Modeling the effects of strain diversity and mechanisms of strain competition on the potential performance of new tuberculosis vaccines

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While bacillus Calmette–Guérin vaccination plays an important role in reducing the morbidity of tuberculosis (TB) infection during childhood, new tuberculosis vaccines are necessary to disrupt the transmission of disease and improve global control of this pathogen. Growing evidence of the presence of meaningful *Mycobacterium tuberculosis* strain diversity, coupled with the possibility that new vaccines may differentially protect against infection or disease with circulating *M. tuberculosis* strains, suggest that these vaccines may have complicated effects on disease dynamics. We use a mathematical model to explore the potential effects of strain diversity on the performance of vaccines and find that vaccines offer great promise for improving tuberculosis control, but the expected benefits of mass vaccination will be eroded if strain replacement with *M. tuberculosis* variants that are not effectively targeted by vaccines occurs. Determining the likelihood of strain replacement will require additional knowledge of the strain specificities of current vaccine candidates, and an improved understanding of the mechanisms of strain interaction, which are responsible for maintaining the diversity of *M. tuberculosis* within communities.

bacillus Calmette–Guérin | mathematical model | strain replacement

Despite the availability of effective antibiotics and the widespread use of the Bacille Calmette-Guérin vaccine (bacillus Calmette–Guérin), tuberculosis (TB) remains a major cause of morbidity and mortality globally, leading to nearly nine million new cases per year and two million deaths. Although the bacillus Calmette–Guérin vaccine has been shown to protect against childhood forms of TB, it is far less effective in preventing the adult pulmonary forms of disease that lead to respiratory transmission of the infection. Consequently, a major priority of current global research efforts is the development of new, more effective anti-TB vaccines, capable of having a substantial impact on TB control. To date, this effort has yielded >200 new vaccine candidates, many of which are now undergoing animal testing and early clinical trials; these include recombinant bacillus Calmette–Guérin and other attenuated live mycobacterial vaccines, subunit vaccines, and DNA vaccines (1–2).

Vaccine discovery efforts have largely focused on the identification of *M. tuberculosis* (*Mtb*) antigens that are capable of eliciting effective human T cell responses. Because previous studies had suggested that there was little genetic diversity within *Mtb* in general and within possible protein targets of host immune surveillance in particular (3, 4), the vaccine development effort has not prioritized issues associated with potential strain variation in immune targets. However, tools for the large-scale genetic typing of mycobacterial strains have generated substantial evidence of important genetic differences among clinical isolates (5). Subsequent studies have revealed a global population structure of *M. tuberculosis* with several distinct lineages (6, 7) and have provided evidence of heterogeneity in virulence and transmissibility (8–10), host-specificity (11, 12), and potential for immune system activation (13–18). Taken together, these data raise the possibility that antigens identified from a limited set of *Mtb* strains may be differentially present in clinical isolates, and thus vaccines directed at these antigens may protect less well against some strains of mycobacteria than others.

The hypothesis that a vaccine may be less effective against specific strains of TB was first offered as a possible explanation for the observation that the Beijing family of strains predominated in several countries in East Asia where bacillus Calmette–Guérin coverage was widespread (19). While an initial epidemiological investigation did not find an association between bacillus Calmette–Guérin vaccination status and risk of TB with a Beijing-type strain (20), other work suggests that bacillus Calmette–Guérin vaccination may be associated with disease because of a subgroup of typical Beijing strains (21). The hypothesis that the emergence of the Beijing family of strains may be related to bacillus Calmette–Guérin has continued to circulate (22) and is supported by experiments that have found that bacillus Calmette–Guérin protects relatively poorly against disease because of Beijing-type strains, at least in animal models (9, 23, 24).

Recent evidence also suggests that current subunit vaccine candidates may target antigens that are not uniformly present among *Mtb*. Hebert *et al.* investigated the genomic diversity of the pepA and PPE18 genes that code for the protein products composing the Mtb72F subunit vaccine currently under clinical investigation (25). Using *Mtb* isolates from two different geographical areas, these investigators identified single nucleotide polymorphisms and insertions/deletions within regions reported to be T cell epitopes in a modest proportion of isolates for both sites and consequently suggested that this subunit vaccine may not induce protective immunity to a fraction of clinical *Mtb* strains.

