JOURNAL ARTICLE

Early Therapy for Latent Tuberculosis Infection

Elad Ziv, Charles L. Daley, Sally M. Blower

American Journal of Epidemiology, Volume 153, Issue 4, 15 February 2001, Pages 381–385, https://doi.org/10.1093/aje/153.4.381

Published: 15 February 2001 **Article history ▾**

Abstract

The risk of developing active tuberculosis is highest within the first 2 years of infection. Therefore, an intervention that targets persons with recent infection, such as identifying contacts of active cases, could be particularly effective as an epidemic control measure. A mathematical model of a tuberculosis epidemic is formulated and used to evaluate the strategy of targeting therapy to persons with recently acquired latent tuberculosis infection. The model is used to quantify the effectiveness of therapy for early latent tuberculosis infection in reducing the prevalence of active tuberculosis. The model is also used to demonstrate how effective therapy for early latent tuberculosis infection has to be to eliminate tuberculosis, when used in conjunction with therapy for active tuberculosis. Analysis of the model suggests that programs such as contact investigations, which identify and treat persons recently infected with *Mycobacterium tuberculosis*, may have a substantial effect on controlling tuberculosis epidemics.

Keywords: antitubercular agents, models, theoretical, *Mycobacterium tuberculosis*, tuberculosis, pulmonary

Keywords: LTBI, latent tuberculosis infection

Issue Section: ORIGINAL CONTRIBUTIONS

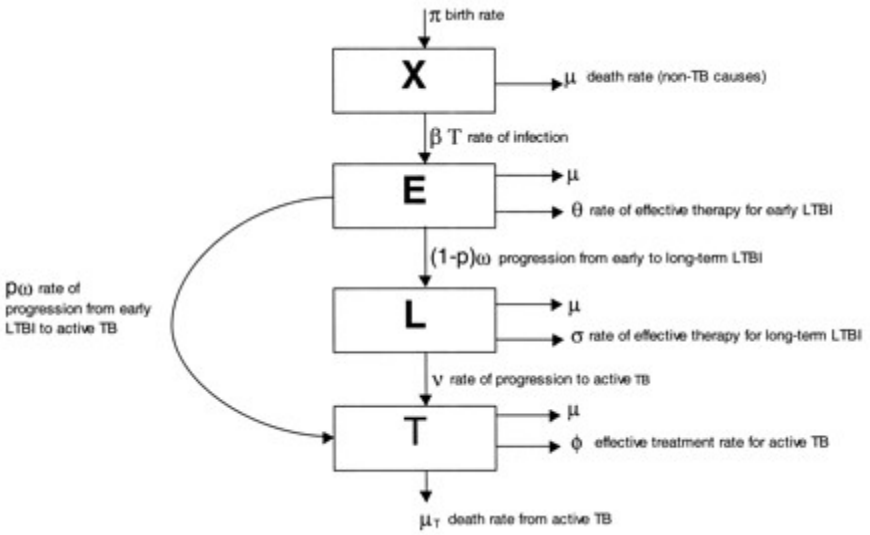
Despite effective antimicrobial chemotherapy, tuberculosis remains a leading cause of death from an infectious disease. Persons with latent tuberculosis infection (LTBI) are considered at highest risk of developing active disease during the first 2 years of infection, during which approximately 5 percent of persons develop active tuberculosis (1). Newly infected persons may be identified by investigation of close contacts of an infectious case. The Centers for Disease Control and Prevention recommend identifying and offering therapy to all close contacts of persons with active tuberculosis (2). The International Union against Tuberculosis and Lung Disease recommends treating children under 5 who are contacts of infectious cases (3). Therapy for recently infected persons may not only be beneficial to those treated but also serve as an effective tuberculosis epidemic control measure. We use a mathematical model of a tuberculosis epidemic to evaluate the potential effect of an intervention program targeting recently infected persons as an epidemic control measure.

Mathematical models of tuberculosis have contributed to the understanding of tuberculosis epidemics and the potential impact of control strategies (4–10). We extend the previous theoretical framework of Blower et al. (5) to evaluate epidemic control strategies that are based on treating active tuberculosis cases and persons with LTBI. In particular, we quantify how much treatment of early latent infection reduces the incidence of tuberculosis. We demonstrate how effective a program that treats early latent infection cases needs to be to eliminate tuberculosis. We compare the strategy of treating early latent infection versus treating long-term latent infection as epidemic control measures for eliminating tuberculosis. These two strategies correspond to either aggressively seeking close contacts of persons with active tuberculosis and targeting therapy to that group or performing large scale population screening and offering preventive therapy to those with evidence of latent tuberculosis infection.

