The Theoretical Influence of Immunity between Strain Groups on the Progression of Drug-Resistant Tuberculosis Epidemics

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Background. Emerging research suggests that genetically distinct strains of Mycobacterium tuberculosis may modulate the immune system differently. This may be of importance in high-burden settings where ≧1 genetic group of M. tuberculosis confers significant morbidity.

Methods. A dynamic mathematical model was constructed to evaluate how different degrees of cross-immunity among M. tuberculosis groups could affect epidemics of drug-resistant tuberculosis (TB).

Results. Simulated populations with immunogenically distinct TB strain groups experienced a heightened risk of drug-resistant TB, compared with populations without such strain diversity, even when the same rates of case detection and treatment success were achieved. The highest risks of infection were observed in populations in which HIV was prevalent. Drug-resistant strains with very low transmission fitness could still propagate in environments with reduced cross-immunity among different strain groups, even after common targets for case detection and treatment success are reached.

Conclusions. It is possible that the propagation of drug-resistant strains could depend not only on the rate of development of resistance and the fitness of the drug-resistant strains but, also, on the diversity of the strains in the region. The risk of infection with drug-resistant strains could be amplified in locations where there is reduced cross-immunity between originating strain groups. This amplification may be most profound during the first few decades of TB treatment expansion.

Approximately one-third of the world’s population is infected with Mycobacterium tuberculosis, which is primarily present in a dormant, latent state [1]. Immunity to tuberculosis (TB) is incompletely effective and is complicated by host, environmental, and genetic factors. When previously infected persons are reinfected, their risk of developing active TB may be mitigated by partial immunity [2]. However, historical data sets from which the degree of partial immunity has been estimated reflect immunity in populations with limited genetic diversity in tuberculosis lineages [2–4]. Genetic differences between M. tuberculosis strains can influence the ability of M. tuberculosis to spread effectively, resist the host immune response, and, subsequently, cause active TB [5–14]. Increasing evidence now suggests that M. tuberculosis strains with a significantly different genetic makeup can elicit distinct immune responses [10, 11, 13, 15]. Specific host-pathogen relationships can mediate which genetic types of TB appear among which host populations, as well as the form in which TB may become manifest in human hosts [16, 17].

The degree of cross-immunity that protects previously infected individuals from secondary infection with a significantly different strain is unclear. Identification of this degree of cross-immunity is becoming increasingly important, because there is more genetic diversity in high-burden settings than in the American and European settings that have been traditionally studied to assess immunity. Most regions outside of America and Europe are affected by ≧2 dominant strain lineages, with the exception of sub-Saharan Africa, where ≧6 lineages appear to confer significant morbidity [18].
The fact that immunogenicity may differ among genetically distinct *M. tuberculosis* strains poses an obvious problem for the development of new TB vaccines. It is less clear, however, what influence such immune dynamics could have on the current Global Plan to Stop TB, in which expansion of TB treatment constitutes a major available means by which to reduce mortality associated with the disease [19].

The cure rates for drug-susceptible disease appear to be roughly equivalent in different regions affected by distinct circulating strain groups, when treatment programs are effectively implemented using standard protocols [1]. Low cross-immunity among circulating strains could increase the prevalence of disease and slow the rate of decrease in the prevalence associated with treatment expansion. Nevertheless, the expansion of treatment programs should decrease the overall morbidity and mortality associated with disease due to circulating drug-susceptible strains, regardless of genetic diversity.

Drug-resistant disease poses a different problem. Newly resistant strains can emerge stochastically and can amplify to different degrees of resistance, changing treatment success rates and complicating the expected decrease in TB burden associated with expanded treatment. Transmission of resistant strains from one strain group may be more rapid if much of the affected community has partial immunity from strains of an immunogenically distinct group. Successful reinfection could be more likely in areas with greater strain diversity, because, in such areas, newly acquired drug resistance could amplify more rapidly than it could in areas with more genetically homogeneous strains. Therefore, in a reversal of current trends, regions with significantly different strain diversity may require more extensive and, potentially, more rapid deployment of resistance detection and treatment capacity than areas with limited strain diversity. The potential significance of this theoretical problem has yet to be examined.

