Potential Impact of Tuberculosis Vaccines as Epidemic Control Agents

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We use 2 simple mathematical models (one a preexposure vaccine model and the other a postexposure vaccine model) to provide general insight into the effects of vaccination on tuberculosis epidemics. We discuss how these models can be used as health policy tools: to identify which vaccines are “equivalent,” to design control strategies, and to predict the epidemiological impact of different vaccination strategies. Our results show that even moderately effective vaccines could have a significant effect on reducing tuberculosis epidemics if they can be coupled with moderate to high treatment rates. We suggest that both preexposure and postexposure tuberculosis vaccines can be used to help eliminate tuberculosis in developing countries. In developed countries, only a preexposure vaccine (used in combination with a high level of treatment) would be necessary to eliminate tuberculosis.

The first model builders in tuberculosis met with considerable opposition from those who maintained that many essential parameters were not established with sufficient precision, although paradoxically, those very opponents apparently had their own intuitive models on which to base highly assertive decisions.

World Health Organization, 1973

Transmission models can be used as health policy tools to understand and to predict the epidemiological consequences of medical and behavioral interventions [1, 2]. A transmission model consists of a series of equations that are formulated on the basis of specific biological assumptions about the transmission processes, the effects of medical regimens, and the pathogenic mechanisms of the pathogen. We have developed and analyzed a series of mathematical models that can be used to understand, predict, and design epidemic-control strategies for tuberculosis epidemics [1, 3–9]. In our earliest studies we focused on formulating models of untreated tuberculosis epidemics [5–7, 9]; we analyzed these models to provide new insight into the historical epidemiology of tuberculosis.

We analyzed these untreated tuberculosis models in order (1) to derive the epidemic doubling time [9]; (2) to calculate the probable length of a tuberculosis epidemic (which we found to be ~100 years) [9]; (3) to estimate the value of the basic reproductive number \( R_0 \) [7]; (4) to predict the temporal dynamics of the incidence and prevalence of infection and disease [5, 9]; and (5) to evaluate the effect that tuberculosis epidemics may have had in the historical decline of leprosy epidemics [6]. We then used these models as a basis for developing epidemic control models for tuberculosis, in order to design tuberculosis control strategies based upon treatment of active cases and chemoprophylaxis of latently infected individuals [8], to predict the emergence and transmission of drug resistant strains [1, 3, 4, 8], and to evaluate the potential epidemiological impact of preexposure and postexposure vaccines when used in conjunction with treatment. We review our vaccine work and discuss how our models can be used to assess the potential impact of tuberculosis vaccines as epidemic control agents.

Tuberculosis Vaccine Models

We have developed 2 tuberculosis vaccine models to predict the epidemiological effects of 2 different types of vaccines: preexposure vaccines and postexposure vaccines. Preexposure (also called preinfection or prophylactic) vaccines are given before infection, for example, at birth. Postexposure (also called postinfection or therapeutic) vaccines are given after evidence of infection, for example, after skin testing with PPD reveals evidence of exposure to *Mycobacterium tuberculosis* [10]. Each vaccine model consists of a series of linked ordinary differential equations; the structure of both models is described in the Appendix.

Our 2 vaccine models build on our earlier models of tuberculosis epidemics [1, 3–8, 10], which include the essential features of tuberculosis pathogenesis: (1) once infected with *M. tuberculosis*, an individual can be either a “fast” progressor to...
tuberculosis or a “slow” progressor to tuberculosis, and (2) many individuals who are latently infected with *M. tuberculosis* will never progress to active disease.

Our preexposure vaccine model enables us to quantify the potential epidemiological effects of vaccines such as BCG that are given to uninfected individuals; these vaccines are assumed to act either by preventing infection or by allowing infection but preventing subsequent disease. Our postexposure vaccine model enables us to quantify the potential epidemiological effects of vaccines that are given to individuals who are latently infected with *M. tuberculosis*; it is assumed that these vaccines act by slowing the progression to disease.

Both models allow for the possibility that latently infected individuals may be reinfected. When evaluating the potential epidemiological effects of tuberculosis vaccines, it is necessary to simultaneously evaluate the effect of treating active cases on epidemic transmission dynamics. Consequently, both our preexposure and postexposure vaccine models include treatment of tuberculosis.

