Amplification Dynamics: Predicting the Effect of HIV on Tuberculosis Outbreaks

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Summary: HIV affects the pathogenesis and the transmission of *Mycobacterium tuberculosis*. We used a discrete event simulation model to predict the potential impact of HIV on increasing the probability and the expected severity of tuberculosis outbreaks. Our predictions reveal that an HIV epidemic can significantly increase the frequency and severity of tuberculosis outbreaks, but that this amplification effect of HIV on tuberculosis outbreaks is very sensitive to the tuberculosis treatment rate. At moderate or low treatment rates, even a moderate HIV epidemic can cause the average size of tuberculosis outbreaks to almost double in comparison with the expected outbreak size when HIV is absent. However, we determined that the amplification effect of HIV can be substantially reduced if the treatment rate of tuberculosis is very high. We discuss the significant implications of these results for the global control of tuberculosis. Our results also reveal that occasionally a "normal-virulence" strain of *M. tuberculosis* can be expected to generate a large outbreak. We discuss the implications of these results in understanding the virulence of *M. tuberculosis* and in the planned elimination of tuberculosis in the United States. **Key Words:** Disease outbreaks—Tuberculosis—Therapy—HIV—Prevention and control.

The size of tuberculosis outbreaks can be determined by using molecular epidemiologic data to identify which clusters of cases are infected with the same strain of *M. tuberculosis* (1–8). Analyses of typical datasets reveal that most cases of tuberculosis generate very small outbreaks and that only a few cases generate large outbreaks (Fig. 1). In fact, often the index case may not transmit the infection to any other susceptible individuals, and hence the entire "outbreak" consists of only one person (Fig. 1). The emergence of HIV has changed the epidemiology of tuberculosis, because HIV infection affects both the pathogenesis and transmission of *M. tuberculosis* (9–12). Large outbreaks of tuberculosis have arisen among people infected with HIV (3,13); hence, it has been sug-

gested that HIV has significantly increased the incidence of tuberculosis in certain locations (14–19). To quantify this potential impact of HIV, we developed a discrete event simulation model of HIV-tuberculosis epidemic amplification dynamics. We use our model to predict the effect of HIV epidemic on increasing the probability and severity of tuberculosis outbreaks. We discuss the implications of our findings for the understanding of virulence of *M. tuberculosis*, for elimination of tuberculosis in the United States and for global control of this disease.