MATERIALS AND METHODS

The model is illustrated schematically in figure 1. Persons are born into a susceptible state (X) and are infected at a rate that depends on the number of cases of active pulmonary tuberculosis in the population (T) and the intrinsic infectiousness of tuberculosis (represented by the parameter β). The model divides LTBI into two stages: an early stage of high risk of developing active tuberculosis, referred to as early LTBI (E), and a later stage of low risk for developing active tuberculosis, referred to as long-term LTBI (L). Infected persons initially progress through the early LTBI stage and then can either progress to active tuberculosis (at a rate $p\omega$) or progress to long-term latent infection (at a rate $(1 - p)\omega$). During the period of long-term LTBI, persons are at low risk of reactivation to active tuberculosis and can slowly progress at a rate ν. Persons with untreated active tuberculosis will die at a rate μ_T. Any person is also at risk of death from nontuberculosis causes at rate μ. Persons latently infected with tuberculosis can receive effective treatment during the early LTBI stage (at the rate θ) or during the long-term LTBI stage (at the rate σ). Persons with active tuberculosis receive effective therapy at the rate ϕ.

FIGURE 1.



Flow diagram of the model. Persons are initially born susceptible (*X*) and then become infected at a rate β*T*. Infected persons progress to the early latent infection period (*E*) during which they are at 5% risk of developing active tuberculosis (TB). Infected persons can also progress to a long-term latent infection period (*L*) during which they are at low risk of developing active tuberculosis. Persons with latent tuberculosis can be effectively treated in either the early phase (at rate θ) or the long-term phase (at rate σ), and persons with active tuberculosis are effectively treated at rate ϕ. LTBI, latent tuberculosis infection.

The model is specified by four ordinary differential equations as follows: $dX/dt = \pi - \beta XT - \mu X$

$$dE/dt = \beta XT - (\mu + \omega + \theta)E$$

$$dL/dt = (1-p)\omega E - (\mu + \nu + \sigma)L$$

$dT/dt = p\beta XT + \nu L - (\mu + \mu_T + \phi)T$ Using these equations, we derived the reproductive rate (*R*) for the model. The reproductive rate (*R*) is defined as the number of secondary cases caused by the introduction of one case of infectious tuberculosis into a population of susceptible persons (4, 5). If *R* is less than 1, the epidemic is eventually eliminated. If *R* is greater than 1, the

epidemic spreads in a susceptible population.

The calculated reproductive rate for the model is

$$R = (\beta\pi/\mu)\{1/(\mu + \mu_T + \phi)\}[p\omega/(\mu + \omega + \theta) + (1-p)\omega\nu/\{(\mu + \omega + \theta)(\mu + \bar{\omega} + \sigma)\}]$$

By setting $R = 1$, we calculate the rates of effective treatment for active tuberculosis (ϕ), effective treatment of early LTBI (θ), and effective treatment for long-term LTBI (σ) that would eliminate the epidemic. We demonstrate the effect of increasing treatment rates for active tuberculosis and increasing treatment rates for early LTBI on decreasing incidence of tuberculosis by providing numerical solutions of the model. For each scenario in the numerical solutions, we assume steady-state initial conditions with 50 percent treatment rate.

