The impact of HIV/AIDS on the control of tuberculosis in India

B. G. Williams*, R. Granich[†‡], L. S. Chauhan[§], N. S. Dharmshaktu[¶], and C. Dye*[‖]

*World Health Organization, 20 Avenue Appia, Geneva 1212, Switzerland; [†]Office of World Health Organization Representative to India, New Delhi 11011, India; [‡]International Research and Programs Branch, Division of TB Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control, Atlanta, GA 30333; [§]Ministry of Health and Family Welfare, 523 C, Nirman Bhavan, New Delhi 11011 India; and [¶]National AIDS Control Organization, Ministry of Health and Family Welfare, New Delhi 11011, India

Edited by Kenneth W. Wachter, University of California, Berkeley, CA, and approved May 17, 2005 (received for review February 27, 2005)

Epidemics of HIV/AIDS have increased the tuberculosis (TB) caseload by five or more times in East Africa and southern Africa. As HIV continues to spread, warnings have been issued of disastrous AIDS and TB epidemics in ''new-wave'' countries, including India, which accounts for 20% of all new TB cases arising in the world each year. Here we investigate whether, in the face of the HIV epidemic, India's Revised National TB Control Program (RNTCP) could halve TB prevalence and death rates in the period 1990–2015, as specified by the United Nations Millennium Development Goals. Using a mathematical model to capture the spatial and temporal variation in TB and HIV in India, we predict that, without the RNTCP, HIV would increase TB prevalence (by 1%), incidence (by 12%), and mortality rates (by 33%) between 1990 and 2015. With the RNTCP, however, we expect substantial reductions in prevalence (by 68%), incidence (by 41%), and mortality (by 39%) between 1990 and 2015. In India, 29% of adults but 72% of HIV-positive adults live in four large states in the south where, even with the RNTCP, mortality is expected to fall by only 15% between 1990 and 2015. Nationally, the RNTCP should be able to reverse the increases in TB burden due to HIV but, to ensure that TB mortality is reduced by 50% or more by 2015, HIV-infected TB patients should be provided with antiretroviral therapy in addition to the recommended treatment for TB.

millenium development | goals | infectious disease control | dynamical simulation model

In many countries of East and southern Africa, tuberculosis (TB) notification rates have increased by five or more times as a result of the HIV epidemic (1–3). If this were to happen in India, which accounts for 20% of the global burden of TB (1), the total number of TB cases in the world would more than double. At present, <1% of Indian adults are infected with HIV, but that is about five million people (4), second only in number to South Africa (5, 6). It has been suggested that the prevalence of HIV infection in Indian adults could reach 5%, or ≈25 million people (7–9), and an HIV epidemic on this scale would have severe consequences for the burden not only of AIDS but also of TB.

In 1993, the Government of India launched a pilot project to explore the implementation of the World Health Organization's DOTS strategy for TB control, based on combination chemotherapy (10, 11). In 1998, the Revised National TB Control Program (RNTCP) began to expand DOTS services across India. By the end of 2003, 740 million people had access to DOTS, and a further 10 million were gaining access each month. In DOTS areas in 2003, an estimated 69% of new smear-positive TB cases were detected, and 87% were successfully treated (1). Without the HIV epidemic, the RNTCP might have been expected to reduce TB incidence, prevalence, and mortality rates by ≈5% per year (12–14).

In this paper, we use a dynamical simulation model to investigate the impact of the HIV epidemic and the RNTCP DOTS program on TB in India from 1990 to 2015. In particular, we ask whether the RNTCP could halve TB prevalence and death rates, as specified by the United Nations Millennium Development Goals (MDGs), in the face of the HIV epidemic (1, 15).

Methods

Model Structure. The TB model is based on previous work (12, 16) and full details are available from the authors on request. We include only adults, who account for >90% of TB cases and all HIV cases, apart from children who are infected through vertical transmission. We do not separate adults into different age classes. People enter the model at 15 years of age, some with a latent TB infection. Among adults who acquire infection, a fraction progress immediately to active TB, whereas the rest enter the latent class. Of those that develop active disease, a fraction have infectious sputum-smear-positive (SS+) TB. The rest have noninfectious sputum-smear-negative TB (SS−, pulmonary and extrapulmonary disease), which may progress to SS+ disease. Individuals in the latent class are less likely than people in the susceptible class to develop TB as a result of reinfection. Individuals with active TB disease die at a per capita rate higher for SS+ than SS− cases. Case detection by the RNTCP removes individuals with active SS+ or SS− disease from the prevalent pool at a fixed per capita rate.

To model HIV, we use estimates of the HIV prevalence over time for women attending antenatal clinics (ANCs). Following UNAIDS (The Joint United Nations Programme on HIV/AIDS) (17), we assume this is a good approximation to community prevalence in adults. From changes in prevalence over time, we calculate the HIV incidence over time assuming a Weibull survival distribution from the time of infection (details available from the authors). As people infected with HIV progress toward AIDS, their risk of developing TB increases (18). We include four stages of HIV infection and allow people infected with HIV to progress from each stage to the next at a constant rate and die when they leave the last stage. The resulting survival distribution is not significantly different from the Weibull distribution (details available from the authors).

