ratio of infections in each network: half of all transmission events due to close contacts occur within the first 9 months of infectiousness, whereas only about 35% of transmission to non-household contacts has occurred by that time. Such differences can be partially explained with regard to the relative size of each network and development of immunological protection from repeat infections after initial infection, which limits the number of potential infections. The timing of transmission to casual versus random contacts is remarkably similar, suggesting that, once contact networks reach a certain size (i.e., low probability of reinfection), the timing of infection approaches a limiting shape regardless of the assumed duration and intensity of the contact network.
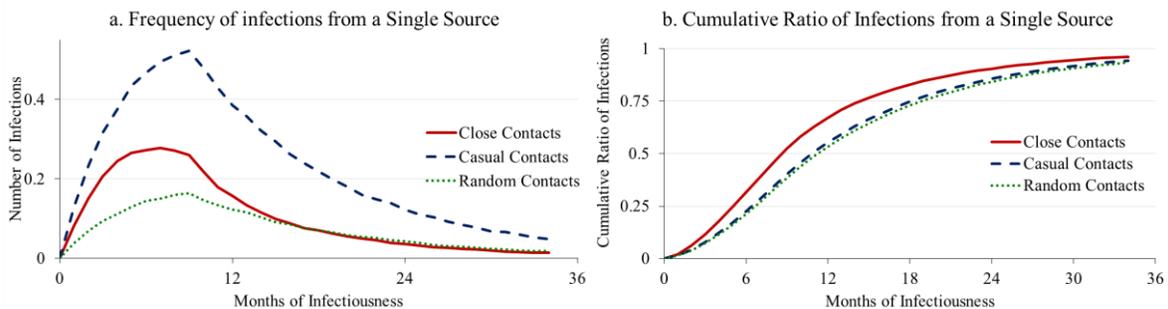

Figure 3: Timing of secondary infections from a single source.

Figure 4 shows the distribution of secondary infections in each network, stratified by type of transmission to an uninfected individual (*new infection*), versus a previously infected individual (*re-infection*). New infections show the earliest increase among close contacts due to the high frequency of household contacts. However, as more household members become infected, the number of new infections rapidly declines, and the number of re-infections increases, such that more household infections represent re-infections than new infections after about 12 months of infectiousness, and this ratio continues to grow

over time (Figure 5). In contrast, casual and random contacts rapidly reach a plateau ratio of new infections to re-infections that remains relatively low, reflecting a large pool of susceptible individuals relative to the number of transmissions occurring.
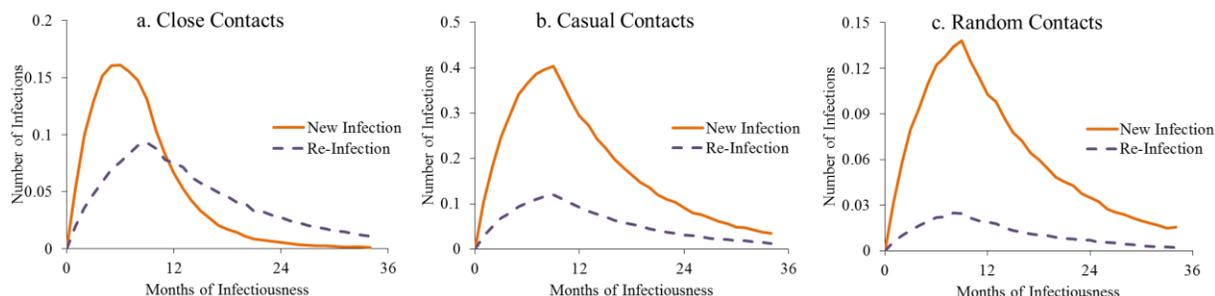

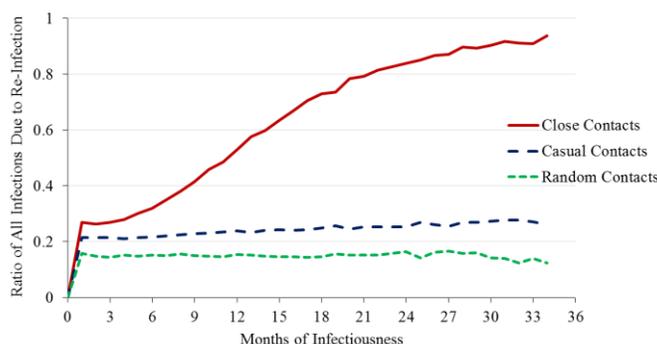Figure 4: Number of secondary infections stratified by type of infection.

Figure 5: Ratio of all infections representing re-infection.