In the present study, we evaluated the influence of immunogenic diversity on the course of drug-resistant TB epidemics, using a dynamic mathematical model of TB transmission.

**METHODS**

We created a simple model to analyze how varying our assumptions about immunity among different *M. tuberculosis* strain groups could influence the qualitative dynamics of drug-resistant TB epidemics. We constructed an environment with 2 circulating strain groups, in which the level of cross-immunity between the groups was varied. In our simulations, drug resistance was allowed to develop and amplify within either group, to explore how the trajectory of emerging drug-resistant strains could be altered by differences in cross-immunity among the groups. We simulated both a fully HIV-negative population and populations affected by HIV.

To produce a model that could be generalized to an arbitrary and expanding number of strains (with the development of drug resistance), without using an unmanageably large number of compartments to define all states of infection and coinfection, we developed a “history-based” model as an alternative to the traditional “status-based” model. The former model tracks the number of cases of latent and active TB that include infection with or previous exposure to each strain, by use of a system of differential equations [20, 21]. This strain-centric approach allows us to model an arbitrarily large number of strains and infections with the use of few equations that can be generalized to a large number of modeling scenarios (see the Appendix for equations and a detailed explanation) [20]. The number of strains can expand with the emergence of drug resistance; therefore, it is not possible to depict the model in a simple flow diagram. Figure 1A provides the framework for understanding the model from the perspective of 1 strain.

The model follows a description of TB pathogenesis adopted by previous models of TB transmission, and it is focused on simulating transmission in an adult population [4, 23, 24]. As in models discussed elsewhere [4, 25, 26], primary progressive disease was defined as the rapid manifestation of disease after infection. After infection, the remaining infected persons experienced latent disease, from which reinfection (subject to partial immunity) and reactivation of disease could occur. Following the standard World Health Organization (WHO) models [4, 27], chemotherapeutic recovery was defined by disease remission, consistent with available data [28, 29]; as in previous models [30], we also added natural self-cure to this process, with the potential for relapse. These states and flows are depicted in figure 1A.

To use the model to investigate our research question, we first simulated an environment with 2 groups of strains of equal prevalence. Our simulation of this environment is consistent with current empirical data [16, 18], which suggest that most regions outside of America and Europe have 2 dominant circulating lineages of roughly equal prevalence, although the identities of the 2 lineages differ among regions. We introduced these strain groups into an uninfected population and ran the model to equilibrium in the absence of treatment, to symbolize the prechemotherapeutic era. We then simulated the introduction and expansion of case detection, where the rate of such detection followed the average expansion rate among countries surveyed by WHO (as modeled using the logistic curve shown in figure 1B). We adopted the definition of case detection used in WHO statistics and models, where the detection rate was converted to an annual rate of detection, and where the treatment rate was based on the ratio of treated cases to incident cases per year [4, 31, 32].

Once treatment was available, we allowed resistant strains to develop, with the probabilities of acquired and amplified resistance adopted from an analysis of drug resistance performed in 47 countries [32] (table 1). We assumed that mutations confer-
Primary progressive disease is defined as rapid progression to active disease after infection. Latently infected persons may experience exogenous reinfection or reactivation. Following the standard World Health Organization (WHO) model [4], recovery is defined by remission of disease from active to latent status. Acquired and amplified resistance can occur among treated patients with active TB. Births and deaths are not shown, but they are included in the model as specified in the Appendix. An arbitrarily large number of strains can be incorporated into the model. B. Case detection rate for sputum-positive cases (as determined using directly-observed therapy, short-course) comparing the observed global average (gray circles), WHO projections (white circles), and the standard model (gray line, single logistic curve). C. Logistic growth of the prevalence of HIV infection among adults for the TB/HIV infection simulations. Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates for sub-Saharan African averages (gray circles and error bars) vs. the standard UNAIDS Estimation and Projections Package model (gray line, single logistic curve) [22].
ring resistance do not produce genetic changes that are significant enough to alter the cross-immunity among strains within the same genetic group, an assumption consistent with available data [10, 11, 13, 15]; therefore, only the cross-immunity between groups was of relevance.