The basic TB model is therefore repeated four times, once for each stage of HIV. People move within these submodels as they do in the primary model, except that (*i*) the parameters involving the risk, progression, and infectiousness of TB depend on their HIV stage, and (*ii*) people move between equivalent TB classes but different HIV stages according to the calculated incidence of HIV (uninfected to HIV stage 1) or the rate of progression (HIV stages 1–4).

This paper was submitted directly (Track II) to the PNAS office.

Freely available online through the PNAS open access option.

Abbreviations: TB, tuberculosis; RNTCP, Revised National TB Control Program; MDG, Millennium Development Goals; DOTS, Directly Observed Therapy Short Course; SS+, sputum smear positive; SS−, sputum smear negative; ARI, annual risk of TB infection; STI, sexually transmitted infection; IVDU, intravenous drug users; ANC, antenatal clinic.

[‖]To whom correspondence should be addressed. E-mail: dyec@who.int.

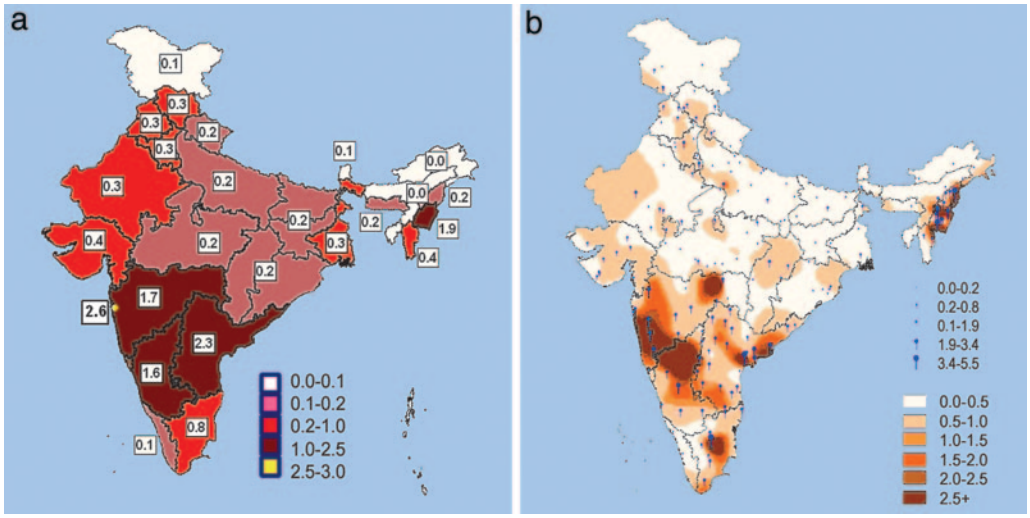

Fig. 1. Percent prevalence of HIV infection among women attending ANCs in 2000. (*a*) The colors show the percent prevalence of HIV in each state (yellow dot is Mumbai). (*b*) Blue symbols indicate the location of each ANC site; the size of the symbol shows the prevalence. Individual data points were interpolated and smoothed, using a Krieging algorithm in ARC-VIEW (ESRI, Redlands, CA), to obtain the contour plot of prevalence with the values indicated by the different colors.

Data Sources. We determine TB parameters using data from the literature (2, 12); from prevalence and incidence studies in Chennai, India (19); from recent studies of the annual risk of TB infection (ARI) in India (20–23); and from the RNTCP (1). We estimate current levels and future trends of HIV infection using prevalence data from sentinel sites and population estimates for each state provided by the National AIDS Control Organization (24) (data available from the authors on request). Starting in 1998, HIV prevalence data have been collected from ANCs, sexually transmitted infection (STI) clinics, intravenous drug users (IVDUs), and blood donors. Data are available from the U.S. Bureau of the Census (25) for the early years of the HIV epidemic and are used to establish the timing of the initial rise in the prevalence of HIV (details available from the authors). To determine TB parameters for HIV-positive people, we used the results of a previous analysis (18) to determine the relative values of the parameters determining the risks of TB in the different stages of HIV and scaled these to match the values for late stage HIV we obtained previously (2) (details available from the authors).

Here the most important TB parameters are those that vary with the stage of HIV infection. From a study of the relative risk of TB as a function of $CD4^+$ cell count, we estimate the relative risk of progressive primary TB and endogenous reactivation for each of the four stages of HIV (17). We allow the proportion of progressive primary cases that are infectious, the rate of smear conversion, and the infectiousness of people with HIV to decline with decreasing $CD4^+$ cell count (26–35).

We assume that TB was in a steady state before the advent of HIV/AIDS. World Health Organization estimates are used to set the initial SS+ and SS− incidence of TB (1). Recent estimates have been made of the prevalence of SS+ and SS− TB in India, and we use these values here (36).

Tuberculin surveys of the prevalence of TB infection in four zones covering India (details available from the authors) give estimates of the ARI ranging from 1.2% in the southern zone to 1.9% in the northern zone (37).