Previously, we (20–25) and other researchers (18,19,26–30) modeled the effects of different control strategies on tuberculosis epidemics based on both chemoprophylaxis and treatment. Here, we extend our previous deterministic mathematical models of tuberculosis transmission dynamics (20–25,31,32) by including the effects of HIV on the pathogenesis and transmission of *M. tuberculosis* and stochastic effects. We used a multivariate "birth-and-death" process (33,34) that we implemented as a discrete event simulation model. This sto-
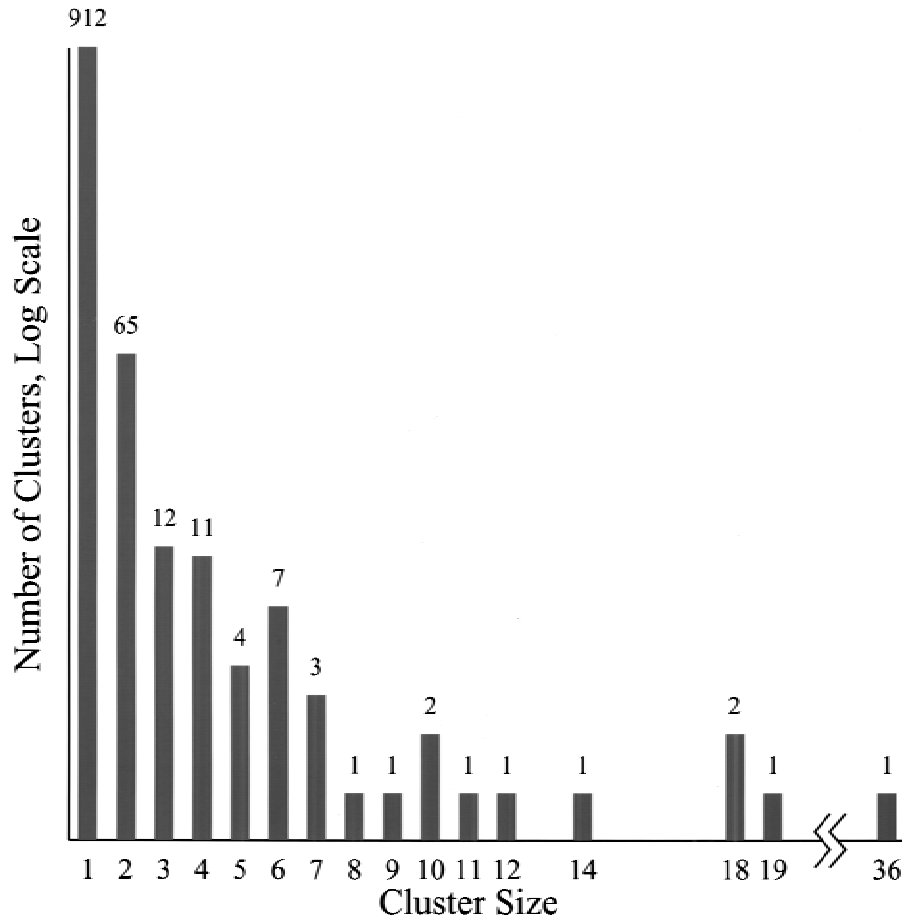
FIG. 1. Distribution of tuberculosis outbreak sizes in San Francisco, as revealed by restriction fragment length polymorphism (RFLP) analysis of *Mycobacterium tuberculosis* from cases reported in patients between 1991 and 1996. During this time, RFLP fingerprints were obtained from 87.3% of the 1569 culture-confirmed cases. The size of an outbreak is defined to be the number of people whose isolates yielded a matching RFLP pattern based on IS*6110*, and PGRS (for those isolates with five or fewer IS6110 hybridizing bands) (37).

chastic formulation enabled us to model the transmission of "normal-virulence" strains of *M. tuberculosis* but also enabled us to include random variation in the biologic and transmission properties of the "normal-virulence" strain. Thus, we modeled low genetic variability among the *M. tuberculosis* strains (i.e., we assumed that they all had the same fitness).

METHODS

Model Structure

Our model structure is shown in the form of a flow diagram in Figure 2. Individuals can be: uninfected (represented by the black circle (S_0)), infected only with HIV (represented by the four turquoise circles (S_1, S_2, S_3 and S_4)), infected only with *M. tuberculosis* (represented by the one black square (A_0) and the four black circles (B_0, C_0, D_0 and E_0)), or dually infected with both pathogens (represented by all remaining states). HIV-positive individuals are further subdivided according to their stage of HIV infection into states I, II, III, or IV according to a modified staging system of the World Health Organization (WHO) (35). Only individuals with active tuberculosis are infectious (these individuals are represented by red circles in Fig. 2) and can transmit *M. tuberculosis* to others. Infectious individuals can become noninfectious

as a result of either treatment or death. At each timepoint, individuals in any disease state can move to any of the other disease states that they are linked to by the arrows shown in the flow diagram; gray arrows represent disease progression due to HIV. Further details of the model are given in the legend for Figure 2.

Parameter Estimates

Those individuals who do not develop primary progression to tuberculosis enter a latent state (labeled D in Fig. 2) from which reactivation is possible (36). The further advanced an individual's HIV-infection, the greater is the likelihood of reactivation of tuberculosis disease (9). For individuals in advanced stages of HIV infection (stage IV), we assumed that no latent state of tuberculosis infection was possible. As an individual progresses from HIV stage I through to stage IV of infection, both the progression rate to tuberculosis and the probability of death caused by tuberculosis increases (11). The disease progression rate v_i in HIV-negative individuals and for individuals in stage I of HIV infection was 0.0002133/month, resulting in 5% of infections (over a lifetime) developing tuberculosis (31). For individuals in stages II, III, and IV, the disease progression rates were set to be 9×10^{-4}, 0.04167, and 2.0 per month. For individuals without HIV infection or those in stage I of HIV infection, few (5–10%) individuals infected with *M. tuberculosis* develop primary progressive pulmonary tuberculosis within 2 years after infection (31). HIV accelerates the progression of tuberculosis infection; thus, we assumed that the values of the prob-

ability of primary progressive tuberculosis in stages II, III, and IV of HIV infection to be 20%, 80% and 100%, respectively.