*The preexposure vaccine model.* A preexposure vaccine would be given to uninfected individuals. A perfect preexposure vaccine would be 100% effective, preventing disease in everyone who is vaccinated. However, preexposure vaccines are unlikely to be perfect. Consequently, we included in the model 3 different mechanisms by which a preexposure vaccine could fail, and we called these mechanisms “take,” “degree,” and “duration.”

The term “take” in our model specifies the fraction of vaccinated individuals in whom some level of protective immunologic response is induced by the vaccine. Thus the value of take can vary from 0 (if a protective immune response is not induced in any of the vaccinated individuals) to 1.0 (if a protective immune response is induced in all of the vaccinated individuals).

The term “degree” specifies the degree of vaccine-induced protection that we assumed the vaccine could confer in those individuals in whom the vaccine “took.” We modeled the degree effect as either reduced susceptibility to infection upon exposure or reduced progression to disease by both the “fast” and the “slow” route. The value of the degree effect can vary from zero (no protection) to 1.0 (complete protection).

We assumed that the “duration” of vaccine-induced immunity could decay exponentially with time in those vaccinated individuals in whom the vaccine “took” and induced a certain degree of protection. The duration of vaccine-induced immunity can have any value; hence, the duration of vaccine-induced immunity can range from a very short duration to lifelong immunity.

*The postexposure vaccine model.* A postexposure vaccine would be given to latently infected individuals. A perfect postexposure vaccine would be 100% effective, preventing progression to disease in everyone who is latently infected with *M. tuberculosis* and is vaccinated. However, postexposure vaccines (like preexposure vaccines) are also unlikely to be perfect. Consequently, we included in the model 3 different mechanisms by which a postexposure vaccine could fail: “take,” “degree,” and “duration.” These mechanisms were included in the same manner as in the preexposure model, except in this case the degree effect was modeled only as reduced progression to disease by the “slow” route.

*Mechanisms of vaccine failure.* By including several clearly defined mechanisms of failure in our vaccine models, we could evaluate the epidemiological effects of each specific mechanism of failure. Figure 1 shows the effect on the incidence of tuberculosis for 3 postexposure vaccines that differ only in their duration of vaccine-induced immunity (each vaccine blocks 50% of progression to disease). For the first few years after vaccination, the 3 vaccines produce the same reduction in the incidence of disease; however, over time the 3 vaccines have very different epidemiological effects (figure 1). If the postexposure vaccine induces lifelong immunity, then the incidence of disease continues to decrease with time; however, if vaccine-induced immunity wanes, then the incidence of disease will begin to increase (figure 1), unless subjects are revaccinated.

![Figure 1. Incidence of tuberculosis after a vaccination program starts will vary over time, depending on the rate at which the vaccine wanes. The vaccine in this simulation is a postexposure vaccine that blocks 50% of progression to disease. The postexposure vaccine is continuously given to latently infected individuals at a rate such that eventually 88% of latently infected individuals are vaccinated. The vaccines provide protection on average for 15 years, for 30 years, or for a lifetime. The vaccine is introduced into a community in which the treatment rate is already 50% and in which the *R₀* of tuberculosis (see text) is 5.](image)
using the following equation: efficacy = \((1 - \text{incidence rate in the vaccinated group}) / \text{incidence rate in the unvaccinated group}\). The measure of efficacy that is calculated from clinical trial data is based simply upon incidence rates (and hence changes over time) and does not include any information regarding the mechanisms of failure of the vaccine. Epidemic control models that include mechanisms of vaccine failure can be used to calculate a time-independent measure of vaccine efficacy [2, 11–15] (that we shall distinguish in this paper by referring to it as “efficacy”), where the formula for “efficacy” includes the specific mechanisms of vaccine failure.

“Efficacy” is a measure of how much herd immunity the vaccine generates and hence can be used to calculate what “efficacy” levels and vaccination coverage levels are necessary to eliminate disease [2, 11–15]. Herd immunity has been defined as “the resistance of a group to attack by a disease to which a large proportion of the members are immune, thus lessening the likelihood of a patient with a disease coming into contact with a susceptible individual” [16]. We have derived “efficacy” measures for our preexposure and postexposure tuberculosis vaccine models (see Appendix).