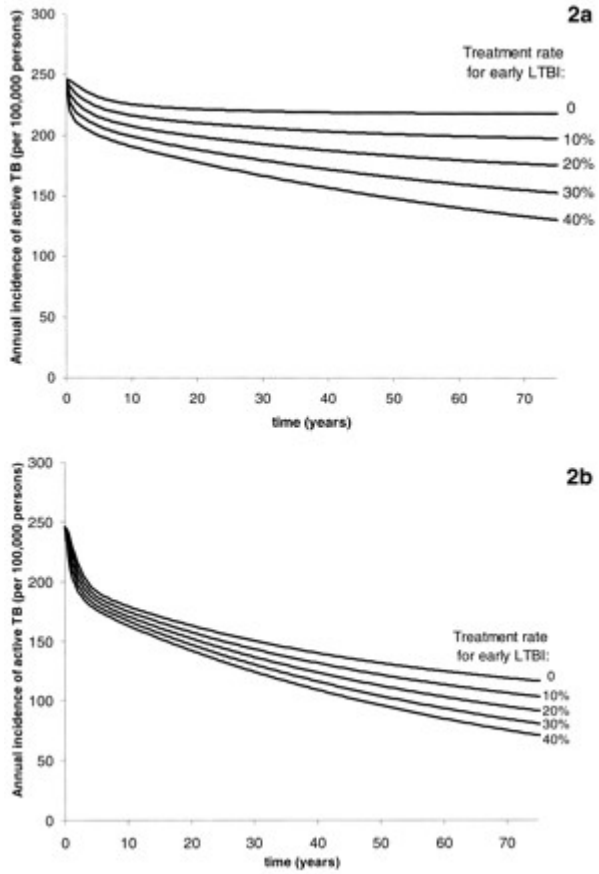
The parameter values are set so that uninfected persons live on average for 50 years ($\mu = 0.02$); $\pi = 2 \times 10^5$ (birth rate is set so that the population size is 1×10^6, without infection); $\beta = 7 \times 10^{-6}$ for a moderate epidemic (corresponding to seven new infections per infectious case per year); $p = 0.05$ (the probability of progressing to active tuberculosis during early LTBI without treatment); $\nu = 0.00256$ corresponding to 5 percent probability of development of disease over 20 years during the long-term LTBI stage; $\mu_T = 0.139$ corresponding to a 50 percent death rate in 5 years for untreated active tuberculosis. These parameter values have been previously discussed by Blower et al. (4). We assume that 95 percent of infected persons progress through the early LTBI phase in 2 years ($\omega = 1.5$) (1).

RESULTS

The impact of therapy for early LTBI is greatest when treatment rates for active tuberculosis are lower. Figure 2 demonstrates the effect of increasing treatment for early LTBI on tuberculosis incidence over time. If the treatment rate for active tuberculosis is increased from 50 percent to 60 percent, adding therapy for early

LTBI substantially reduces tuberculosis incidence (figure 2a). In contrast, if the treatment rate for active tuberculosis is increased from 50 percent to 80 percent (figure 2b), the additional impact of increasing therapy for early LTBI is less important in determining the decline in tuberculosis incidence. However, even when treatment rates for active tuberculosis are high, treatment of early LTBI may be necessary to eliminate tuberculosis.

FIGURE 2.

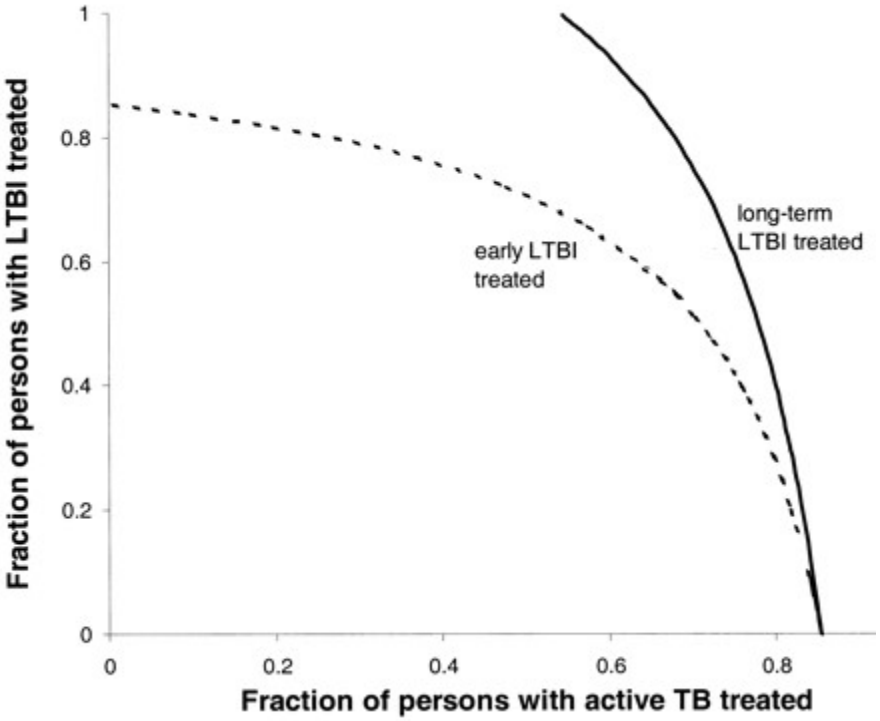


Effect of control measures on tuberculosis (TB) incidence is demonstrated over time. In each scenario the incidence of tuberculosis is initially constant at 246 cases per 100,000 persons per year, with the treatment rate for active tuberculosis at 50%. 2a, demonstration of the impact of increasing treatment rates of active tuberculosis to 60% and adding 0, 10%, 20%, 30%, and 40% treatment for early latent tuberculosis infection (LTBI); 2b, demonstration of the effect of increasing treatment rates for active tuberculosis to 80% and adding 0, 10%, 20%, 30%, and 40% treatment for early latent tuberculosis infection.