We ran the model while varying the degree of cross-immunity between the 2 simulated \textit{M. tuberculosis} strain groups. While varying this parameter over a range of possible values (from complete cross-immunity to no cross-immunity), we examined changes in the risk of infection with drug-resistant \textit{M. tuberculosis}, as well as the following secondary statistics of interest: (1) the incidence of multiple infections and (2) how the influence of cross-immunity varied with changes in strain fitness and HIV prevalence.

In the base-case scenario, we simulated the conservative case in which the fitness of increasingly resistant strains decreased with the accumulation of more mutations (i.e., decreased by a factor of 30\% for each new mutation, such that a single-drug resistant strain was 70\% as transmissible as the drug-susceptible strain, a finding consistent with observed data, [32, 39]); however, treatment efficacy decreased as well (by 12\% for each new mutation, as estimated from a study of 6 countries for which detailed drug-resistance data were available [40]). Both factors were varied in sensitivity analyses.

For the scenario in which we added HIV to the simulation, a logistic curve describing the prevalence of HIV infection in high-burden countries in sub-Saharan Africa (figure 1C) was used to weight the data, with use of the parameters shown in table 1, such that the rates of TB progression in the simulated population were the weighted averages of HIV-negative and HIV-positive parameters. We used Latin hypercube sampling to provide a sense of how the uncertainty in parameter estimates for TB pathogenesis might influence the uncertainty regarding the results of the model [41]. We also performed a sensitivity analysis around all of the parameter values of the models, using the ranges shown in table 1.

### Table 1. Typical parameter values used to describe the pathogenesis of tuberculosis (TB) in HIV-negative and HIV-positive individuals.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>HIV-negative value (range)</th>
<th>HIV-positive value (range)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Lambda^a$</td>
<td>Population birth/recruitment rate</td>
<td>0.0165</td>
<td>0.0165</td>
<td>[33]</td>
</tr>
<tr>
<td>$\beta^a$</td>
<td>Per capita transmission rate$^a$</td>
<td>9.8 (7.0–12.6)$^b$</td>
<td>9.8 (7.0–12.6)$^b$</td>
<td>[34]</td>
</tr>
<tr>
<td>$f$</td>
<td>Fraction of TB cases that are infectious</td>
<td>0.65 (0.5–0.65)</td>
<td>0.3 (0.19–0.4)</td>
<td>[4]</td>
</tr>
<tr>
<td>$\mu^a$</td>
<td>Background (non-TB-associated) mortality rate</td>
<td>0.015 (0.01–0.04)</td>
<td>0.098 (0.093–0.103)</td>
<td>[4,35]</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Proportion of newly infected persons with PPD</td>
<td>0.14 (0.08–0.25)</td>
<td>0.67 (0.36–0.8)</td>
<td>[4]</td>
</tr>
<tr>
<td>$d^a$</td>
<td>Detection and treatment rate</td>
<td>Converted from a proportion$^d$ to an annualized rate</td>
<td>Converted from a proportion$^d$ to an annualized rate</td>
<td>[36,37]</td>
</tr>
<tr>
<td>$k^a$</td>
<td>Proportion of treated persons that were cured</td>
<td>0.7 (0.6–0.8)$^a$</td>
<td>0.7 (0.6–0.8)$^a$</td>
<td>[32]</td>
</tr>
<tr>
<td>$n^a$</td>
<td>Rate of self-cure</td>
<td>0.2 (0.15–0.25)</td>
<td>0.1 (0–0.15)</td>
<td>[4,38]</td>
</tr>
<tr>
<td>$\psi^a$</td>
<td>Rate of reactivation of LD</td>
<td>1.13 $\times$ 10$^{-4}$ (10$^{-4}$ to 3 $\times$ 10$^{-4}$)</td>
<td>0.17 (0.04–0.2)</td>
<td>[4]</td>
</tr>
<tr>
<td>$x$</td>
<td>Proportion of persons with LD reinfected with the same strain and susceptible to PPD</td>
<td>0.35 (0.1–0.6)</td>
<td>0.75 (0.5–1.0)</td>
<td>[4]</td>
</tr>
<tr>
<td>$\mu^a$</td>
<td>Rate of death due to TB</td>
<td>0.3 (0.2–0.4)$^f$</td>
<td>1.0 (0.75–1.0)$^g$</td>
<td>[4]</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Proportion of patients with therapy failure who acquire resistance</td>
<td>0.07 (0.008–0.18)</td>
<td></td>
<td>[32]</td>
</tr>
<tr>
<td>$\varphi$</td>
<td>Susceptibility to second strain group$^h$</td>
<td>Varied from x to 1</td>
<td></td>
<td>. . .</td>
</tr>
</tbody>
</table>