**Tuberculosis Vaccine Models as Health Policy Tools**

Tuberculosis vaccine models can be used as health policy tools to identify which vaccines are “equivalent,” to design control strategies, and to predict the epidemiological impact of different vaccination strategies.

**Identifying which vaccines are “equivalent.”** The “efficacy” measure can be used to identify which vaccines are “equivalent” in terms of their potential epidemic-control effects. For example, consider 2 hypothetical preexposure tuberculosis vaccines. Vaccine A prevents 65% of infections progressing to disease and induces immunity that lasts for an average of 15 years. Vaccine B prevents only 20% of infections progressing to disease but provides lifelong immunity. By using the equations for “efficacy” (see Appendix) it can be calculated that vaccine A and vaccine B are actually “equivalent” in terms of the herd immunity that they generate. This means that vaccine A and vaccine B will both require the same vaccination coverage level in order to achieve the eventual elimination of tuberculosis.

**Designing epidemic-control strategies.** Transmission models can be used as health-policy tools to design epidemic-control strategies [1, 2, 4, 8, 14, 17]. In order to design an epidemic-control strategy, it is necessary to define a goal and a planning horizon (i.e., a time by which the goal should be achieved) [4]. There are many different goals that can be specified [4], for example, disease elimination, a specified reduction in the incidence rate (of infection or disease), a specified change in the prevalence (of infection or disease), or a specified decrease in the death rate. Once the goal has been specified, then it is necessary to decide on a reasonable planning horizon. Then the model can be analyzed to determine how to achieve the desired goal.

For several childhood infectious diseases, mathematical models have been used to design vaccination strategies [18]; for such diseases, it is necessary to model only the effects of vaccination. However, when designing vaccination strategies for tuberculosis epidemics, it is necessary to simultaneously model the effects of vaccination and treatment of active cases of tuberculosis. The effect of treatment and vaccination on controlling tuberculosis epidemics can be assessed by calculating the effect of these medical interventions on reducing the effective reproductive number, \(R\) (where \(R\) specifies the average number of cases of infectious tuberculosis that are caused by 1 case of infectious tuberculosis in a population where everyone is susceptible and a program of mass vaccination and treatment is in place). Thus \(R\) is a measure of the severity of the epidemic; if \(R > 1\), the epidemic continues, and if \(R < 1\), the epidemic will be eliminated [8].

We have used our preexposure and postexposure vaccine models to derive an analytical expression for \(R\), which is: \(R = R_0(1 - CE)(F_t)\), where \(R_0\) is the basic reproductive number, \(C\) is the vaccination coverage level, \(E\) is the vaccine “efficacy,” and \(F_t\) is the fraction of active tuberculosis cases that are effectively treated. Hence the expression for \(R\) can be used to quantify the “trade-offs” between vaccination and treatment (i.e., to determine how many individuals would have to be vaccinated to achieve the same epidemic-control effect of treating any specified number of active cases of tuberculosis) and to determine what epidemic-control strategies (specified in terms of both vaccination strategy and treatment rate) are necessary to achieve elimination of tuberculosis. The critical vaccination rates and the critical treatment rates that are necessary for tuberculosis elimination can be calculated by setting the value of \(R\) to unity and then solving for all possible combinations of the fraction effectively vaccinated (where the fraction effectively vaccinated is calculated as vaccination coverage times vaccine “efficacy”) and \(F_t\) (where \(F_t\) specifies the fraction of tuberculosis cases that are treated). Our analyses have revealed that for any specific epidemic there are many different epidemic-control strategies (that is, a specified combination of vaccination and/or treatment) that would be effective in eliminating tuberculosis (i.e., many epidemic-control strategies will ensure that \(R < 1\)).

Tuberculosis could eventually be eliminated by an extremely high rate of effective treatment or by complete coverage with a highly effective vaccine. The fact that a 2-arm strategy (i.e., both treatment and vaccination) can be used against tuberculosis epidemics is extremely fortuitous. However, high treatment rates are not feasible in some areas, and there may be a fundamental limit to the possible efficacy of a tuberculosis vaccine. Analysis of our models reveals that treatment and vaccination work independently. Therefore, use of a moderately effective tuberculosis vaccine, combined with a moderately high treat-
Figure 2. Epidemiological effects of a preexposure vaccine and antibiotic treatment are independent; therefore the combined effects of both interventions can be substantial. This figure shows the effects of a preexposure vaccine when either 50% or 80% of the active cases of tuberculosis are treated. The preexposure vaccine is 50% effective in preventing progression to disease and never wanes; 88% of newborns are vaccinated [24].