Figure 3 demonstrates the combinations of treatment rates for

active tuberculosis and treatment rates for either early LTBI or long-term LTBI that will eliminate tuberculosis. Each curve represents the threshold rates of therapy for active cases and LTBI that will lead to elimination. For example, if 80 percent of active tuberculosis cases are effectively treated, then a program that treats greater than 25 percent of early LTBI cases would result in eventual elimination. In general, the rates of treatment of LTBI required to eliminate tuberculosis are always lower for early LTBI than for long-term LTBI (figure 3). For example, if 75 percent of active tuberculosis cases are effectively treated, then a program that treats greater than 41 percent of early LTBI cases would result in elimination. Under the same conditions, a program that treats greater than 61 percent of persons with long-term LTBI would also result in elimination. As the treatment rate for active tuberculosis cases decreases, the difference between the strategy of therapy for early LTBI infection and therapy for long-term tuberculosis infection increases. Furthermore, in certain situations, effective therapy for long-term LTBI cannot eliminate the epidemic even if it is universally applied, while the addition of enough therapy for early LTBI will always eliminate the epidemic. For example, if fewer than 54 percent of active tuberculosis cases are treated, then the addition of therapy for long-term LTBI cannot eliminate the epidemic. Under the same conditions, effective treatment of 67 percent of the early LTBI cases will eliminate the epidemic.

FIGURE 3.



Critical thresholds for tuberculosis (TB) elimination. The curves represent the fraction of persons with either early latent tuberculosis infection (LTBI) (– – –) or long-term LTBI (–) who require therapy to eliminate tuberculosis in relation to the fraction of active tuberculosis cases treated. All values of treatment greater than this threshold will lead to the eventual elimination of the epidemic.

Since almost all infected persons progress through the period of early LTBI in 2 years, the group of persons with early LTBI remains a relatively small fraction of the population. In contrast, as the epidemic becomes more severe, the majority of the population may be in the long-term LTBI phase. Therefore, the difference between the strategy of treating early LTBI and that of long-term LTBI is further magnified when considering what fraction of the general population is required to treat to eliminate tuberculosis. For example, in a moderate epidemic in which 75 percent of active tuberculosis cases are treated, if only long-term LTBI is targeted, the model predicts that over 20 percent of the general population would require therapy to eliminate tuberculosis. However, under the same conditions, if early LTBI alone is targeted, less than 0.3 percent of the general population would require therapy to eliminate tuberculosis.

DISCUSSION

Recent estimates suggest that as much as 32 percent of the world's population is infected with *Mycobacterium tuberculosis* (11). Although therapy for LTBI is effective in reducing the probability of developing active tuberculosis, providing therapy for such a large fraction of the population is not feasible. An alternative strategy may be to focus on identifying and treating those at highest risk for developing active tuberculosis, such as recently infected persons. Although contact investigation programs have been implemented in many communities, their efficacy in identifying and treating contacts may vary. For example, investigators in San Francisco noted a rise from a median of one contact per case in 1991 to three contacts per case in 1997 with improvement of the contact investigation program (12).

Mathematical models of tuberculosis have been used to evaluate the epidemic effect of treating active tuberculosis cases (5, 7, 9, 10), vaccinating against tuberculosis (7, 8, 13), and providing therapy for cases of latent infection (5, 7, 10). Although others have examined the epidemic effect of providing therapy for latent infection, to our knowledge, no previous model has examined different targeting strategies for subgroups of those latently infected. Here, we evaluate the strategy of therapy for early latent infection and quantified its efficacy as an adjunct to therapy for active disease in controlling tuberculosis epidemics. We demonstrate that the addition of a program that treats up to 40 percent of persons with early LTBI will have a substantial impact on the epidemic. We also quantify how effective a program of treatment for cases of early LTBI needs to be to eliminate tuberculosis, when used in conjunction with treatment for active tuberculosis. We compare the strategy of treating early LTBI cases with treating long-term LTBI cases and demonstrate that a smaller proportion of early LTBI cases needs to be treated to eliminate tuberculosis. The difference between these two strategies becomes greater when treatment rates for active tuberculosis are lower. Furthermore, even if a large proportion of

