PROSPECTS FOR GLOBAL TUBERCULOSIS CONTROL

UNDER THE WHO DOTS STRATEGY

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BACKGROUND

WHO advocates the use of Directly-Observed Therapy using a Short-course drug regimen, but the potential global impact of the DOTS strategy has not been evaluated.

METHODS

We developed an age-structured mathematical model to explore the principles of tuberculosis control under DOTS, and to forecast the impact of improved case finding and cure on TB epidemics in different regions of the world.

FINDINGS

Where TB incidence is now stable and HIV absent, a control programme which reaches the WHO targets of 70% case detection and 85% cure would reduce the incidence rate by 11%/yr (range 8-12%/yr) and the death rate by 12%/yr (9-13%/yr).

If TB has been in decline for some years, the same case detection and cure rates would have a smaller impact on incidence. DOTS saves a greater fraction of deaths than cases, and the difference is bigger in the presence of HIV. HIV epidemics cause a increase in TB incidence, but need not markedly reduce the preventable fraction of cases and deaths. Without greater control effort, annual TB incidence is expected to increase by 41% (21-61%) between now and 2020, from 7.4m to 10.6m cases/yr. Reaching WHO targets by year 2010 would save 23% (15-30%) or 48m cases by year 2020.

INTERPRETATION

The potential impact of chemotherapy (delivered as DOTS) on tuberculosis is greater in many developing countries now than it was in industrialised countries 50 years ago. To exploit this potential, case detection and cure rates urgently need to be improved in the principal endemic countries of the world.
INTRODUCTION

Short-course chemotherapy (SCC) is currently the most efficacious treatment for the majority of patients with tuberculosis (TB), and direct observation helps many patients to complete the 6-8 month treatment regimen\textsuperscript{1-3}. Passive case detection (PCD) is recommended because country-wide, active case finding would be prohibitively expensive in most countries, and because population surveys typically find that 4 in 5 cases have already sought medical attention at the time of detection by mass screening\textsuperscript{4}. Moreover, evidence from industrialized countries indicates that active case finding has very limited impact on the transmission of infection. PCD, coupled with treatment which ensured high cure rates, clearly contributed to the accelerated rates of TB decline in industrialized countries\textsuperscript{5} after 1950. Preventive therapy, the main alternative to treating active cases, is recommended for persons at high risk of developing TB (e.g. contacts of known cases, HIV-positive individuals\textsuperscript{6}), but not for entire populations because incidence rates are lower than 0.2%/yr in most parts of the world. For these reasons, the WHO DOTS strategy for global TB control embraces passive case detection using smear microscopy, directly-observed short-course chemotherapy with the recording and reporting of treatment outcomes, plus mechanisms to ensure a regular drug supply\textsuperscript{7,8}.

This partial justification for the DOTS strategy lacks two critical elements. First, we require a formal quantitative evaluation of the likely global impact of improving rates of case detection and cure. Second, there is a need to investigate how to reach and cure more patients. This paper deals with the first of these questions: we use a mathematical model which brings together data from fundamental studies of the biology of TB, and from the history of successful TB control in the developed world, in order to assess the potential impact of DOTS in those developing countries where the disease is most prevalent today.
METHODS

Model of tuberculosis

We have developed a new, age-structured tuberculosis model framed in difference equations (discrete time). Our aim has been to construct the simplest model capable of answering the questions at hand, though the result is a moderately complex compartmental\textsuperscript{18-21} model. Details of the model are in the attached technical appendix. TB arises as progressive primary disease in persons recently infected, or by endogenous reactivation (post-primary disease) or exogenous reinfection in those with remote (latent) infections. TB cases are either infectious (pulmonary, sputum smear positive) or non-infectious (pulmonary but sputum smear negative, or extra-pulmonary); both suffer an elevated death rate if untreated, the former higher than the latter. We do not distinguish between cases in men and women. Case detection is measured as the number of infectious cases diagnosed and treated/year divided by the estimated annual incidence of new infectious cases. Following convention, we refer to this as a 'rate' even though it is actually a ratio. The case detection rate is also applied to a fraction of non-infectious cases, but that fraction varies between regions of the world (Table). The interpretation of case detection rate in terms of incidence corresponds with the WHO definition; an alternative is to define case detection as the per capita rate of removal of prevalent, infectious cases\textsuperscript{7}, but this has different implications for the impact of control.

Patients who complete SCC are ‘cured’ of TB but remain infected. They move (back, for some) into the latent class, and may later reactivate. New DOTS programmes concentrate at first on achieving high cure rates; improving case detection is the second step. We therefore assume that cases who would otherwise have received inferior treatment are enrolled instead in DOTS cohorts where the cure rate is 85%; extra cases are detected and treated only when all such patients have been recruited to the new programme. Patients who do not complete treatment include those who, in the terminology of cohort analysis, ‘fail’, ‘default’ or ‘transfer out’\textsuperscript{7}. They have the same death rate as other individuals without active TB, but a fraction remains infectious (those which fail, by definition, plus a proportion of the others), and all have a higher chance of re-developing full TB than those who have been cured. Here we use the term ‘treatment failure’ to cover all three groups. Some cases resolve their disease without treatment (self-cured), but these too are assumed to have a higher chance of relapsing to full TB.