Nosocomial outbreaks of tuberculosis among severely immunocompromised patients indicate that there is a minimum incubation period (i.e., time from infection to disease) of approximately 1 month (3,11). In individuals uninfected with HIV, the minimum incubation period has been shown to be 1 to 3 months (37). To model the minimum incubation state we included a delay state; this delay state ensured that disease progression was delayed for 3 months in HIV-uninfected individuals, HIV-infected stage I or II individuals, and also for 2 months for HIV-infected stage III individuals. We modeled the rate of fast progression by the parameters γ_i (Fig. 2). We assumed, for the expected time to primary tuberculosis: 6 months for those uninfected with HIV and for HIV-infected individuals in stages I and II, 4 months for HIV-infected

individuals in stage III, and 2 months for HIV-infected individuals in stage IV (3). After individuals developed infectious tuberculosis, we assumed that each case of tuberculosis could give rise to 7 new infections per year (31).

In patients uninfected by HIV, we assumed that the mortality rate caused by tuberculosis was 13% per year (31). For individuals with advanced HIV, we used an untreated survival time with tuberculosis of 1 month (3). Intermediate values of tuberculosis mortality were used for HIV-infected stages II and III. Excess mortality resulting from untreated tuberculosis was set at 0.0116 per month for HIV-negative or HIV-positive individuals in stage I (for a mean untreated lifetime of 7.2 years neglecting HIV progression) (20). For HIV stage II individuals, the mean lifetime (neglecting HIV progression) was 3.6 years, for HIV stage III, the mean lifetime was assumed to be 2.5 months.
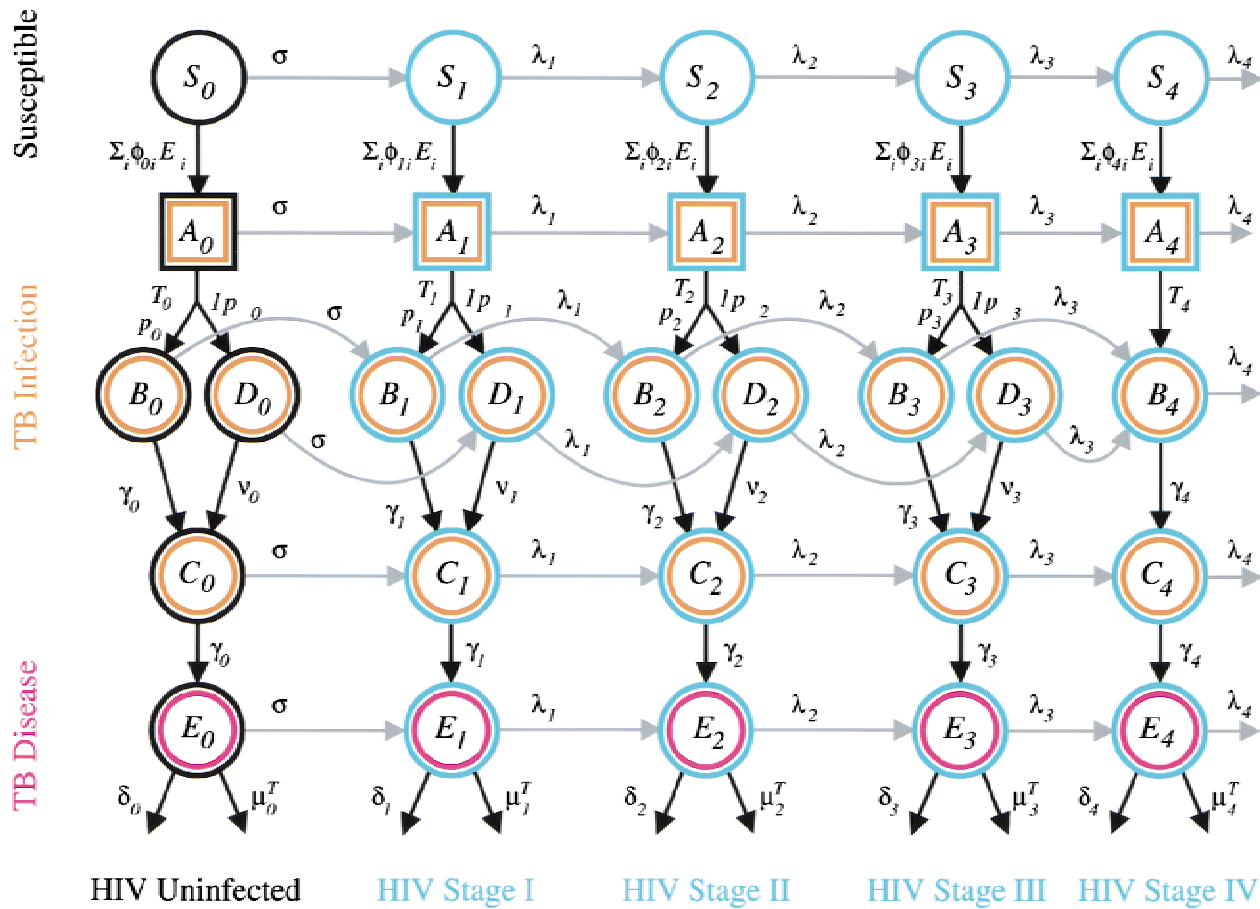