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\textbf{NOTE.} LD, latent disease; PPD, primary progressive disease.

$^a$ Rate is in units of 1/year.

$^b$ Divided by population size and proportioned among strains in the simulation.

$^c$ 30\% lower for each drug-resistant mutation.

$^d$ See figure 1B.

$^e$ Drug susceptible (increased to 0.85 in sensitivity analyses); 0.12 lower for each drug-resistant mutation.

$^f$ For proportion $f$, $\mu^a$ = 0.21 (0.18–0.25) for proportion (1 $- f$).

$^g$ For all cases of active TB.

$^h$ When latently infected with strain from 1 group (1 $- \text{cross immunity}$).
RESULTS

Our model tracked changes in the risk of infection associated with drug-susceptible and drug-resistant *M. tuberculosis* strains over time. We present our results in terms of the annual risk of infection (ARI) with drug-resistant strains, which is a common indicator of changes in the transmission patterns of *M. tuberculosis*. Measurement of new cases of active disease alone could discount the influence of reinfections or acquired resistance among those persons already infected with drug-susceptible strains (which we explore further, below). However, changes in the ARI reflect the actual risk of disease transmission, serving as a useful comparison index for modeling changes in transmission dynamics in scenarios with different degrees of cross-immunity.

“Baseline” simulation. In our baseline simulation, the degree of cross-immunity between the 2 groups of simulated strains was just as strong as the degree of intragroup immunity. The degree of immunity to exogenous reinfection among HIV-negative persons was previously estimated to be ~65%, on the basis of analyses of European populations [4] (range, 40%–90%) (table 1). By use of a Bayesian inference procedure, the degree of immunity to reinfection among HIV-positive persons was previously estimated to be ~25% [42] (range, 0%–25%) (table 1).

In our model, we used the term “full cross-immunity” to denote a level of cross-immunity equal to these levels of intragroup immunity (i.e., the baseline scenario). We used the term “half cross-immunity” to denote a value that was one-half of these values and the term “no cross-immunity” to denote complete susceptibility to reinfection with strains of the other group.

The ARI with drug-susceptible strains was ~2% in the model without HIV and ~6% in the model including HIV over the past decade, matching global estimates [36]. The baseline ARI with drug-resistant strains is shown in figure 2, which illustrates the emergence of drug resistance as an increase in the ARI from 0 in the prechemotherapeutic era to a peak of 0.07% and 0.58% in the HIV-negative and HIV-positive scenarios around year 2004, respectively (corresponding well to available data on global trends [43]). After 2004, this increase was followed by a decline in the ARI to a new lower level (of 0.01% and 0.41% in the HIV-negative and HIV-positive scenarios, respectively, in the year 2050 of this simulation), as case detection and treatment success rates expanded per the WHO curve (figure 1B).