DOTS coverage in India has expanded rapidly and, by 2003, 67% of the population was covered by DOTS (1, 38–40). World Health Organization estimates that in India the cure rate is 42% in areas not covered by DOTS and 87% in areas covered by DOTS, whereas the corresponding case detection rates (the number of notified cases divided by the number of new cases in a particular year) are 58% and 69%, respectively (1). The RNTCP plans to reach full national coverage with DOTS by the end of 2005, with a SS+ case detection rate of 70%, while maintaining the performance of the program thereafter.

Model Implementation. We initialize the model using demographic parameters for India and start with TB transmission parameters from an earlier study (2). We then vary (*i*) the proportion of people in each TB class of the model to ensure an initial steady state and (*ii*) the ARI and the rate of relapse from failed treatment to active TB to fit, by least squares, the initial incidence and prevalence of SS+ and SS− TB, assuming that before the RNTCP or the advent of the HIV epidemic, TB was in a steady state. (Parameter values are available from the authors.)

Curve Fitting, Error Estimates, and Sensitivity Analysis. To determine temporal trends in the prevalence of HIV, we fitted logistic curves to the ANC data for each state using maximum likelihood. If there was evidence that the data deviated significantly from the logistic curve, we fitted a double logistic curve (2) to check for evidence that the prevalence had declined significantly in recent years. For each state, we determined 95% confidence limits from the inverse of the information matrix (41) and used Monte Carlo sampling of the parameters to determine 95% confidence limits for the estimated trends in the prevalence of HIV in each state of India. Estimated errors are 95% confidence limits throughout (additional details are available from the authors).

The focus of this paper is the impact of HIV on TB and the extent to which this will compromise the impact of the RNTCP on the TB epidemic. The main source of uncertainty in the model arises from the lack of data on the impact of HIV on TB at a population level. Confidence limits for the projections were therefore obtained by allowing for the uncertainty in the parameters that determine the impact of HIV on TB using Monte Carlo sampling to determine 95% confidence limits for the model outputs. We carried out a separate sensitivity analysis to determine which of the parameters in the model, other than those that determine the impact of HIV on TB, have the greatest effect on the projected TB prevalence, incidence and mortality (details available from the authors).

Results

Model Validation. In the initial state, the ARI is 1.5% in agreement with the value of 1.5% ± 0.3% obtained recently (37). The

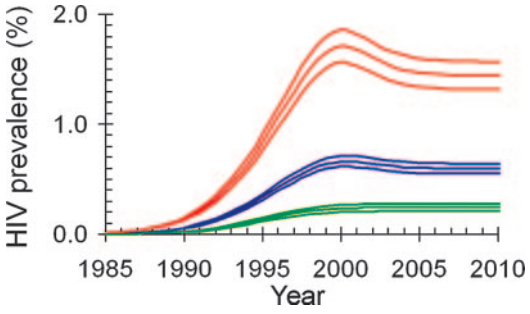

Fig. 2. Estimated prevalence of HIV infection among women attending ANCs in India. Blue lines, all India; red lines, high-prevalence states in south India (Maharashtra, Mumbai, Andhra Pradesh, Tamil Nadu, and Karnataka); green lines, low-prevalence states in north India (and Kerala). Lines are weighted averages of double logistic curves fitted to state data with 95% confidence bands as described in the text.

predicted ratio of the prevalence of HIV in TB patients to that in the general population rises to 8.8 in 2000, in agreement with data from Pune, where the prevalence of HIV in women attending ANCs between 1999 and 2001 was 3.1% (4) and in TB patients was 26% (42), giving a ratio of 8.3.

Temporal Trends and Spatial Variation in HIV Prevalence. The prevalence of HIV in India varies among states and risk groups, and it is important to examine the trends in each of them. We first analyzed data on the prevalence of HIV among women attending ANCs for each state in India and carried out statistical tests (details available from the authors) for evidence that the prevalence of HIV infection had increased or decreased between 1998 and 2003. In Andhra Pradesh, there was a statistically significant decline in prevalence after the year 2000. In no state was there a statistically significant increase after 2000. However, there may be risk groups among whom infection rates are only now starting to increase and from which infection could spread to the general population. We therefore carried out a similar analysis of HIV-prevalence data for IVDUs and STI clinic attendees. We found no evidence that the prevalence of infection is increasing in IVDUs or STI clinic attendees in any state, whereas among IVDUs in Manipur, of whom ≈30–40% are infected with HIV, and among STI clinic attendees in Maharashtra, Gujarat, and Andhra Pradesh, there is evidence that the prevalence of HIV is declining.

The spatial distribution of HIV prevalence among women attending ANCs in India in the year 2000 is shown in Fig. 1. The prevalence of infection in four southern states, Maharashtra, Andhra Pradesh, Tamil Nadu, and Karnataka, and in Manipur in the extreme east of India, is 5–10 times higher than in the remaining states in the north of India and in Kerala in the southwest (Fig. 1*a*). Interpolating the data for individual ANC sites gives a contour map of the distribution of HIV prevalence (Fig. 1*b*). The data for individual sites may not always be reliable, but together they suggest that the prevalence is particularly high across an area stretching from Mumbai down to Karnataka, in an area in the northeast of Maharashtra, along the north coast of Andhra Pradesh, and in the center of Tamil Nadu. The spatial distribution of HIV infection among IVDU, STI patients, and blood donors is similar; HIV infection rates in these groups are strongly correlated with HIV infection rates among women attending ANCs (details available from the authors).