Finally, we performed a series of one-way sensitivity analyses to ascertain the effect of varying each individual parameter on the time to reach 50% of transmissions. We varied the duration of casual contacts from 1 to 60 months, the relative sizes of non-household networks by a factor of two in either direction, and the ratio of transmissions in each network (using a three-level factorial experiment with two factors to cover various settings). In each scenario, the effectiveness of contacts were recalibrated to provide the specified ratios of transmission, and the I_{max} value is tuned to provide the incidence level of 120 per 100000/year. The results show that the time to reach 50% of transmissions is robust to wide but not-unreasonable variation of most parameters, and the only notable effect was observed from increasing the household transmission ratio to a very high level (80%), which resulted in a longer duration of 11 months to reach 50% of transmission in this network.

5   SUMMARY AND DISCUSSION

We propose an ABS approach to study the timing and distribution of TB transmissions through the course of the disease. The ABS provides a flexible yet powerful platform to model the population heterogeneity with regard to personal characteristics and different contact networks. Moreover, the ABS ability to represent the course of an epidemic at a micro (individual) level (as well as at a macro population level) enables us to estimate the timing of TB transmissions in our model.

A main implication of the timing and distribution of transmissions is for the development of TB diagnostic interventions. Our results suggest that nearly half of all TB transmissions occur after an individual

has already been infectious for over one year. Therefore, implementing systems that facilitate diagnosis and treatment of cases in the first year of disease (e.g., annual screening of target populations) can avert a substantial fraction of a population's TB transmission burden. Moreover, our results show that household (close) transmission events occur more quickly in time than transmissions to casual/random contacts. Thus, household-based interventions (e.g., contact tracing) need to occur relatively soon in the infectious course to have maximum impact, whereas population-based interventions (e.g., population screening) may still have important impact if they are widely spaced.

Finally, we detected a remarkably similar pattern for timing of transmissions between non-household contacts, suggesting that there may be a common "shape of transmission over time" outside the household; transmissions to non-household contacts may occur with roughly similar timing regardless of the intensity and duration of contact. This finding may help to simplify future efforts at TB simulation and data collection, by relaxing the requirement to define wide arrays of contact networks, focusing instead on two strata of household vs. non-household (or close vs. other) contacts.

Our work is limited by a relative lack of empirical data on TB transmission and parameter values in the associated contact networks. Our sensitivity analysis of outputs indicates a robust behavior of the results to variation of main parameter values. Nevertheless, additional studies are required to assess the impact of various network structures on timing of transmissions.

Future work include extension of the model to more realistic settings involving multiple interacting communities, age-structured populations, key risk factors (e.g., malnutrition, smoking, poverty), coinfections (especially HIV), and interventions (e.g., household contact tracing) that depend on contact networks and agent's behavior. Subsequent models can also address various policy-making issues such as optimal allocation of TB control resource among multiple populations and interventions (Kasaie and Kelton 2012a, 2012b).

A   FAMILY PROBABILITIES OF CHILD BEARING

A family's probability of child bearing at each month is defined as a decreasing function of the family size, so that the average population size remains constant, and the initial household size distribution keeps a stable shape through the course of the simulation. Using an empirical exponential function (dotted line, Figure 6) to describe the inverse relationship, we tune the individual probabilities for each family size by trial and error. Figure 6 (solid line) shows our final empirical function modeling the decreasing relationship of family size and the probability of child bearing.
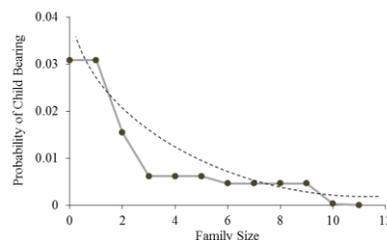

Figure 6: Probability of child bearing for families.

B   CONTACT NETWORK CALIBRATION

Transmission of TB occurs due to contact with an infectious individual, but the probability of transmission depends on several factors, including the duration of exposure, infectiousness of the case, immunity of the contacted individual, etc. Classen et al. (1999) conduct a prospective study in a high-incidence TB setting, and assess the role of social interactions in transmission of TB. Their results show that in such high-incidence areas, contacts outside of the household play an important role in transmission, and ac-

counts for 70% of transmissions. Such contacts usually take place during recreation, which in this setting consist of drinking in social groups at a local neighborhood informal bar or at people's homes.