By estimating the Stylbro ratio (i.e., the ratio of incidence to ARI) for drug-resistant disease, with use of our model’s parameters for each year of the simulation, the Stylbro-positive incidence in our model would have a peak year 2004 value and a long-range year 2050 value of 5.4 and 0.9 cases/100,000 population in the HIV-negative scenario, and values of 47 and 39 cases/100,000 population, respectively, in the model that includes HIV. Estimates of the rate of drug resistance as a proportion of all cases increased from ~1% to ~6% over the past decade in the model without HIV and were 3 times greater than those values in the simulation with HIV, which is similar in trend but slightly lower in magnitude than the observed global drug-resistant TB trend from ~5% to ~20% over the decade (an estimate which is itself subject to sampling biases and is not stratified by HIV) [43, 44]. Limited data are available from countries with a high HIV burden; Botswana has experienced an increase in the rate of drug resistance (from 15% to 22% of all cases) from 1996 to 2002, which is a rate slightly higher than the estimates for our model of the HIV-prevalent scenario [45]. We explored how the model’s estimates would change when cross-immunity was varied among strains (see the Discussion section). The incidence of drug-susceptible disease corresponded well between our model and available data, with incidences of ~150 cases/100,000 population for the HIV-negative simulation and ~400 cases/100,000 population for the HIV-affected population over the past decade [37].

Changes to cross-immunity. We examined how changes in the ARI with drug-resistant strains could result from different degrees of cross-immunity among the 2 strain groups in our model, relative to the baseline simulation in which cross-immunity between the strain groups was just as strong as intragroup immunity. Figure 3 shows the relative ARI over time when the degree of cross-immunity between the 2 strains groups is reduced; this relative ARI is the ARI in the lowered cross-immunity scenario divided by the baseline ARI.

As shown in figure 3A and 3B, when cross-immunity is reduced between the circulating strain groups, the ARI can dramatically increase in the first several decades of treatment expansion in a population. Lower cross-immunity effectively increases the pool of statistical persons available to be infected. In our simulations without HIV, the peak ARIs were increased by 80% and 190% for half immunity and no cross-immunity, respectively. These amplification rates reduced over time, as is shown in figure 3, as population-level equilibration occurred between the transmission rate and the expanded treatment and immunity levels.

When HIV was included in the model, the relative increase in the ARI resulting from reduced cross-immunity was less dramatic (figure 3C and 3D). HIV already lowered the overall population-level immunity in the baseline scenario; therefore, further reduction in the degree of immunity produced an influence relatively smaller than that noted in the HIV-negative sim-
ulation. However, the absolute value of the ARI was higher overall than in the HIV-negative simulation, as we detail further in the Discussion section. The peak ARIs in the HIV-positive simulation were amplified by 75% and 170% for half immunity and no cross-immunity, respectively, compared with values noted for the baseline simulation. As shown in figure 3C and 3D, HIV also accelerated the emergence of the peak ARI, which can be understood by the more rapid progression of infection to active TB among HIV-positive persons [46].

**Sensitivity analyses.** Because the transmission fitness of emerging drug-resistant strains has been classically described as an important parameter for determining the risk of infection [47], we explored how cross-immunity and the fitness costs of resistance could mutually alter the ARI with drug-resistant strains in this model. As shown in the contour plots of figure 4A, cross-immunity and the fitness of drug-resistant strains complement one another’s influence on drug-resistant ARI in the HIV-negative population. Because both the fitness cost of mutations

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**Figure 2.** Baseline annual risk of infection (ARI) with drug-resistant strains in (A) a population unaffected by HIV and (B) a population affected by HIV, by use of the logistic curve shown in figure 1C. Note the change in y-axis scales between the 2 figures and, also, that the peak is exaggerated because of the increase in the case detection rate in this model, whereas true incidence will be a slower-developing curve with gradual progression. All risks are expressed as a percentage (e.g., 0.5 is 0.5%, not 50%).
conferring resistance and the cross-immunity among strain groups were reduced, the ARI increased. Even at very low transmission fitness levels, however, drug-resistant strains maintained a high ARI in this model, even when the cross-immunity between groups was lower than intragroup immunity, with a relative ARI that corresponded to $\frac{1}{50}$ of every 50 incident cases in the low fitness scenario displayed in the bottom left of the contour plot.