the general population is latently infected, the size of the subgroup with early LTBI remains small. Such conditions are generally more likely to exist in the developing world where it is estimated that in some regions up to half of the population is infected with tuberculosis (11). Our model demonstrates that a much smaller scale program to identify those with early LTBI could be more effective in controlling the epidemic in such regions. Although identifying and treating persons with early LTBI as contacts of active cases may require a substantial investment of resources, the benefit of treating these persons is significant in comparison with therapy for those with long-term LTBI.

It is unlikely that even the most comprehensive contact investigation will identify all cases of recently infected persons. Some proportion of those recently infected will have contracted tuberculosis from a brief or casual contact who may not identify them as part of a contact investigation. By varying the proportion of those with early LTBI treated over a wide range, we have demonstrated the possible range of efficacy of contact investigation programs. Our model does not account for coinfection with human immunodeficiency virus and tuberculosis. Persons who are coinfected have a higher risk of progression to active tuberculosis (14). Therefore, care should be taken in extending these results to areas with high rates of human immunodeficiency virus infection.

As tuberculosis control programs develop the ability to find and treat active cases of disease, the next step in tuberculosis control should be to develop methods of preventing new cases. As part of that effort, targeted screening and treatment of early LTBI cases through effective contact investigation programs may substantially contribute to the effort to control tuberculosis.

Reprint requests to Dr. Elad Ziv, Box 111-A1, Division of General Internal Medicine, Veterans' Affairs Medical Center, 4150 Clement St., San Francisco, CA 94121 (e-mail: eziv@itsa.ucsf.edu).

Financial support was from the National Institute of Allergy and Infectious Diseases (R01-AI41935) and the Office of Academic

Affairs, Department of Veterans' Affairs.

The authors are extremely grateful to T. Lietman, H. Gaff, H. Gershengorn, K. Koelle, W. Browner, D. Grady, M. Shlipak, M. Kushel, and T. Ziv for insightful comments on earlier versions of this manuscript.

REFERENCES

1. Ferebee S. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc* 1970;26:28–106.

2. Tuberculosis elimination revisited: obstacles, opportunities, and a renewed commitment. Advisory Council for the Elimination of Tuberculosis (ACET). *MMWR Morb Mortal Wkly Rep* 1999;48(RR-9):1–13.

3. Enarson D, Rieder H, Arnadottir T, et al. Tuberculosis guide for low income countries. Vol 4. Paris, France: International Union against Tuberculosis and Lung Disease, 1996.

4. Blower S, McLean A, Porco P, et al. The intrinsic transmission dynamics of tuberculosis epidemics. *Nat Med* 1995;1:815–21.

5. Blower S, Small P, Hopewell P. Control strategies for tuberculosis epidemics: new models for old problems. *Science* 1996;273:497–500.

6. Blower S, Gerberding J. Understanding, predicting and controlling the emergence of drug-resistant tuberculosis: a theoretical framework. *J Mol Med* 1998;76:624–36.

7. Brewer T, Heymann S, Colditz G, et al. Evaluation of tuberculosis control policies using computer simulation. *JAMA* 1996;276:1898–903.

8. Castillo-Chavez C, Feng Z. Global stability of an age-structured model for tuberculosis and its application to vaccination strategies. *Math Biosci* 1998;151:135–54.

9. Dye C, Garnett GP, Sleeman K, et al. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet* 1998;352:1886–91.

10. Murray C, Salomon J. Modeling the impact of global tuberculosis control strategies. *Proc Natl Acad Sci U S A* 1998;95:13881–6.

11. Dye C, Scheele S, Dolin P, et al. Global burden of tuberculosis. *JAMA* 1999;282:677–85.

12. Jasmer R, Hahn J, Small P, et al. A molecular epidemiologic analysis of tuberculosis trends in San Francisco, 1991–1997. *Ann Intern Med* 1999;130:971–8.

13. Lietman T, Blower SM. Potential impact of tuberculosis vaccines as epidemic control agents. *Clin Infect Dis* 2000;30(suppl 3):S316–22.

14. Daley C, Small P, Schecter G, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. *N Engl J Med* 1992;326:231–5.