FIG. 2. Flow diagram of the stochastic model of HIV and tuberculosis amplification dynamics. *Squares* and *circles* denote states (delay and Markov, respectively) of an individual; *arrows* denote transitions between states. *Turquoise* denotes HIV-infection, *black* denotes uninfected with HIV, and a *red circle* denotes active (infectious) tuberculosis disease. Tuberculosis states are indicated alphabetically (*A*–newly infected, *B*–first intermediate state during development of primary progressive tuberculosis, *C*–intermediate state of infection before development of active disease, *D*–latent state of TB infection, and *E*–active TB). Subscripts denote HIV states (0 denotes patients uninfected with HIV; 1–4 denote the modified WHO stages of HIV-infection [35]). All states are subject to a background mortality rate μ. An individual in HIV-state i, having been infected, enters the delay state A_i; p_i denotes the probability of primary progressive tuberculosis' developing. For example, an individual in state A_0 is subject to seroconversion rate σ and background mortality μ; if neither seroconversion nor death occur, then after the minimum incubation period T_0 has elapsed, the patient enters state B_0 with probability p_0 or state D_0 with probability $1-p_0$. If seroconversion occurs at time $t_0 < T_0$, the patient enters state A_1 and will subsequently enter B_1 or D_1 after T_0-t_0 more time has elapsed, if no further transitions occur. The rate of progression through primary progressive tuberculosis states is γ_i, so that the mean incubation period (given a fixed HIV stage) is $T_i + 2/\gamma_i$. The latent breakdown rate is ν_i, the rate of diagnosis is δ_i, and the excess mortality rate due to TB is μ_i^T. Transitions between HIV states occur at rates λ_i. Finally, E_{ji} is the effective contact rate of susceptibles in state j for cases in state i.

Generating Predictions

We used our model to predict the probability and average expected outbreak size that would be generated in a 2-year period from a single index case of infectious tuberculosis. Only untreated infectious individuals can generate outbreaks. Thus, the population-level treatment rate of tuberculosis (defined as the fraction of infectious cases that are treated per unit of time) is obviously an important factor in determining the probability and the severity of outbreaks. We varied the population-level treatment rate of tuberculosis from 0% to 100% of cases. We also independently varied both HIV prevalence (no HIV prevalence [0%], moderate HIV prevalence [9%], and high HIV prevalence [20%]) as well as the intersection dynamics ("mixing patterns") between the HIV and the tuberculosis epidemics. We investigated two extreme mixing patterns: positive assortative (i.e., "like with like") and proportional (i.e., "random").