Figure 3. Preexposure and postexposure vaccines may have different effects over time. The preexposure vaccine is given to 88% of newborns and blocks 50% of progression to tuberculosis following exposure. The postexposure vaccine is given at a rate such that 88% of latently infected individuals will eventually be vaccinated, and in these people the vaccine blocks 50% of progression to active tuberculosis. Both vaccines provide lifelong immunity, and 50% of active tuberculosis cases are treated with antibiotics. The postexposure vaccine will protect those who have already been exposed and thus may reduce incidence quickly in the short-term. However, the preexposure vaccine, by protecting susceptible individuals, may in the long term eventually be more effective in the elimination of tuberculosis.

The short-term effect of any specified epidemic-control strategy can be predicted by numerically analyzing the models. In order to predict the epidemiological effect of any vaccination strategy, it is necessary to specify the “type” of vaccine (preexposure or postexposure), the “efficacy” of the vaccine, the mechanisms by which the vaccine fails, the prevalence and incidence of tuberculosis, the treatment rate of tuberculosis, the vaccination coverage level that is attained, and the vaccination strategy that is implemented.

Which type of vaccine will be most effective in eliminating tuberculosis will depend upon the level of disease. A postexposure vaccine could quickly reduce disease incidence in the short-term in high-incidence areas, because many people will be latently infected (figure 3). However, a preexposure vaccine, by protecting susceptible persons, could in the long term be more effective in the elimination of tuberculosis (figure 3). These results suggest that in developed countries, where the incidence of tuberculosis is low, only preexposure vaccines will be necessary. However, in order to eliminate tuberculosis in many developing countries, where the incidence is high, it will be necessary to use both postexposure and preexposure vaccines.

Several different vaccination strategies can be used once a preexposure or postexposure vaccine has been selected. For a preexposure vaccine, 3 different vaccination strategies can be used: continuous vaccination of newborns only (which is the current vaccination policy for BCG), a single mass vaccination of uninfected individuals (regardless of age), or a single mass...
vaccination of uninfected individuals plus a program of continuous vaccination of newborns. Figure 4 shows the effect of these 3 different vaccination strategies on the incidence of tuberculosis for a preexposure vaccine that is 50% effective in blocking progression to disease and never wanes.

It is evident that these 3 different strategies will have very different short-term and long-term effects, under conditions where the annual incidence of tuberculosis is high. Under these conditions, the most effective epidemic-control strategy is to continuously vaccinate newborns and also to initiate mass vaccination aimed at uninfected individuals, regardless of their age (figure 3). For a postexposure vaccine, the most effective epidemic-control strategy would be to begin with a mass vaccination of as many of the latently infected individuals as possible and then to continue to vaccinate as many of the newly latently infected individuals as possible.

Recommendations and Conclusions

Mathematical models can be used as health policy tools to design control strategies, to identify which vaccines are “equivalent,” and to predict the epidemiological impact of different vaccination strategies.

The biological mechanisms that cause a vaccine to fail will determine the overall vaccine “efficacy.” In order to predict the effectiveness of tuberculosis vaccines as epidemic-control agents, it is necessary to know the biological and social mechanisms by which a vaccine fails. Therefore, in any future clinical trial of tuberculosis vaccines, these failure mechanisms should be measured.

Even moderately effective vaccines could have a significant effect on reducing tuberculosis mortality and morbidity if coupled with moderate to high treatment rates.

It is necessary to develop both preexposure and postexposure tuberculosis vaccines. In many developing countries where the prevalence of latently infected individuals is high, postexposure vaccines will be most effective in quickly and dramatically reducing the incidence of tuberculosis. However, a preexposure vaccine is necessary to prevent a substantial increase in new infections and may be more effective than a postexposure vaccine for the elimination of tuberculosis. It is likely that the combination of a preexposure vaccine, a postexposure vaccine, and treatment of active tuberculosis would be the most effective epidemic-control strategy for tuberculosis elimination in developing countries. In developed countries, where the prevalence of latently infected individuals is low, then only a preexposure vaccine (used in combination with a high level of treatment) will be necessary to eliminate tuberculosis.