Using the data in Fig. 1*a* to group states, the trends in the ANC prevalence of HIV infection over time are shown in Fig. 2 for the high prevalence states (mainly in the south of India), for the low prevalence states (mainly in the north of India), and for the whole of India. The estimated prevalence for 2002 is 0.64 ± 0.05%, slightly lower than the National AIDS Control Organization estimate for that year of 0.79 ± 0.04% (4).

The Impact of HIV on TB. Fig. 3 shows the impact of HIV, of the RNTCP, and of both together on the prevalence, incidence, and mortality in SS+ and SS− TB patients. Without the RNTCP

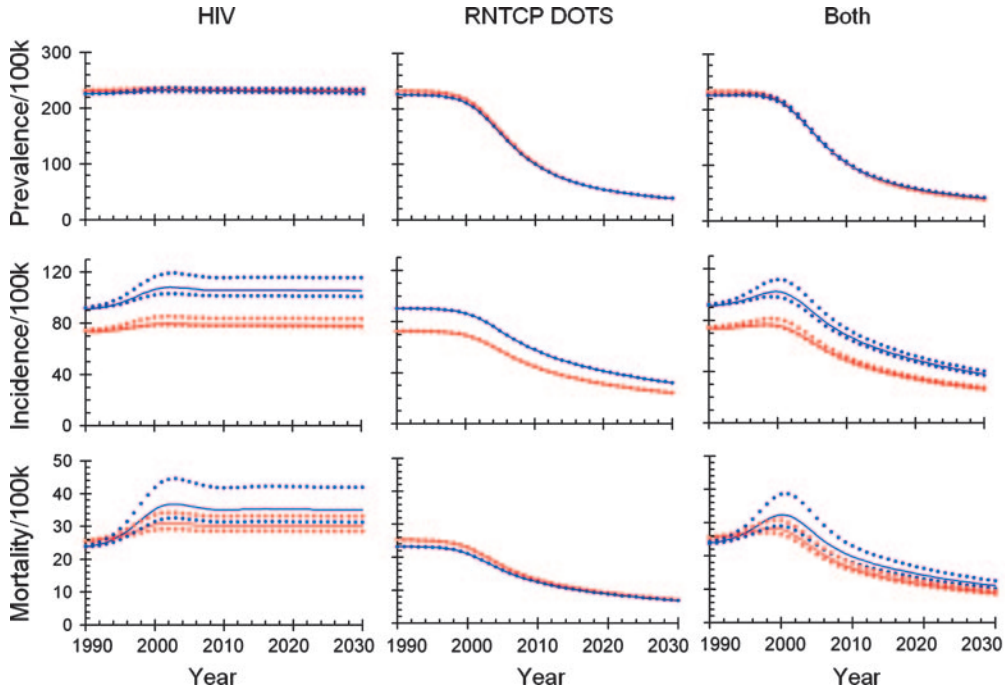

Fig. 3. HIV and TB in India. The impact of HIV (*Left*), the RNTCP DOTS program (*Center*), and both (*Right*) on TB prevalence (*Top*), annual incidence (*Middle*), and annual mortality (*Bottom*). All rates per 100,000 population. Red lines, infectious SS+ TB; blue lines, noninfectious SS− TB. Dotted lines indicate 95% confidence bands, allowing for the uncertainty in the parameters that determine the impact of HIV on TB.

Table 1. The ratio of the prevalence, incidence, and TB death rates in 2015 to those in 1990, allowing for the effects of the HIV epidemic only, of the RNTCP only, and of both together

	Prevalence ratio		Incidence ratio		Mortality ratio	
	SS+	SS−	SS+	SS−	SS+	SS−
HIV, no RNTCP	1.00 (1.00, 1.01)	1.02 (1.01, 1.04)	1.08 (1.05, 1.12)	1.16 (1.11, 1.26)	1.18 (1.12, 1.29)	1.48 (1.33, 1.74)
RNTCP, no HIV	0.31	0.31	0.51	0.53	0.43	0.44
HIV and RNTCP	0.31 (0.31, 0.32)	0.33 (0.32, 0.33)	0.55 (0.54, 0.56)	0.63 (0.60, 0.66)	0.53 (0.51, 0.57)	0.69 (0.64, 0.79)

Data are given separately for SS+ and SS− TB patients. The numbers in brackets are 95% confidence limits for the estimates, allowing for uncertainty in the impact of HIV on TB.

(Fig. 3 *Left* and Table 1), the epidemic of HIV would have led to an increase of 2% (1–4%) in SS− prevalence, 16% (11–26%) in SS− incidence and 48% (33–74%) in deaths among incident SS− cases, between 1990 and 2015. The corresponding increases in SS+ TB would have been 0% (0–1%), 8% (5–12%), and 18% (12–29%), respectively. In the absence of HIV (Fig. 3 and Table 1), the RNTCP could have reduced SS+ and SS− prevalence by 69%, incidence by 48%, and deaths by 57% between 1990 and 2015.