Positive assortative mixing occurs if HIV-positive cases with tuberculosis mix only with HIV-positive individuals and HIV-negative individuals with tuberculosis mix only with HIV-negative individuals (38,39). Proportional mixing occurs if people with tuberculosis mix randomly with HIV-infected individuals; hence the degree to which HIV-infected individuals are encountered is simply in proportion to the prevalence of HIV (38,39). We varied HIV prevalence from 0% to 20% and evaluated the effects of HIV on outbreaks at both moderate (70%) and high (95%) treatment rates. To conduct these analyses we carried out over 1.2 million stochastic simulations, for reasons of space we present in Figures 3 and 4 only 707,700 of these simulations (the results for the remaining 500,00 simulations were in complete agreement with the results shown in Figs. 3 and 4).

RESULTS

Tuberculosis outbreaks were generated for Figure 3A under the assumption that the HIV prevalence was 0%. Outbreaks were generated for Figure 3 and 3C under the assumption that a moderate HIV epidemic (9% prevalence) was intersecting with the tuberculosis epidemic; in 3B we assumed proportional mixing, and in 3C we assumed positive assortative mixing. Results in Figure 3 are shown in terms of the average outbreak size, defined as the average number of tuberculosis cases that are generated in a 2-year period from a single index case (results in red), and also the probability that the index case would generate a tuberculosis outbreak of any specified size (results are shown in terms of a color-coded frequency distribution). The height of the colored regions indicates the probability that the index case would generate a tuberculosis outbreak of size X over a 2-year time period; see Figure Legend 3.

If HIV is not present and treatment rates of tuberculosis are moderate to low then the average (mean) expected outbreak size (in the 2-year period) from a single index case is approximately 0.5 (red data in Fig. 3A). Under these conditions, most index cases do not transmit *M. tuberculosis;* the probability that an index case generates at least 1 additional case is approximately 0.4 (dark blue data); and it is possible (although the prob-

ability is low) that an index case can generate a large outbreak (yellow data) (Fig. 3A). When a large fraction of cases receives treatment both the average outbreak size and the probability of large outbreaks drastically decrease (Fig. 3A). The presence of HIV dramatically changes the short-term dynamics of tuberculosis (Fig. 3). The presence of HIV both increases the average outbreak size (red data) and increases the probability of a large outbreak (orange data), except at extremely high treatment rates (Fig. 3). At moderate or low treatment rates, even a moderate HIV epidemic (Fig. 3B,C) causes the average size of tuberculosis outbreaks (red data) to almost double in comparison with the expected outbreak size when HIV is absent (Fig. 3A). The amplification effect of HIV is influenced by the intersection dynamics between the two epidemics, if tuberculosis treatment rates are low (Fig. 3). Under these conditions, proportional mixing (Fig. 3B) leads to fewer large outbreaks but to a slightly higher average outbreak size than positive assortative mixing (Fig. 3C). However, even in the presence of moderate levels of HIV (and either "mixing pattern") there is a high probability (dark blue data) that an index case will not transmit *M. tuberculosis*; hence many "outbreaks" of size one can be expected (Fig. 3B,C).