Strain variation in immune targets could have wide-reaching implication for TB vaccine design and efficacy, because the selective pressure imposed by a widely used but strain-specific TB vaccine might be tremendous (12). Such selection has been demonstrated for several other bacterial pathogens including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitides*, *Bordetella pertussis* [reviewed in ref. 26]. In these cases, vaccination programs have resulted in increases in the prevalence of nonvaccine-type strains after the introduction of vaccination (i.e., strain replacement). Theoretical work also

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suggests that strain replacement can occur not only because of the differential effectiveness of a vaccine, but also through the use of a pan-effective vaccine when its presence causes additional strain interactions that favor the less-prevalent strains (27). The accumulating evidence of strain variability of *Mtb*, and the existence of multistrain infection (i.e., coinfection) (28) and superinfection (29), suggest that the population dynamic effects of a vaccine program may be complex.

Several examples of such strain variation in immunogenicity have been detected, and multiple investigators have noted differences in immunomodulatory cytokine production in cell and animal models of infection after exposure to different strains of *Mtb*. Most notably, infection with the CDC1551 strain appears to trigger a greater protective Th1 immune response than infection with Beijing HN878 (30–32), a response that may account for the apparent differences in virulence between the two strains. In a study among TB patients in West Africa, T cell responses to the mycobacterial antigen ESAT-6 were attenuated in sera of those infected with *M. africanum* compared to those infected with other *M. tuberculosis* strains (33). Other researchers have detected mycobacterial lipids that are differentially present among *Mtb* strains and that appear to have a profound effect on the efficacy of the host innate immune response (14, 15). These examples suggest that the immune response provoked by some *Mtb* strains may be specific to antigenic determinants that are heterogeneously produced within the species.

Neither the specific mechanisms by which new TB vaccines will provide immunity nor the details of how distinct strains of tuberculosis interact and compete are currently well understood. At this time, evidence suggests that distinct strains of *Mtb* exist and may invoke different immune responses and that some vaccine candidates (especially subunit vaccines) may target only a fraction of clinical strains. To examine the potential effects of strain diversity and vaccine specificity—a combination that has resulted in dramatic examples of strain replacement for other infectious pathogens—we developed simple mathematical models of competing strains of *Mtb* to study the potential impact of new TB vaccines on (*i*) the total prevalence of TB and (*ii*) the relative abundance of strain types. We model vaccines administered before (preexposure) and after infection (postexposure); in both cases we model vaccines that preferentially target the most prevalent strain before the introduction of the vaccine. These models allow us (*i*) to describe a range of possible qualitative behaviors of the system given our uncertainty about how *Mtb* strains compete for hosts and how new vaccines will function, and (*ii*) to identify important unanswered questions about strain interaction and vaccine specificity.

TB Infection Model. We develop a simple compartmental model of tuberculosis in which two strains are in competition; we arbitrarily designate these as strain 1 and strain 2, with strain 1 being more prevalent in the absence of vaccination. Individuals are born susceptible to infection (X). Upon infection, individuals either become latently infected with probability 1-p_i (L_i; where i identifies the infecting strain) or progress immediately to infectious TB (I_i) with probability p_i. Those in the latent state progress to infectious TB at a rate η. Infectious individuals are removed from the infectious class at rate μ_T and either die from TB or control their infection. A fraction (r) of infectious individuals who contain but do not sterilize their infection return to a state of slowly progressing latency from which they have a small annual risk of relapse. Individuals are removed from other classes at a much lower rate μ; all removed individuals are replaced by entry of individuals into the susceptible classes representing an assumption of constant population size.

Individuals with a latent infection remain partially susceptible to reinfection. We compare the effect of vaccines in two closely related models: the first model specifies that reinfection by a new strain displaces the old strain (superinfection model, Fig. 1*A*) while the second model allows that reinfection can result in simultaneous infection with more than one strain type (coinfection model, Fig. 1*B*). To explore a broad range of potential mechanisms by which distinct strains may activate or subvert host immune responses and to represent differential susceptibility of strains to immunity acquired through infection, we model three mechanisms of within-host strain competition on the population-level impact of vaccination programs:

(1) Individuals who are latently infected with either strain 1 or strain 2 are protected equally well against reinfection with either strain 1 or strain 2 (i.e., self-immunity equals cross-immunity and is symmetric).

(2) Individuals who are latently infected with a particular strain are better protected against reinfection with that same strain than against reinfection with the other strain (i.e., self-immunity is greater than cross-immunity and is symmetric).