As shown in figure 4B, the ARI was more sensitive to strain fitness than to cross-immunity in HIV-prevalent populations. The existence of lowered population-level immunity produced limited relative influence from changes in the cross-immunity level, particularly when the strain fitness was low. However, the absolute ARIs were considerably higher (average, $\sim 10$ times higher) (figure 4) than those in the HIV-negative population, even for strains with low fitness.

We also explored the influence of varying parameters in our simulation across a range of plausible values shown in table 1. As shown in figure 5, in the HIV-negative simulation, the calculation of the ARI was most sensitive to changes in the proportion of cases that progress to rapid, primary progressive disease, as is typical of most models of TB transmission [27, 32]. The HIV-positive simulation was sensitive to the rate of acquired resistance, because HIV-positive persons have a higher risk of experiencing progression to active TB and a subsequent higher rate of treatment, which provide more opportunities for acquisition of resistance.

We evaluated how increasing the treatment success rate to 85% and achieving a case detection rate of 70% (common
goals for TB programs) could influence the ARI associated with drug-resistant strains. The peak ARI for the baseline scenario was reduced by 55% after these improvements were implemented, but if cross-immunity was reduced to half immunity or no cross-immunity, then the ARI was 3–4 times higher than this in the case of an HIV-negative population. In the simulated HIV-positive population with improved case detection and treatment success rates, reducing cross-immunity increased the ARI to 1.3–1.5 times the value noted for the baseline scenario.

**DISCUSSION**

Using a simple model of TB transmission to evaluate the qualitative dynamics of drug-resistant TB epidemics, we found that the degree of cross-immunity among different groups of *M. tu-
Figure 5. Sensitivity analysis for tuberculosis (TB) disease parameters. Changes to the annual risk of infection (ARI) ratio are shown when varying each parameter, where the ARI ratio is the ARI in the year 2050 in the half cross-immunity scenario divided by the ARI in the year 2050 in the baseline full cross-immunity scenario. The degree of change shown is in terms of the relative effect (elasticity); hence, a value of 0.5 indicates that the effect of decreasing cross-immunity from full to half was reduced by 50% when the given parameter was changed, whereas a value of 2 indicates the influence of decreasing the cross-immunity doubled when the parameter was changed. We show the effect when each parameter is changed to its value at the low end of its range (as shown in table 1) (green bars) and when each is changed to the high end of its range (as shown in table 1) (red bars). We show the analysis for (A) the HIV-negative simulation and (B) the simulation incorporating HIV.

Mycobacterium tuberculosis strains may profoundly influence the risk of transmission of drug-resistant *M. tuberculosis*. Even when it is assumed that mutations conferring drug resistance do not change the mechanism or degree of immunity conferred by a strain, immunogenic differences between ancestrally distinct groups of strains could profoundly alter the risk of infection with drug-resistant *M. tuberculosis*.
resistant *M. tuberculosis*. As case detection of and treatment for TB expand, the successful propagation of emerging drug-resistant strains could depend not only on the rate of resistance development and the fitness of the drug-resistant strains but, also, on the immunogenicity among circulating strains in the population. Populations outside of Europe and America, which are affected by multiple strain lineages, may experience greater burdens of drug-resistant TB disease simply by virtue of having population-level immunity weakened by differences in the degree of cross-immunity conferred between circulating strain groups.

We found that drug-resistant strains with low transmission fitness could produce significant morbidity in populations with reduced cross-immunity among circulating strain groups. Among locales with 2 immunogenically distinct strain groups, the ARI with drug-resistant strains could nearly double if cross-immunity was halved between the groups, compared with identical regions with complete cross-immunity between strains. In populations affected by HIV, the risk of infection was further increased. HIV accelerates the pathogenesis of TB, increasing the risk of reactivation from latent to active disease, as well as increasing the risk of reinfection. Hence, HIV provides more opportunities for the development of active TB and for the acquisition and subsequent transmission of drug-resistant strains as those cases of active TB are treated.