The effect of HIV prevalence (ranging from 0 to 20%) on the probability and severity of tuberculosis outbreaks is shown for two treatment rates: a very high treatment rate (assuming that 95% of tuberculosis cases are treated) (Fig. 4A,B) and a moderate treatment rate (assuming that only 70% of tuberculosis cases are treated) (Fig. 4C,D). As previously, our predictions are shown in terms of the average outbreak size (red data) and of the probability that an outbreak of any specified size would occur (results shown in terms of a color-coded frequency distribution). In Figure 4A and C, mixing is proportional, and in Figure 4B and D, mixing is positive assortative. As we found previously, the tuberculosis treatment rate is extremely important in determining the effect of HIV on increasing both the probability of outbreaks and the average outbreak size (Fig. 4). Under either mixing pattern, if treatment rates are extremely high then even fairly severe HIV epidemics (with prevalence levels up to 20%) have little effect on increasing either the average outbreak size or the probability that a large outbreak will occur (Fig. 4A,B). Large outbreaks of tuberculosis can occur but are unlikely, and the average outbreak size remains low (Fig. 4A,B). However, when only a moderate number of tuberculosis cases are treated, the HIV epidemic can then significantly amplify the tuberculosis epidemic; both the average outbreak size and the probability of a large outbreak substantially increase with
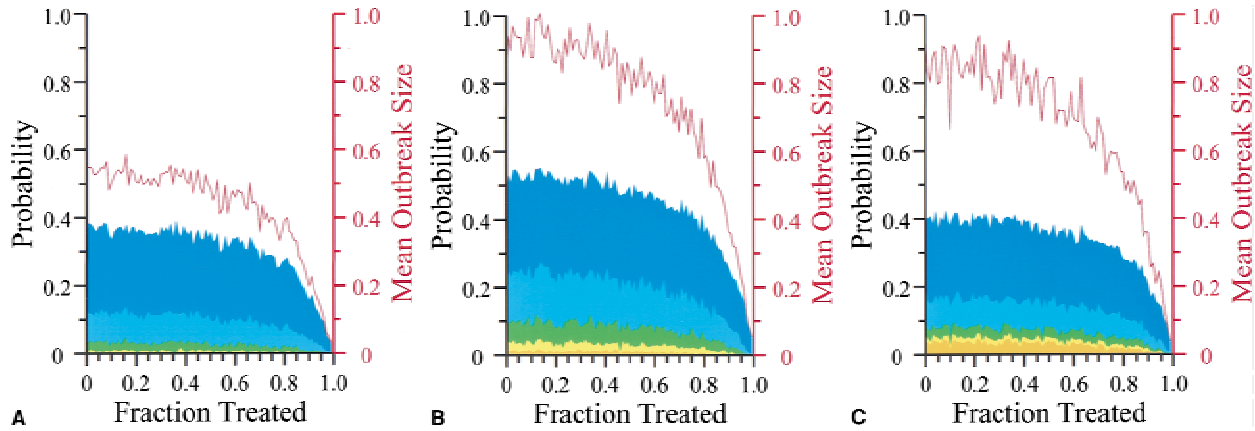
FIG. 3. For each simulation, we began with a single infectious case of tuberculosis and predicted the outbreak size (i.e., total number of new cases: secondary, tertiary and further) that would be generated in a 2-year period by the index case. The figures show the average outbreak size (*red line* and *red axis*), and the color-coded frequency distribution of outbreak size. The probability that an outbreak will be of: size one or more is indicated by the upper boundary of the dark blue region, size two or more by the light blue region, size three or more by the green region, size four or more by the yellow region, and size five or more by the orange region. (**A**) Varying the treatment rate (in terms of fraction of tuberculosis cases treated) when HIV is absent, (**B**) Varying the treatment rate when HIV prevalence is moderate (9%) and mixing is proportional, (**C**) Varying the treatment rate when HIV prevalence is moderate (9%) and mixing is completely positive assortative.
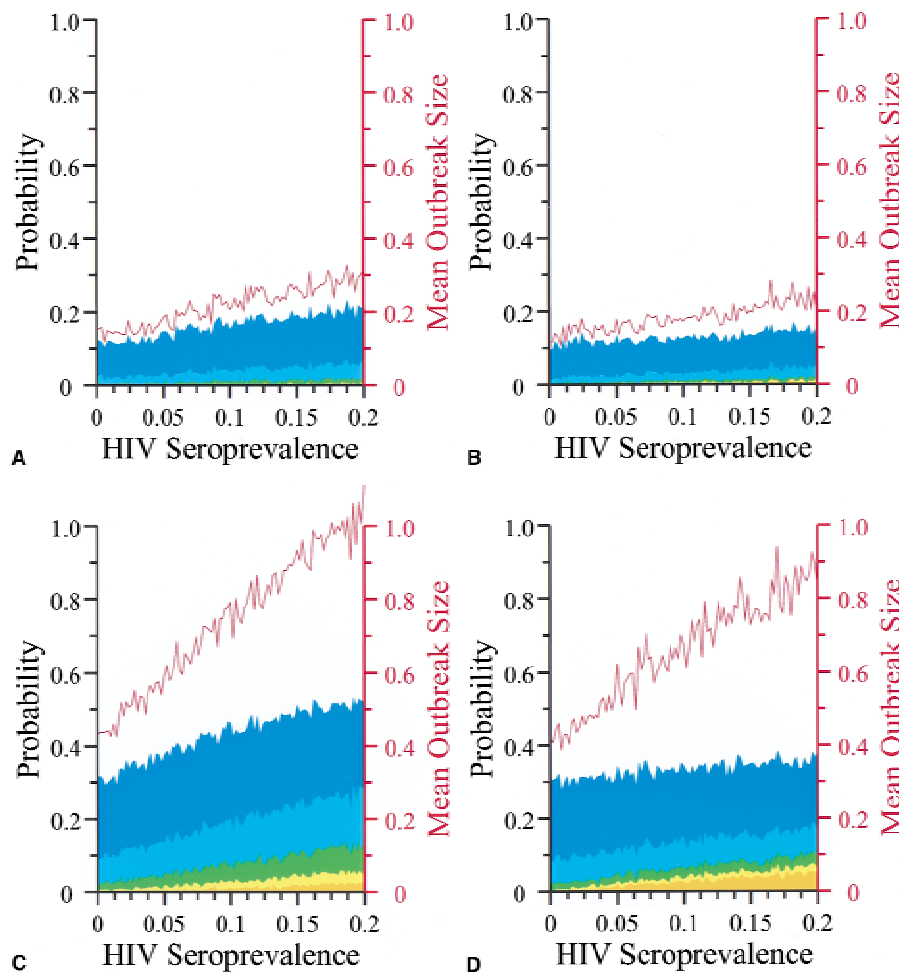