Taking into account the effects of both HIV and the RNTCP (Fig. 3), the model suggests that between 1990 and 2000, the prevalence rate of TB fell by 5% (4–6%), but the incidence rate increased by 8% (4–15%), and the mortality rate increased by 22% (13–39%). After 2001, the model suggests that the RNTCP began to bring the rates of TB down. By 2015, the rates of SS− prevalence, incidence, and annual mortality among incident cases are expected to fall from their 1990 values by 67% (66–68%), 37% (34- 40%), and 31% (21–36%), respectively (Table 1), whereas the corresponding declines for SS+ cases are expected to be 69% (68–70%), 45% (43–46%), and 47% (43–49%), respectively.

Table 2 gives the cumulative number of cases prevented and deaths averted by the RNTCP. Between 1990 and 2015, without HIV or the RNTCP, there would have been a total of 44 million new TB cases, of which 12 million would have died, assuming that the rates remained constant at the 1990 values. The epidemic of HIV without the RNTCP would have increased the cumulative number of TB cases by 4.6 (3.1–7.3) million and the cumulative number of TB deaths by 3.5 (2.4–5.6) million. Without HIV, on the other hand, the RNTCP would have reduced the cumulative number of TB cases by 8.6 million and of deaths among incident cases by 3.4 million between 1990 and 2015. With both HIV and the RNTCP, the cumulative number of TB cases between 1990 and 2015 is expected to fall by 5.0 (3.4–6.1) million, but the cumulative number of deaths is not expected to change significantly (1.5 million fall to 0.5 million rise). Although the positive impact of the RNTCP is somewhat offset by the impact of HIV, the situation would have been substantially worse without the RNTCP. If we include the effect of HIV and compare the outcome with and without the RNTCP, we see that, in the presence of the HIV epidemic, the RNTCP reduces the cumulative number of TB cases by 9.5 (9.2–10.6) million and of TB deaths by 4.3 (3.9–5.1) million in this 25-year period.

Fig. 4 shows the incidence, prevalence, and mortality rates separately for the low- (mainly in north India) and high-prevalence states (mainly in south India). HIV should have little impact on TB in the low-prevalence states in the north of India. In the high-prevalence states of south India, the model suggests that HIV may have increased the incidence of TB by 28% (18–45%) and the annual mortality among new TB cases by 70% (47–109%) between 1990 and 2001. After that, the RNTCP should reduce the prevalence of TB, and it will be possible to reach the MDG of halving the 1990 prevalence of TB disease by 2015. However, the RNTCP will bring the annual mortality among new TB cases back down to only about the same level as it was in 1990. Because the increase in mortality is the result of deaths among HIV-positive TB patients, it will not be possible to reach the MDG goal of halving deaths among incident TB cases unless HIV-positive TB patients have access to antiretroviral therapy.

Discussion

The goal of the RNTCP is to provide DOTS, the essential package of care for TB patients, across the whole of India. The program has grown rapidly since 1998, reaching high case detection (>60%) and cure rates (>85%) within DOTS areas, and full national coverage should be achieved by the end of 2005. If these targets are reached, this model, as other previous models (12), predicts that without HIV, it should be possible to reduce the incidence of TB by an average of ≈5% per year over the next 10 years. However, HIV presents a substantial threat to the RNTCP's ambitious program for controlling TB. Less than 1% of adults are currently infected with HIV, but India already has the second-largest number of people living with HIV/AIDS after South Africa. If the prevalence of HIV infection were to increase by five or more times, as some have suggested (7–9), the impact on the TB epidemic and the RNTCP would be devastating.

The results of this analysis are reassuring but point to some improvements that will be vital in the development of India's TB and HIV control programs. Our investigation of HIV epidemiology

Table 2. The number of incident TB cases prevented and TB deaths averted [millions (M)] considering the impact on TB of HIV only, of the RNTCP only, of both, and the impact of the RNTCP given the impact of HIV, between 1990 and 2015

	Cases averted, M		Deaths prevented, M	
	SS+	SS−	SS+	SS−
HIV, no RNTCP	−1.29 (−2.08, −0.85)	−3.28 (−5.19, −2.22)	−1.05 (−1.65, −0.72)	−2.49 (−3.90, −1.71)
RNTCP, no HIV	3.97	4.62	1.80	1.63
HIV and RNTCP	2.91 (2.52, 3.33)	2.04 (0.84, 2.80)	1.01 (0.62, 1.22)	−0.20 (−1.09, 0.29)
Both − HIV only	4.20 (4.59, 4.18)	5.32 (6.03, 5.02)	2.06 (2.28, 1.94)	2.29 (2.81, 2.00)

Data are given separately for SS+ and SS− TB patients. The numbers in brackets give 95% confidence limits for the estimates, allowing for uncertainty in the impact of HIV on TB. Negative numbers indicate increases in cases or deaths. The last row gives the difference between the third and first scenarios.