We found that, even when common goals for case detection and treatment success were met, the risks of drug-resistant TB infection remained high and did not alleviate the amplifying effect of low cross-immunity among strain groups. Given that the emergence of drug-resistant disease can be explosive, detection of drug resistance and treatment efforts may be particularly important to introduce either along with or soon after the introduction of drug-susceptible treatment, particularly in areas affected by strain diversity.

As with all modeling studies, these conclusions are subject to the assumptions of the models themselves. We used a very simple description of TB pathogenesis to assess qualitative epidemic trends in a manner that can be extended to more-complex and locally specific epidemics. We assumed that exogenous reinfection could occur, although it has not been firmly established as a principal determinant of TB incidence at a population level. We also simulated the simple case in which 2 strain groups circulate in the simulated population, corresponding to available data about the distribution of TB lineages [18]. However, it is unknown whether lineages or sublineages or, even, less distinct strains of TB could have significantly different immunogenicity; in the latter case, our results could be viewed as conservative. We also produced conservative drug-resistant TB risk simulations by assuming a fitness cost resulting from each mutation, without accounting for potential compensatory mutations or the fact that evolutionary pressures may select for more-fit drug-resistant strains over time [48]. Compensatory mutations and fitter strains would further strengthen our conclusions. The magnitude of our observations was also sensitive to the rate of primary progressive disease among infected individuals and the rate of acquired resistance, which remain matters of investigation and which may vary among regions in the context of different HIV prevalence and treatment programs.

To date, there are few empirical data concerning what distinctions among strain groups may lead to significant differences in their immunogenic properties [10, 11, 13, 15]; hence, our study remains a theoretical modeling experiment at a time when this subject remains under active investigation. However, recent studies of drug-resistant TB epidemics have revealed that reinfection and superinfection occurring in environments with strain diversity may be important ongoing phenomena, in spite of our limited information on the subject [49]. In the context of increasing concern about drug-resistant TB, our simulations suggest that immunogenic diversity deserves further investigation not only for the future development of TB vaccines but, also, because of their potential to profoundly affect the incidence of drug-resistant TB incidence under current TB treatment strategies. Strain diversity could also help to explain why rates of drug-resistant disease remain high and widely varied in regions with similar rates of case detection and treatment success.

**APPENDIX**

**EQUATIONS USED IN THE MODEL**

In the model, we describe a set of equations that can be extended to a system of an arbitrarily large and expanding number of strains. The number of fully susceptible persons $S$ is expanded by entry of new susceptible persons (through births and immigration) into the population at rate $\Lambda$ and is decreased by deaths due to causes other than tuberculosis (TB) at rate $\mu$. Susceptible persons can become infected with *Mycobacterium tuberculosis* of any type at rates $\lambda_i(t)$ and $\lambda_j(t)$ (subscripts $i$ and $j$ denote strains in group $m$, and subscripts $i'$ and $j'$ denote strains in the genetically distinct group $n$ in the equations below):

$$\frac{dS}{dt} = \Lambda - (\sum_i \Lambda_i + \sum_j \Lambda_j + \mu)S .$$

The number of persons with latent disease who are infected with strain $i$ in group $m$, among people without exposure to strains in group $n$, is designated $e_i(t)$, irrespective of the status of these persons with regard to other group $m$ strains $i'$. The number of persons with latent disease who are infected with strain $j$ in group $n$, among those unexposed to group $m$ strains, is designated $e_j(t)$, irrespective of the status of these persons with regard to strains $j'$. We write the equations in terms of the transmission rates (or forces of infection) $\lambda_i(t)$ and $\lambda_j(t)$. The number of
persons with active disease who are infected with strain $i$ is $\lambda_i / (\beta_i f)$, irrespective of status regarding other strains.