FIG. 4. The average outbreak size and outbreak size frequency distribution after 2 years, starting from a random index case, because HIV prevalence varies. Average outbreak size is shown by the *red line* and the *red axis*; outbreak size frequency distribution is indicated by the *colored shading* as stated in the legend to Figure 3. (**A**) High tuberculosis treatment rate (95%) and random mixing. (**B**) High tuberculosis treatment rate (95%) and positive assortative mixing. (**C**) Moderate tuberculosis treatment rate (70%) and random mixing. (**D**) Moderate tuberculosis treatment rate (70%) and completely positive assortative mixing.

increasing HIV prevalence (Fig. 4C,D). As the HIV prevalence increases from 0 to 20%, the average outbreak size more than doubles (Fig. 4C,D). At high HIV prevalence levels, positive assortative mixing (in comparison with proportional mixing) substantially increases the probability of a large outbreak (compare Fig. 4C with 4D).

CONCLUSIONS

Our stochastic predictions are in agreement with molecular epidemiologic data that reveal that the incidence rate of tuberculosis is composed of a few large and many small outbreaks (Fig. 1). A consistent finding of population-based molecular epidemiologic studies is the occasional occurrence of large outbreaks of tuberculosis even in the context of apparently good control programs (5,7,40). When large outbreaks have occurred they have generally been ascribed to two deterministic causal mechanisms: either failed control practices or to the transmission of *M. tuberculosis* strains with enhanced virulence (4,41–45). Obviously these mechanisms can lead to large outbreaks; however, our stochastic results identify the significance of a third explanation for the occasional occurrence of large outbreaks. Our results show that an occasional large outbreak can happen simply as a result of chance, and a large outbreak can occur even if HIV prevalence is extremely low, tuberculosis treatment rates are high, and the strain generating the outbreak has only "normal-virulence" (i.e., the *M. tuberculosis* strain generating the outbreak does not have to have a higher than average fitness). Our results imply therefore that it is important for investigators of outbreaks not to assume that a strain of *M. tuberculosis* has enhanced virulence (or a greater than average fitness) simply because it has generated a single large outbreak. In fact, our results imply that there may be little to no genetic variability between the outbreak strain and the non-outbreak strains.