(3) Latent infection with strain 1 protects equally well against reinfection with strain 1 or 2, but infection with strain 2 does not protect against reinfection with either strain 1 or 2. That is, strain 1 is immunogenic and primes the immune system effectively to reexposure with any strain, but primary infection with strain 2 does not trigger an effective immune response.

We adopt this agnostic approach toward modeling the means by which strains may either stimulate or be vulnerable to immune responses and these three general mechanisms represent a wide range of strain interactions that are biologically plausible given the available evidence. Mechanism 1 is most likely if observed

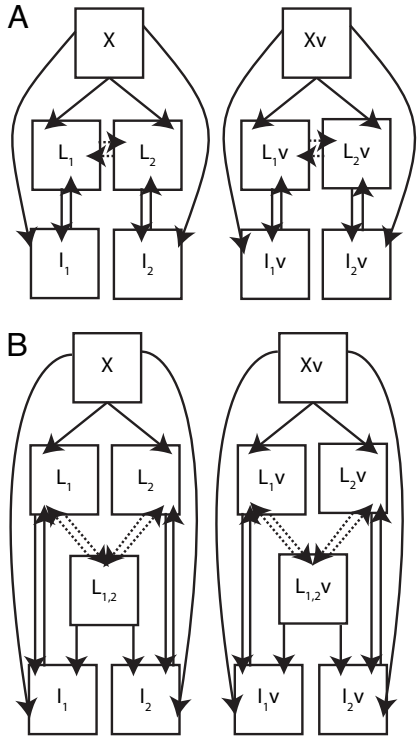

Fig. 1. Model structures (*A*) Superinfection model: Individuals are assigned to unvaccinated (S) or vaccinated (S_v) groups upon entry into population and may be infected with either strain 1 or strain 2. Individuals with latent infection (L) and active disease (I) are indexed by strain type (1 or 2) and vaccination status (vaccinated individuals designated by $_v$). In this version of the model, reinfection of individuals with latent infections can result in strain replacement (dotted arrows). State transitions are as described in the text and by the system of equations presented in the *SI Appendix*. (*B*) Coinfection model: In this variant of the model, reinfection of those in the latent state may result in a state of mixed strain coinfection (L_{12} and L_{12v}).