In this sense, we define our contact network in three levels representing the close contacts inside households, and the casual and random contacts outside households. In this definition, random contacts represent short-term encounters with non-related individuals in settings such as transportation, exhibitions, etc. Casual contacts, however, represent a more stable relationship with a smaller population of friends, co-workers, neighbors, etc. who are contacted multiple times for the duration of the relationship. We allow each individual to form his or her networks of contact with a certain likelihood at each time step (e.g., a person may choose to have no random-contact at a given month), and once a network is formed, the members continue to contact each other.

In order to determine the size of each network, we refer to Mossong et al. (2008), who conducts a prospective study on mixing patterns and contact characteristics relevant to the spread of infectious disease. Their results suggest a mean value of 13.4 daily contacts for each person, with 20% of contacts' occurring at home. We therefore estimate a frequency of 11 daily contacts outside of households, corresponding to 330 contacts in each month. Consequently, we calibrate out contact network parameters as follows:

We let the likelihood of attendance represent the individual's likelihood of forming a contact network. Once a network is formed, it lasts for the duration of contact and the mutual contacts among the network members are executed at each time step. We assume that the probability of attendance in close contacts is 1 (all family members are engaged in a contact), and estimate the likelihood of attendance in casual contacts from Classen et al. (1999). Moreover, we assume that the close contacts have infinite duration (so that the family members are always in contact with each other), while the duration of casual contacts is one year (12 steps) and random contacts last for one month. With regard to the definition of each network, we restrict the domain of close contacts to household members, and casual contacts to neighborhood residents. We let the total casual and random network size be around 330 people (Mossong et al. 2005), and assign about 35% of these contacts to the casual network (Classen et al. 1999). These assumptions are then used to calibrate the number and size of neighborhoods in our model. Table 2 shows a list of network parameters and their values in the simulation model.

Table 2: List of Contact Network Parameters

Parameters	Contact Type		
	Close	Casual	Random
Domain (Average Size)	Household (5)	Neighborhood (200)	Community (10200)
Duration	Forever	1 Year	1 Month
Target Network Size	Household Size	90	210
Likelihood of Attendance	1	0.65	0.15
Estimated Network size for an Individual in Long Term	Household Size	85	230
Effectiveness of Contacts	1	0.09	0.009

C   SIMULATION ALIGNMENT AGAINST A DETERMINISTIC MODEL

We use a simplified instance of the TB ABS model with homogenous mixing, using only random contacts, and align the model against a corresponding deterministic model of TB. The models' parameters are set to the corresponding values in the main simulation model, and the contact rates are calibrated to provide the estimated TB prevalence of 112 per 100,000 person/year. Figure 7 shows the comparison of the TB compartment sizes in both models
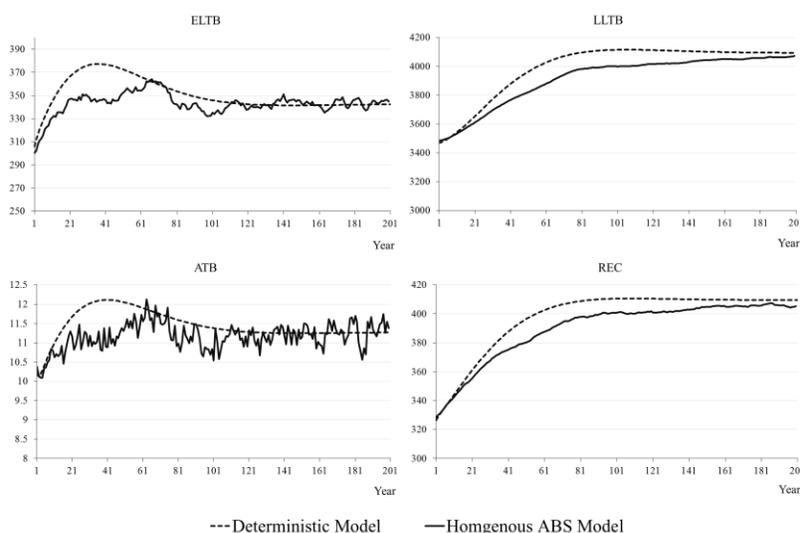
Figure 7: Aligning the homogenous ABS model against the deterministic model.

D   SIMULATION OUTPUT IN THE BASE SCENARIO

Table 3 shows the main outputs of the simulation model.

Table 3: ABS Outputs (scale people/year)

Output	Mean +/- 95% Half-Width Interval	Output	Mean +/- 95% Half-Width Interval
Incidence	12.24 +/- 0.33	Slow Progression	1.9 +/- 0.04
Prevalence	11.2 +/- 0.33	ATB Mortality	1.36 +/- 0.04
Duration	10.94 +/- 0.05	Recovery	1.34 +/- 0.04
Fast Progression	10.33 +/- 0.31	Treatment	9.37 +/- 0.26

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