In the United States, a renewed commitment to tuberculosis control has resulted in a recent dramatic decrease in tuberculosis rates and in plans to refocus control efforts towards tuberculosis elimination (14). The Institute of Medicine has recently proposed a strategy for the elimination of tuberculosis in the United States (14). The elimination goal is <1 case per million by the year 2010 (which would translate into < 300 cases in the United States per year) (14); the 1999 incident rate in the United States was 6.4 cases per 100,000 individuals per year (14). Our results suggest that even as intensified control efforts effectively decrease the incidence rate, sporadic large outbreaks of tuberculosis will continue to occur. As

conventional control programs reduce tuberculosis incidence to a low level, these outbreaks are likely to dominate the epidemiology. Thus, at a very low incidence rate, further progress in disease control will require that the interpretation of surveillance data and control efforts be based on an understanding of the stochastic processes that generate outbreaks. Novel statistical approaches (that go beyond counting cases and plotting incidence) will be required to detect (at low incidence rates) the underlying trend in incidence data.

We have shown that HIV will increase the severity and the probability of tuberculosis outbreaks, but that this amplification effect could be substantially reduced by extremely high tuberculosis treatment rates. Thus, our results imply that in geographic locations with extremely good tuberculosis control programs, such as San Francisco (where 95% of cases are treated [11]), HIV epidemics are not likely to substantially increase the number or size of tuberculosis outbreaks. However, HIV can be expected to remain a significant risk factor in generating the few large outbreaks that will occur. Conversely, our results imply that if tuberculosis treatment rates are only moderate, as is the case in most developing countries, HIV is likely to significantly amplify the tuberculosis epidemic. In our current analysis we have modeled only the number of cases of tuberculosis resulting from recent transmission (i.e., outbreaks) that will occur in a 2-year time period; we have not modeled the tuberculosis incidence rate. The tuberculosis incidence rate at any place at any time will be composed of both "fast" (recent transmission) and "slow" (reactivation) cases of tuberculosis (20,31,32). HIV epidemics can increase the tuberculosis incidence rate by increasing the numbers of cases of tuberculosis resulting from reactivation, as well as by speeding up rapid transmission (as we have shown here). Hence, our results imply that in developing countries—where there are both significant numbers of individuals latently infected with tuberculosis and low tuberculosis treatment rates—HIV epidemics will lead to substantial increases in the tuberculosis incidence rates. The WHO target treatment levels for tuberculosis have yet to be attained in most countries; currently, 88% of the estimated cases of tuberculosis occur in countries where treatment levels are well below the target levels (47). However, our results suggest that the WHO target treatment levels (46) are gross underestimates of the treatment levels that are necessary for the global control of drug-resistant tuberculosis, because the WHO calculations did not include the amplification effect of HIV on tuberculosis. Thus, we suggest that WHO should significantly increase their target treatment levels for tubercu-

losis in countries that are heavily burdened by both tuberculosis and HIV.

In developing countries that have a severe HIV epidemic there are two approaches for controlling tuberculosis epidemics: the tuberculosis epidemic can be controlled directly (by chemoprophylaxis and treatment); and the tuberculosis epidemic can be controlled indirectly by treating the HIV epidemic. We strongly advocate that both approaches be deployed. Previously, we have shown that widespread usage of combination antiretroviral therapies would generate an epidemic of drug-resistant HIV (48), but such use would be extremely effective in decreasing HIV transmission rates (48,49) (as well as AIDS-related death rates (49)). As we have shown in this current analysis, decreasing the prevalence of HIV would also decrease the incidence of tuberculosis. Consequently, we advocate the expanded use of combination antiretroviral therapies in developing countries both for the beneficial direct effects on the HIV epidemic, as well as for the beneficial indirect effects on the tuberculosis epidemic. We also stress that the tuberculosis epidemic should be directly controlled by substantially increasing the rates of chemoprophylaxis (of latently-infected individuals) (24) as well as treatment rates (of active cases). Methodologies for the cost-effective provision of basic anti-tuberculosis therapy are well established. Our results clearly imply that tuberculosis epidemics in developing countries could be significantly reduced—even in the presence of HIV epidemics—simply by substantially increasing tuberculosis treatment rates. Clearly, it is now a necessity in many developing countries to try to simultaneously control both epidemics.

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