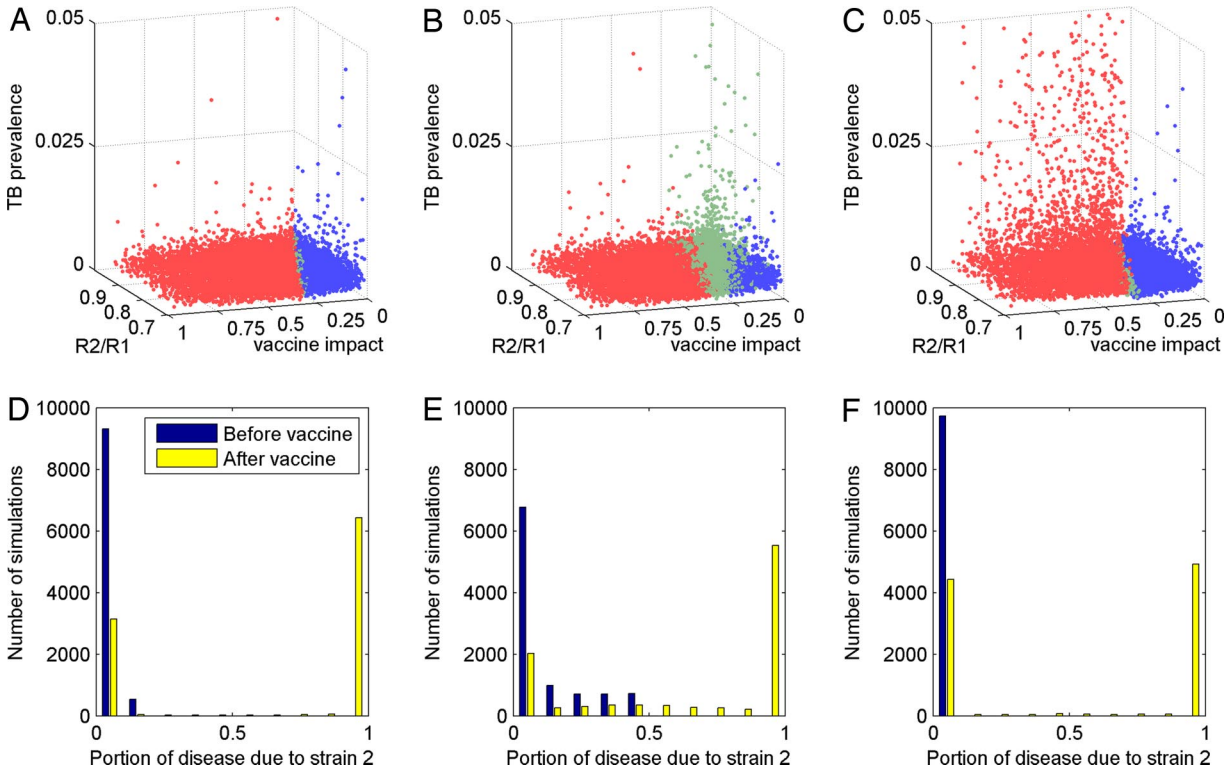

Fig. 2. Effects of preexposure vaccines in superinfection model. The equilibrium effects of vaccination on total TB prevalence under the three different mechanisms of strain interaction (*A*, mechanism 1; *B*, mechanism 2; and *C*, mechanism 3). These figures show the results of 10,000 simulations with parameters drawn randomly from uniformly distributed ranges listed in Table S1. Red points indicate simulations in which only strain 2 persists after vaccination, blue points indicate simulations in which only strain 1 persists after vaccination, and green points indicate simulations in which both strain 1 and strain 2 persist after vaccination. Vaccine impact is a function of coverage and efficacy and is calculated according to the equation in the text. R2/R1 indicates the relative reproductive number of strain 2 compared to strain 1. Panels *D*, *E*, and *F* show the relative abundance of strain 2 before and after vaccination under the same three mechanisms of strain interaction.

strain diversity does not translate into functional differences in either the triggering of or the susceptibility to immune responses; mechanism 2 is most likely if each distinct strain triggers an immune response that is most effective against future assault by a similar strain; and mechanism 3 is most likely if there are some strains that do not elicit and may also subvert acquired immune responses—in reality, some combinations of these mechanisms may be at work. Changes to the immunity-related parameter values for these mechanisms of competition are presented in supporting information (SI) Table S1, along with the values and ranges for the other parameters used in simulations. The formula for calculating vaccine impact is provided in the *Methods*, the descriptions for the model compartments are listed in the legend for Fig. 1, and the differential equations for these models are available in *SI Appendix*.

Results

We examine the effects of introducing a vaccine into populations with a total median equilibrium TB prevalence of ≈220/100,000; the global TB prevalence was estimated to be 219/100,000 in 2006 (34). At this time in the simulations, strain 2 is the minority strain in the population. The proportion of the total TB prevalence that is strain 2 before vaccination varies with the mechanism of strain interaction assumed (Fig. 2*D–F*, dark bars). Under interstrain competition mechanisms 1 (equal and symmetric self- and cross-immunity) and 3 (strain 1 protects against all, strain 2 provides negligible immunity), there is essentially no stable coexistence of strains at equilibrium; hence, we introduce a very small amount of strain 2 into the population at the same time as vaccination, to simulate the sporadic appearance of a vaccine-resistant variant through migration. Under the assumption that individuals in the mixed strain infection states from the coinfection model ($L_{1,2}$ and $L_{1,2}v$) can return to the singly infected states upon reinfection (L_1, L_2, L_1v, and L_2v), we find that the effects of pre- and postexposure vaccines with equivalent effects on reducing the reproductive number of strain 1 have similar, although not identical, impact on the total equilibrium TB prevalence and on the relative frequency of strain types in both the superinfection and coinfection models. If, on the other hand, the state of mixed infection is relatively protected and thus reinfection is not likely to result in a return to homogenous infection, the coinfection model predicts substantially increased levels of strain diversity. For simplicity, we present only the preexposure vaccine effects in the superinfection model in the main text and figures; the results for the coinfection model (including those in which reinfection of those in the mixed infection states does not result in return to single strain infection states) are available as *SI Appendix*.

We report the results of 10,000 simulations on parameter sets randomly selected from the uniformly distributed parameter ranges listed in Table S1. We introduce vaccination as an ongoing policy as the TB prevalence approaches equilibrium, and we report the values of TB prevalence and relative strain abundance after the system reaches equilibrium in the presence of vaccination.