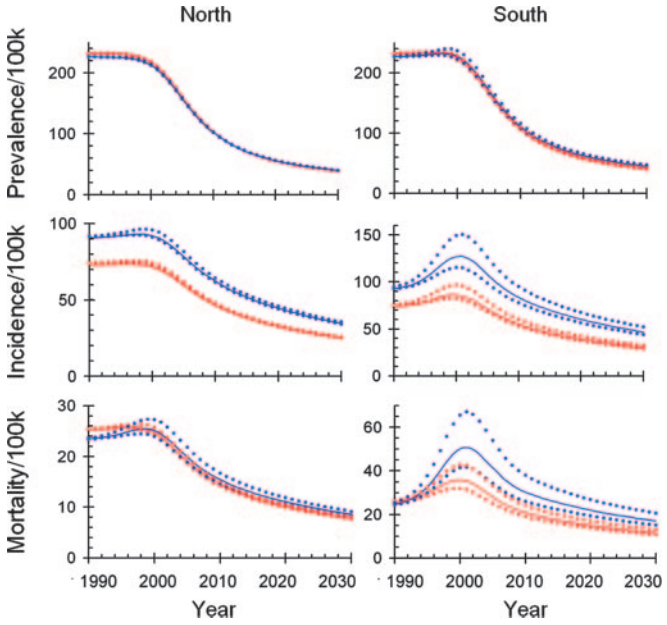

Fig. 4. The impact of HIV and the RNTCP on TB prevalence (*Top*), annual incidence (*Middle*), and annual mortality (*Bottom*) in the low-HIV-prevalence states of north India and Kerala (*Left*) and the high-HIV-prevalence states of south India (*Right*). All rates per 100,000 population. Red lines, infectious SS+ TB; blue lines, noninfectious SS− TB. Dotted lines indicate 95% confidence bands, allowing for the uncertainty in the parameters that determine the impact of HIV on TB. The states are grouped using the data in Fig. 1, as discussed in the text.

finds no evidence that the prevalence of infection is increasing significantly in any of the states in India or among any particular risk group, and there are signs that it is declining among women attending ANCs in Andhra Pradesh; among IVDUs in Manipur;, and among STI clinic attendees in Maharashtra, Gujarat, and Andhra Pradesh. However, the data are variable, and India's HIV epidemic is marked by substantial geographical differences. The National AIDS Control Organization is developing a systematic program of HIV testing (4) to describe and explain the distribution of infection more accurately across India. Although a recent study (43) shows that the ARI in the south of India may be about half of that in the north of India, these estimates are uncertain, and the difference is much less than the 10-fold variation in HIV prevalence between the north and south of India.

Having evaluated HIV prevalence and trends, the main purpose of this study was to investigate whether the RNTCP can overcome the expected HIV-driven increases in TB incidence, prevalence, and death rates. HIV has a relatively small impact on the prevalence of TB, a greater impact on the incidence of TB, and an even greater impact on TB mortality. Because HIV-positive TB patients progress more rapidly to disease, suffer much higher mortality, and are less infectious than their HIV-negative counterparts, they contribute less to TB transmission, as has been shown in other studies (44). For these reasons, a good DOTS program should be able to reduce the prevalence of TB and hence the overall risk of infection.

The possibility remains that even without the epidemic of HIV, the RNTCP would not be able to achieve the rates of reduction in TB incidence predicted by this model. In the worst-case scenario, the RNTCP would have no impact on HIV transmission, and the outcome would be as predicted by the model, in which we do not include any impact of the RNTCP. The results presented here suggest that, if the impact of the RNTCP were only half as great as has been predicted in this paper, the increase in incident cases and deaths due to HIV between now and 2015 would more or less balance the decrease due to the RNTCP, and there would be no net gain in either over the next 10 years. After 2015, the HIV epidemic would have had its full impact, and the incidence of TB would then continue to fall.

The United Nations MDG provide the principal frame of reference for evaluating TB control. Target 8 of the MDG is to have halted and begun to reverse the incidence of major diseases including TB by 2015. Two additional and more demanding objectives are to halve prevalence and death rates between 1990 and 2015 (1, 15). Our results suggest that any increase in the incidence of TB in India due to HIV has already been halted and reversed by the RNTCP, and that the RNTCP can, despite the spread of HIV, reduce TB prevalence and death rates sufficiently to satisfy the MDG nationally. However, in those states, mainly in the south, where the prevalence of HIV among adults exceeds 1%, TB mortality may fall by only 15% between 1990 and 2015. We have shown previously (17) that, whereas antiretroviral drugs are unlikely to reduce the population incidence of TB, they should save the lives of many HIV-positive TB patients. To be confident of reducing TB death rates by 50% or more by 2015, it will be important to ensure that patients have access to HIV-testing services and to antiretroviral drugs if they are HIV-positive, especially in those districts of India where the prevalence of HIV infection is high.