Infected or reinfected persons who do not have primary progressive disease experience progression to latent disease with the following probability: $(1-p)$. An additional pool of persons with active disease who are infected with strain $i$ and who were previously exposed to group $m$ strains only ($\lambda_i / (\beta_i f)$) can be detected (rate $d$) and can undergo either chemotherapeutic remission (proportion $k$) or natural remission (rate $n$), to enter the latent state $e_i$. Latency can be left through reactivation (rate $v$), reinfection with primary progression (rate $p\lambda$), or death from causes other than TB (rate $\mu$). Reinfections due to group $m$ strains are subject to partial susceptibility $x(1−\text{partial immunity})$, whereas reinfections due to group $m$ strains are subject to partial susceptibility $\varphi_{i,p}$, which is varied in simulations to reflect cross-immunity between the groups. Note that we add and subtract reinfection terms to allow for mixed latent disease, because the equations are in strain-specific, rather than person-specific, terms:

$$\frac{de_i}{dt} = (1-p)\lambda_i(S + \sum_{j\neq i} xe_i) + \left(\frac{\lambda_i}{\beta_i f}\right)(dk_i + n) - [\mu + v + p\sum_{\forall \, j \in m} x\lambda_j + \sum_{j} \varphi_{i,j}\lambda_j]e_i.$$

The expression for $e_{i}(t)$ is analogous, with $i$ and $j$ switched in the equation above. In the remaining equations, we type the form for strain $i$, and the reader can interpret the type $j$ equations equivalently by switching $i$ and $j$.

For persons who have been exposed to both strain groups, we designate $\gamma_j$ as the per capita transmission rate divided by the total population (and proportioned among the lineages to produce the same overall risk of infection as the one-lineage model at the prechemotherapeutic equilibrium, for the experimental comparison). In our simulations, we additionally modify the force-of-infection equation from this generalizable scenario to the scenario where acquired or amplified resistance can produce new strains. To do so, we subtract the rate $d(1-k)\alpha$ from the force-of-infection equation for each progenitor strain, and we add it to the corresponding offspring strain within each group to signal the emergence or amplification of resistant strains. The annual risk of infection is calculated as per the standard method of integrating the first part of the above force-of-infection equations for each year (which is equivalent to the effective contact rate multiplied by the incidence of disease in a 1-strain model without coinfection) [50].

Active disease can also be reached through reactivation of latent disease (rate $v$) and left by remission (chemotherapeutic remission, contingent on detection rate $d$ and cure rate $k$; or natural remission, rate $n$). Persons with active disease experience both non-TB-associated ($\mu$) and TB-associated ($\mu_i$) mortality (where the latter is proportioned by $f$, given differential rates among those with infectious and noninfectious disease):

$$\frac{d\lambda_i}{dt} = \beta_i [ve_i + p\lambda_i(S + \sum_{\forall \, j \in m} xe_j)] - [dk_i + n + \mu + \mu_i]\lambda_i$$

and

$$\frac{d\lambda_j}{dt} = \beta_j [v\gamma_i + p\lambda_j(\sum_{j} \varphi_{j,i}\lambda_j + \sum_{\forall \, j \in m} x\gamma_j + \sum_{\forall \, j \in m} x\gamma_{i,j})] - [dk_i + n + \mu + \mu_i]\lambda_j.$$

In these equations, $\beta_i$ is the per capita transmission rate divided by the total population (and proportioned among the lineages to produce the same overall risk of infection as the one-lineage model at the prechemotherapeutic equilibrium, for the experimental comparison). In our simulations, we additionally modify the force-of-infection equation from this generalizable scenario to the scenario where acquired or amplified resistance can produce new strains. To do so, we subtract the rate $d(1-k)\alpha$ from the force-of-infection equation for each progenitor strain, and we add it to the corresponding offspring strain within each group to signal the emergence or amplification of resistant strains. The annual risk of infection is calculated as per the standard method of integrating the first part of the above force-of-infection equations for each year (which is equivalent to the effective contact rate multiplied by the incidence of disease in a 1-strain model without coinfection) [50].

References