Interstrain Competition Mechanism 1. If latent infection with strain 1 or strain 2 provides equal protection against reinfection with

either strain, we find unsurprisingly that, on average, higher total vaccine usage and efficacy is associated with a lower total TB prevalence (Fig. 2*A*). In scenarios where vaccine coverage and the relative reproductive number of strain 2 are relatively high, we observe an increased probability that strain 2 replaces strain 1. We note that despite this strain replacement, there is still a lower total level of disease after vaccination is implemented, because we enforce that strain 2 always has a lower reproductive number than strain 1 in these simulations. The histogram (Fig. 2*D*) shows the relative abundance of strain types before and after vaccination and reveals that this mechanism of strain interaction does not support the stable coexistence of the two strain types.

Interstrain Competition Mechanism 2. If there is strain specificity to the immune response such that latent infection with either strain protects more effectively against reinfection by the same strain than the other strain, we again observe lower mean total equilibrium TB prevalence when vaccination coverage and efficacy are at relatively high levels (Fig. 2*B*). However, in this scenario where intrastrain competition is stronger than interstrain competition, strain 1 and strain 2 can stably coexist and it is possible that the total TB prevalence can be higher after the introduction of the vaccine (Fig. 2*B*). Because infection with either strain opposes its own takeover, this mechanism of interstrain competition strongly facilitates strain coexistence (Fig. 2*E*) and allows that at levels of vaccine impact and relative reproductive number of strain 2 that permit coexistence, use of a vaccine may actually lead to increased disease levels. As vaccine impact is increased to high enough levels that strain 1 is successfully suppressed, this perverse vaccine effect is not observed.

Interstrain Competition Mechanism 3. If latent infection with strain 1 protects equally well against reinfection with strain 1 or strain 2, but latent infection with strain 2 does not protect against reinfection by either strain, vaccines which specifically target strain 1 may not improve control of TB. This result is not unexpected as under these assumptions vaccination may result in the replacement of an immunogenic strain by a nonimmunogenic one. In particular, when the relative reproductive number of strain 2 is high, implementation of more effective vaccines at higher levels can actually cause a higher equilibrium prevalence of tuberculosis (Fig. 2*C*), although this perverse effect occurs in only a modest proportion of the simulations in which strain 2 replaces strain 1 (yellow bars, Fig. 2*F*). When the relative reproductive number of strain 2 is high and there is high vaccine coverage level with a vaccine that can successfully suppress strain 1, the total postvaccination prevalence of TB can exceed the prevaccination levels (Fig. S3 displays the combinations of parameter values that result in this pernicious effect). As with interstrain competition mechanism 1, we observe that stable coexistence of strains is not a generic feature of this mechanism of strain interaction (Fig. 2*F*).

Effects of Preexposure and Postexposure Vaccination. Our primary focus is to explore the effects of strain diversity and competition on the effect of vaccines, accordingly, our simulations include only pre- and postexposure vaccines with equivalent ability to reduce the reproductive number of strain 1. This allows us to examine the effect of vaccine mechanism rather than vaccine strength and is not intended to imply that pre- and postexposure vaccines under development are likely to have equal impact on the basic reproductive number of tuberculosis. Other researchers have considered in greater detail the likely benefits of each vaccine approach (35–37). While preexposure and postexposure vaccines with equivalent effects on R_{01} have similar effects on the projected quantity and distribution of tuberculosis strains at equilibrium, they differ in the timing of their impacts on TB epidemics. We find that the postexposure vaccines have a slower impact on disease dynamics than preexposure vaccines with differences persisting for decades (results not shown); this observation is consistent with previous models of TB vaccines.

Discussion

In this study, we use mathematical models to examine a range of possible long-term effects of large-scale vaccination programs with new vaccines against *M. tuberculosis*. For simplicity, we model the diversity of *Mtb* using only two strains, and we allow these strains to compete against each other and to be differentially suppressed by vaccination. We examine the sensitivity of the models to combinations of parameter values and explore a range of scenarios in which the mechanisms of competition between strains were allowed to vary. In general, these models suggest that the public health impact of vaccination programs with new TB vaccines will depend crucially on (*i*) the diversity of circulating *Mtb* strains, (*ii*) the mechanisms of competition between strains, and (*iii*) the strain specificity of these vaccines.