There are a number of uncertainties in this analysis. Because there are few data for the early stages of the HIV epidemic, the initial timing may be less certain than indicated in Fig. 2. We can be more confident about the course of the epidemic between 1998 and 2002. The most important conclusion, based on the data available up to 2002, is that HIV prevalence will not increase substantially between now and 2015. It is of course to be hoped that effective control measures will begin to bring down the prevalence of HIV and hence reduce the impact on the TB epidemic still further.

There are also uncertainties surrounding the parameters of the TB–HIV model. By far the greatest is in the impact that HIV has on the risk of TB infection, progression to active disease, and mortality. Our best estimates of the risk of developing active TB as a function of the progression of HIV infection are known only to within a factor of 2 (18). Precise data on the time course of HIV and TB in the same population would make it possible to calibrate the parameters that link TB and HIV in the model more precisely, but such data are not yet available. However, these uncertainties are captured by the wide confidence limits on the results in Figs. 3 and 4 and Table 1. They do not change the essential conclusions of this analysis, which are first that India's RNTCP should be able to reverse the rise in TB incidence and halve TB prevalence and death rates by 2015, notwithstanding the epidemic of HIV, and second, that to halve deaths by 2015, it will be necessary to ensure that TB patients are given life-saving antiretroviral therapy in addition to the recommended treatment for TB.

We thank Drs. Charles Wells, Jose Becerra, Michael Iademarco, Kenneth Castro, Dora Warren, and Eleanor Gouws for helpful comments on this manuscript. We thank Ajay Goel for preparing the map shown in Fig. 1*b* and Avijit Choudhray for compiling data on TB notification rates.

1. World Health Organization (2005) *World Health Organization Global Tuberculosis Control Surveillance, Planning, and Financing* (World Health Organization, Geneva).
2. Currie, C. S. M., Williams, B. G., Cheng, R. C. & Dye, C. (2003) *AIDS* **17,** 2501–2508.
3. Corbett, E. L., Watt, C. J., Walker, N., Maher, D., Williams, B. G., Raviglione, M. C. & Dye, C. (2003) *Arch. Intern. Med.* **163,** 1009–1021.
4. National AIDS Control Organization (2004) *National AIDS Control Organization Annual Report 2002–2004* (National AIDS Control Organization, Delhi, India).