Previously, we and others have used mathematical models to quantify the potential epidemiological impact of BCG [19–24]. Here, we have used simple mathematical models to provide general insight into the epidemiological effects of vaccination for a wide variety of hypothetical preexposure and postexposure tuberculosis vaccines. Our vaccine models can be used as a basis for developing more detailed models to address specific health policy questions.

These detailed models should include both population age-structures and interactions between tuberculosis and HIV. Since many developing countries have a high prevalence of HIV infections, the epidemiological impact of preexposure and postexposure vaccines in communities that have high levels of HIV infection will have to be carefully evaluated. Such models can be used to identify strategies that will lead to tuberculosis elimination and to evaluate the cost-effectiveness of such strategies.

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APPENDIX

A Preexposure Vaccine Model

Individuals are born into the susceptible class, $X$, at an annual rate, $P$, and a fraction of these are effectively vaccinated; this fraction is the product of the coverage level, $C$, and the take, $q$ (the fraction of vaccinated individuals in whom the vaccine induces some degree of protection). Unvaccinated susceptible persons become infected at a rate that is dependent on
their susceptibility, $\beta$, and the total number of infectious cases, $T$. In addition, all individuals may die of causes other than tuberculosis at a per capita annual rate, $\mu$. In the unvaccinated latently infected individuals, $L$, infection may become reactivated or reinfection may occur.

The vaccine may fail by any of 3 mechanisms: take, duration, or degree. In some individuals, the vaccine may offer no protection whatsoever (i.e., may not take). The protection offered or degree. In some individuals, the vaccine may offer no protection stage, such that individuals have an altered susceptibility rate, $\mu_T$, (in excess of the normal mortality rate) and may be effectively treated. The effective treatment rate, $\delta$, is a summary parameter that reflects the case-finding rate in the community and the compliance and effectiveness of the treatment once instituted.

The equations for a preexposure vaccine model are the following:

$$dX/dt = (1 - Cq)\Pi - \beta X T + \pi X_T - \mu X_n$$
$$dX_T/dt = Cq\Pi - \beta X_T T - \pi X_T - \mu X_T$$
$$dL_n/dt = (1 - p_\gamma)\beta X T - \nu(T)\mu L_n$$
$$dL_v/dt = (1 - p_\gamma)\beta X T - \nu(T)\mu L_v$$
$$dT/dt = p_\gamma\beta X T + p_\gamma\beta X T + \nu(T)\mu L_v + \nu(T)\mu L_v - \mu - \mu_T + \delta T$$

### Summary Parameters Derived from the Model

$R_0$ is the average number of infectious cases produced by a primary infectious case in an untreated, unvaccinated population:

$$R_0 = R_{0\text{fast}} + R_{0\text{slow}} = \beta T/\mu + \mu_T/\nu(T)\mu$$

$R_v$ is the average number of infectious cases produced by a primary infectious case in a treated, unvaccinated population:

$$R_v = R_{v\text{fast}} + R_{v\text{slow}} = \beta_T T/\mu + \mu_T/\nu(T)\mu$$

$R_v$ is the average number of infectious cases produced by a primary infectious case in an untreated, unvaccinated population:

$$R_v = R_{v\text{fast}} + R_{v\text{slow}} = \beta_T T/\mu + \mu_T/\nu(T)\mu$$

$W$ is the fraction of vaccinated individuals in whom the vaccine wanes, for a preexposure vaccine, $W_{pre} = \omega/\mu$, and for a postexposure vaccine, $W_{post} = \omega/\nu(T) + \omega$. $C\text{post}$ is the vaccine coverage level for a postexposure vaccine: $C_{post} = \gamma/\nu(T) + \mu T$.

$D$ is the fraction of infectious cases who will ever receive treatment: $D = [\delta (\delta + \nu) + \nu(T)]$.

$E_{pre}$ is the vaccine “efficacy” of a preexposure vaccine:

$$E_{pre} = \gamma/\nu(T) [1 - R_{0\text{post}}]$$

$E_{post}$ is the vaccine “efficacy” of a postexposure vaccine:

$$E_{post} = \gamma/\nu(T) [1 - R_{0\text{post}}]$$
References