As information about the immunogenicity of strains, the specificity and magnitude of immune responses to previous infection, and the strain specificity of vaccine candidates is limited, we present simple conceptual models that cover a broad range of biologically plausible scenarios. While this approach accurately represents the lack of relevant data and necessarily limits our ability to make quantitative predictions about the effect of new TB vaccines, it does allow us to describe those behaviors that do not appear to depend on these areas of ignorance and identify important uncertainties that are expected to greatly affect the performance of new vaccines. Encouragingly, we find that increasing vaccine coverage and efficacy results in substantial reductions in the predicted TB burden under most assumptions about the strain interactions and vaccine specificity. However, we also find that the benefits of vaccination are reduced if the preferential removal of one competitor allows a previously outcompeted nonvaccine-type strain to emerge. These observations are consistent with results of previous models for other pathogens and with the observed strain replacement that has occurred after strain-specific vaccines have been introduced. We also demonstrate that if a vaccine preferentially targets a strain that provides cross-immunity against a nonvaccine strain, which itself does not provide substantial immunity, the vaccine may cause an absolute increase in the TB burden. Similar perverse effects of vaccines were previously discussed by both McLean (39) and Lipsitch (40), using models for different diseases.

Although vaccination programs reduced TB prevalence in most of our simulations, they also resulted in a shift in strain composition that can potentially undermine some of the benefits of this effect. For example, several studies have reported a positive association between the Beijing genotype and antituberculosis drug resistance within particular locations (41–43). A vaccine that reduces the total number of TB cases but results in an increased frequency of Beijing-type strains may lead to the proliferation of strains that are either drug resistant or have an increased potential to become drug resistant.

The mechanisms by which vaccination can shift the competitive balance between competing pathogen strains have been the focus of other mathematical models. In our two-strain models, we consider the effect of a vaccine that selectively suppresses one strain and thus may potentiate the ascent of the other. This approach is similar to other models that have explored the effects of vaccines on the ecology of pathogen strains (44, 45). While this approach has the advantage of simplicity, there are several limitations to the models we present here. Here we assume that the two strains differ in their ability to infect and cause rapid progression to disease, but specify that the duration of infectivity and the rate of slow progression from latency to disease are

similar for both strains. We choose to allow the relative infectivity and fraction of infections that lead rapidly to disease to be the traits by which strains differ because, on the basis of other TB models (44, 45), these are characteristics that may have strong impact on disease dynamics. Differences in the expected duration of illness or the rate of endogenous reactivation would likely have resulted in different quantitative results, but similar qualitative conclusions as those presented here. While it is not possible to evaluate the sensitivity of the model to all possible structural assumptions, we have attempted to provide several simple alternatives here and in the SI. While the likelihood of strain coexistence and replacement does show some sensitivity to the structural assumptions used, the central message that *M. tuberculosis* strain diversity can erode TB vaccine performance is unchanged.

An additional limitation of our approach is that it does not simulate strain evolution, which will occur over the long time scales in which these dynamics unfold. Some modelers have focused on the stochastic effects of mutation on strain diversity and the resultant selection of vaccine-resistant variants under the pressure of vaccination programs (46, 47). These approaches require the specification of parameters governing strain mutation and selection for which we have very little relevant data for *Mtb*. Thus, the qualitative insights from our models (e.g., Under which combinations of vaccine performance and mechanisms of strain interaction might strain replacement occur?) are more informative than the specific quantitative results (e.g., What is the expected prevalence of disease after vaccine is introduced? How many years after vaccination starts would we expect to see the emergence of nonvaccine-type strains?). We note that any process by which strains mutate and are selected under the pressure of vaccination is likely to erode the benefits of vaccination projected by our simple models.

Previous mathematical models have been used to estimate the impact of new vaccines on the control of TB epidemics and to compare the relative effectiveness of preexposure and postexposure vaccination on the burden of disease (35–38, 48). Our models are structured to explore the effects of vaccination on both the total levels of disease and the relative abundance of strain types under various assumptions about between- and within-host competition between strains. While our results largely support previous findings that new vaccines promise to improve disease control, we also find that the shifting population dynamics of *Mtb* in response to vaccination can limit these benefits.