5. Williams, B. G. & Gouws, E. (2001) *Philos. Trans. R. Soc. London B* **356,** 1077–1086.
6. Marais, H. (2004) *AIDS Epidemic Update, December 2004* (Joint United Nations Programme on HIV/AIDS, Geneva).
7. Potts, M. & Walsh, J. (2003) *Br. Med. J.* **326,** 1389–1392.
8. Gordon, D. F. (202) *The Next Wave of HIV/AIDS: Nigeria, Ethiopia, Russia, India, and China* (U.S. National Intelligence Council, Washington, DC).
9. Nagelkerke, N. J. D., Jha, P., de Vlas, S. J., Korenromp, E., Moses, S., Blanchard, J. F. & Plummer, F. A. (2002) *Bull. World Health Org.* **80,** 89–96.
10. Anonymous (1999) *What is DOTS? A Guide to Understanding the World Health Organization-Recommended TB Control Strategy Known as DOTS* (World Health Organization, Geneva).
11. Raviglione, M. C. & Pio, A. (2002) *Lancet* **359,** 775–780.
12. Dye, C., Garnett, G. P., Sleeman, K. & Williams, B. G. (1998) *Lancet* **352,** 1886–1891.
13. Styblo, K. & Bumgarner, J. R. (1991) *Tuberculosis Surveillance Research Unit of the IUATLD Progress Report* **2,** 60–72.
14. Suarez, P. G., Watt, C. J., Alarcon, E., Portocarrero, J., Zavala, D., Canales, R., Luelmo, F., Espinal, M. A. & Dye, C. (2001) *J. Infect. Dis.* **184,** 473–478.
15. Anonymous (2000) *United Nations Millennium Declaration: Resolution Adopted by the General Assembly, Fifty-Fifth Session, 18 September 2000, Agenda item 60(b)* (United Nations, New York), United Nations Publication A/RES/55/2.
16. Dye, C. & Williams, B. G. (2000) *Proc. Natl. Acad. Sci. USA* **97,** 8180–8185.
17. Grassly, N. C., Morgan, M., Walker, N., Garnett, G., Stanecki, K. A., Stover, J., Brown, T. & Ghys, P. D. (2004) *Sex. Transm. Infect.* **80,** i31–i38.
18. Williams, B. G. & Dye, C. (2003) *Science* **301,** 1535–1537.
19. Narmada, R., Narain, R., Raju, V. B., Naganna, K. & Sundaram, R. S. (1977) *Indian J. Med. Res.* **65,** 171–183.
20. Chadha, V. K., Jagannatha, P. S., Vaidyanathan, P. S., Singh, S. & Lakshminarayana (2003) *Int. J. Tuberc. Lung Dis.* **7,** 528–535.
21. Chadha, V. K., Vaidyanathan, P. S., Jagannatha, P. S., Unnikrishnan, K. P. & Mini, P. A. (2003) *Bull. World Health Org.* **81,** 573–580.
22. Chadha, V. K., Vaidyanathan, P. S., Jagannatha, P. S., Unnikrishnan, K. P., Savanur, S. J. & Mini, P. A. (2003) *Int. J. Tuberc. Lung Dis.* **7,** 536–542.
23. Chadha, V. K., Kumar, P., Gupta, J., Jagannatha, P. S., Lakshminarayana, Magesh, V., Jameel, A., Sanjay, S., Srivastava, R. K., Prasad, N., *et al.* (2004) *Int. J. Tuberc. Lung Dis.* **8,** 537–544.
24. National AIDS Control Organization (2004) *Annual Report 2002–2004* (National AIDS Control Organization, Ministry of Health and Family Welfare, Government of India, Delhi, India).
25. U.S. Census Bureau (2000) *HIV/AIDS Country Profile India, September 2000* (Population Division, International Programs Center, U.S. Census Bureau, Washington, DC).
26. Elliott, A. M., Hayes, R. J., Halwiindi, B., Luo, N., Tembo, G., Pobee, J. O., Nunn, P. P. & McAdam, K. P. (1993) *AIDS* **7,** 981–987.
27. Espinal, M. A., Peréz, E. N., Baéz, J., Henriquez, L., Fernandez, K., Lopez, M., Olivo, P. & Reingold, A. L. (2000) *Lancet* **355,** 275–280.
28. Colebunders, R. L., Ryder, R. W., Nzilambi, N., Dikilu, K., Willame, J. C., Kaboto, M., Bagala, N., Jeugmans, J., Muepu, K., Francis, H. L., *et al.* (1989) *Am. Rev. Respir. Dis.* **139,** 1082–1085.
29. Meeran, K. (1989) *Br. Med. J.* **298,** 364–365.
30. De Cock, K. M., Gnaore, E., Adjorlolo, G., Braun, M. M., Lafontaine, M. F., Yesso, G., Bretton, G., Coulibaly, I. M., Gershy-Damet, G. M., Bretton, R., *et al.* (1991) *Br. Med. J.* **302,** 496–499.
31. Githui, W., Nunn, P., Juma, E., Karimi, F., Brindle, R., Kamunyi, R., Gathua, S., Gicheha, C., Morris, J. & Omwega, M. (1992) *Tuber. Lung Dis.* **73,** 203–209.
32. Sassan-Morokro, M., De Cock, K. M., Ackah, A., Vetter, K. M., Doorly, R., Brattegaard, K., Coulibaly, D., Coulibaly, I. M. & Gayle, H. (1994) *Trans. R. Soc. Trop. Med. Hyg.* **88,** 178–181.
33. Nunn, P., Mungai, M., Nyamwaya, J., Gicheha, C., Brindle, R. J., Dunn, D. T., Githui, W. & McAdam, K. P. W. J. (1994) *Tuber. Lung Dis.* **75,** 25–32.
34. Cauthen, G. M., Dooley, S. W., Onorato, I. M., Ihle, W. W., Burr, J. M., Bigler, W. J., Witte, J. & Castro, K. G. (1996) *Am. J. Epidemiol.* **144,** 69–77.
35. Espinal, M. A., Reingold, A. L., Perez, G., Camilo, E., Soto, S., Cruz, E., Matos, N. & Gonzalez, G. (1996) *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* **13,** 155–159.
36. Tuberculosis Research Centre (2001) *Int. J. Tuberc. Lung Dis.* **5,** 142–157.
37. Chadha, V. K., Vaidyanathan, P. S. & Jagannatha, P. S. (2003) *Annual Risk of Tuberculosis Infection in Different Zones of India: A National Sample Survey 2000–2003* (Tuberculosis Research Centre, Indian Council of Medical Research, Chennai, India).
38. Khatri, G. R. & Frieden, T. R. (2000) *Int. J. Tuberc. Lung Dis.* **4,** 193–200.
39. Khatri, G. R. & Frieden, T. R. (2002) *Bull. World Health Org.* **80,** 457–463.
40. Anonymous (2002) *TB India 2002: RNTCP Status Report* (Ministry of Health and Family Welfare, New Delhi, India).
41. Williams, B. G. & Dye, C. (1994) *Parasitol. Today* **10,** 489–493.
42. Tripathi, S., Joshi, D. R., Mehendale, S. M., Menon, P., Joshi, A. N., Ghorpade, S. V., Patil, M. & Paranjape, R. S. (2002) *Ind. J. Tuberc.* **49,** 17–20.
43. Chadha, V. K., Vaidyanathan, P. S. & Jagannatha, P. S. (2003) *Annual Risk of Tuberculosis Infection in Different Zones of India: A National Sample Survey 2000–2003* (Tuberculosis Research Centre, Indian Council of Medical Research, Chennai, India).
44. Corbett, E. L., Charalambous, S., Moloi, V. M., Fielding, K., Grant, A. D., Dye, C., De Cock, K. M., Hayes, R. J., Williams, B. G. & Churchyard, G. J. (2004) *Am. J. Respir. Crit. Care Med.* **170,** 673–679.