These simple models identify several important loci of ignorance that may be addressed in future studies. First, larger studies of geographically diverse clinical strains of tuberculosis, as suggested by Hebert *et al.* (25), would help to clarify to what extent candidate vaccine antigens may be differentially present in clinical strains. If conserved antigens (or combinations of antigens), which are essential for mycobacterial viability and which are capable of eliciting strong T cell responses, can be identified and used to develop new vaccines, the risk of strain replacement would be minimized. Although subunit vaccines targeted at selected antigens are most likely to exert selective pressures, it is also possible that recombinant bacillus Calmette–Guérin or other live attenuated mycobacterial vaccines can have this effect. Limited epidemiological and laboratory evidence consistent with the hypothesis that bacillus Calmette–Guérin vaccination may not offer equal protection against Beijing-type strains suggests that further study of the potential selectivity of these types of vaccines is also warranted. Studies in which vaccinated animals are challenged with diverse *Mtb* strains (at minimum, a virulent Beijing-type strain in addition to the usual H37Rv or Erdman strain) can shed light on the potential selectivity of vaccine candidates.

Furthermore, these models reveal that the mechanisms by which *Mtb* strains compete also will affect the performance of vaccines; while molecular strain typing methods allow the detection of reinfection and multiple strain infection events, very little is yet known about how strains differ in their ability to stimulate effective immune responses and how specific these immune responses are. Determining the likelihood of strain replacement by nonvaccine-type strains requires a better understanding of the degree to which there is strain-specific induction and vulnerability to host immune responses and a clearer picture of which other mechanisms are responsible for maintaining the diversity of *Mtb* within communities.

Methods

Strain Differences. We assume that strain 2 suffers reproductive deficits compared with strain 1; we specify that strain 2 is less transmissible than strain 1 ($\beta_2 < \beta_1$) and that a smaller proportion of those infected with strain 2 progress immediately to disease ($p_2 < p_1$). For simplicity, we assume that the rate of endogenous reactivation from latency and the duration of infectivity associated with the two strains does not differ for the two strains. The differences between the individual reproductive capacities of the two strains can be calculated by comparing the basic reproduction number for each strain (R_0), which is defined as the expected number of secondary cases of infectious disease produced by a single infectious individual entering a completely susceptible population. While models that allow for superinfection and coinfection can allow for a strain with a lower reproductive number to outcompete a strain with a higher reproductive number (49), we do not observe this effect in the ranges of the parameters specified in our models and before the introduction of vaccination, the prevalence of strain 1 is highest. The reproductive number for each strain in this model is defined as:

$$R_{0i} = \frac{p_i \beta_i}{\mu_T} + \frac{(1 - p_i)\beta_i \eta}{\mu_T(\mu + \eta)}$$

where i indexes strain type. The first term in this expression is the contribution from those who proceed immediately to disease upon infection and the second is the contribution from those who progress slowly from latency.

When choosing randomized parameters for our simulations, we constrain R_{01} to be equal to two but allow the parameters p_1 and β_1 to vary. For each simulation we also randomly select a parameter (z) for strain 2 between 0.8 and 1.0; z is the scalar by which we multiply the parameters p_1 and β_1 to set the values of p_2 and β_2. In these models, for values of z below this range, we do not observe emergence of strain 2. We report the relative reproductive capacity of strain 2 compared with strain 1 for each simulation by calculating the ratio R_{02}/R_{01}.

Vaccination. Here we consider vaccines that protect individuals from infection and/or disease with the most abundant strain (strain 1) and do not have any direct effect on the minority strain (strain 2). The preexposure vaccine reduces the risk of infection, reduces the probability of immediate progression to disease upon infection, and reduces the rate of progression from latency to disease, each by an equal fraction. The postexposure vaccine operates solely by reducing the rate of progression from latency to disease. To simulate the effect of a postexposure vaccine of comparable strength to the preexposure vaccine, we calibrate the reduction of the progression rate necessary to achieve an equivalent impact on the basic reproductive rate of strain 1 in the presence of vaccine. The population level total vaccine impact (VI) can be quantified as

$$VI = c\left(1 - \frac{R_{01v}}{R_{01}}\right)$$

where c is the fraction of the population receiving vaccine, where R_{01v} is the reproductive number for strain 1 in a population where everyone is vaccinated and R_{01} is the reproductive number for strain 1 in a population where nobody is vaccinated. We assume that vaccination status has no impact on the infectiousness of individuals with active disease and that there is no waning of the vaccine effect.

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