We used a separate HIV/AIDS model (modified from ref. 12) to calculate the incidence rate of HIV infection by age. HIV-positive individuals may be in any of the above states, except that self-cure from TB is excluded. Those who have been infected with HIV for more than 6 years on average suffer higher rates of breakdown to TB when infected or reinfected with Mycobacterium tuberculosis (Mtb). Further details are in the technical appendix.
Whereas some previous studies have explored the long-term impact of control (the transition from high to low endemicity, or to elimination)\textsuperscript{9}, the focus in this paper is on the potential decline in TB between now and year 2020. Numerical simulations were carried out with a time and age step of one year. Projections were made for each of the 6 WHO regions (sub-Saharan Africa, Americas, Eastern Mediterranean, Europe divided into East and West, South East Asia, Western Pacific) beginning in 1910 for Europe and 1950 for other regions, assuming that TB incidence was steady (in equilibrium) at these starting years.

Sources of data

Parameter values for the model (best estimates, with lower and upper bounds) were obtained by a comprehensive review of the literature, and by fitting to the number of incident TB cases arising in different age classes of the Dutch population 1951-89 (see technical appendix). Current case detection and cure rates in each region were based on published data\textsuperscript{6,13}, and on other data available to WHO. Rates of decline in TB since 1950 varied between regions (0.5-5%\%/yr\textsuperscript{14,15}), and were adjusted in the model by reducing the contact rate between infectious cases and others in the population. Current HIV infection rates and regional forecasts are approximately as estimated by UNAIDS\textsuperscript{16} (plus unpublished data) and we used UNPD statistics\textsuperscript{17} on population age-structures and growth rates. The values of key indicators and input variables are given in the Table.
Table. Input data and indicators for regional calculations.

<table>
<thead>
<tr>
<th>INPUT DATA (1995 unless indicated)</th>
<th>AFR</th>
<th>AMR</th>
<th>EMR</th>
<th>WEUR</th>
<th>EEUR</th>
<th>SEAR</th>
<th>WPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>annual risk of infection (ARI %)</td>
<td>2.6</td>
<td>0.6</td>
<td>1.0</td>
<td>0.1</td>
<td>0.5</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>incidence rate (all forms/100K/yr)</td>
<td>215</td>
<td>62</td>
<td>102</td>
<td>13</td>
<td>61</td>
<td>188</td>
<td>94</td>
</tr>
<tr>
<td>incidence rate (infectious cases/100K/yr)</td>
<td>106</td>
<td>34</td>
<td>55</td>
<td>7</td>
<td>34</td>
<td>102</td>
<td>52</td>
</tr>
<tr>
<td>ratio incidence rate infectious cases : ARI</td>
<td>40</td>
<td>63</td>
<td>57</td>
<td>86</td>
<td>65</td>
<td>49</td>
<td>58</td>
</tr>
<tr>
<td>Prevalence rate (infectious cases/100K)</td>
<td>201</td>
<td>55</td>
<td>101</td>
<td>8</td>
<td>55</td>
<td>184</td>
<td>83</td>
</tr>
<tr>
<td>death rate (all forms/100K/yr)</td>
<td>92</td>
<td>21</td>
<td>40</td>
<td>3</td>
<td>21</td>
<td>73</td>
<td>33</td>
</tr>
<tr>
<td>fall annual risk infection (%/yr)</td>
<td>-0.3</td>
<td>-3.2</td>
<td>-2.9</td>
<td>-5.6</td>
<td>1.3</td>
<td>-0.9</td>
<td>-1.8</td>
</tr>
<tr>
<td>fall incidence rate (%/yr)</td>
<td>2.7</td>
<td>-2.5</td>
<td>-2.1</td>
<td>-5.0</td>
<td>1.1</td>
<td>-0.3</td>
<td>-1.2</td>
</tr>
<tr>
<td>fall death rate (%/yr)</td>
<td>2.9</td>
<td>-2.7</td>
<td>-2.2</td>
<td>-4.6</td>
<td>0.7</td>
<td>-0.7</td>
<td>-1.6</td>
</tr>
<tr>
<td>fall in contact rate (%/yr)</td>
<td>-0.7</td>
<td>-0.8</td>
<td>-1.0</td>
<td>-0.5</td>
<td>-0.9</td>
<td>-0.5</td>
<td>-0.6</td>
</tr>
<tr>
<td>HIV infection in TB cases, 2020 (%)</td>
<td>21</td>
<td>2.5</td>
<td>0.2</td>
<td>0.5</td>
<td>0.5</td>
<td>4.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Population growth (%/yr)</td>
<td>2.8</td>
<td>1.4</td>
<td>2.7</td>
<td>0.4</td>
<td>0.4</td>
<td>1.7</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Control variables

| max case detection rate; new programme | 70  | 70  | 70  | 80   | 70   | 70   | 70  |
| case detection rate; old programme    | 50  | 70  | 60  | 80   | 60   | 60   | 60  |
| relative case detection rate of non-infectious cases | 0.5 | 0.7 | 0.6 | 0.8  | 0.7  | 0.6  | 0.7 |
| fraction cured; new programme         | 85  | 85  | 85  | 85   | 85   | 85   | 85  |
| fraction cured; old programme         | 40  | 60  | 50  | 75   | 60   | 50   | 60  |

Notes: Negative rates indicate decline. WHO regions: AFR, Sub-Saharan Africa; AMR, Americas; EMR, Eastern Mediterranean; WEUR, Western Europe; EEUR, Eastern Europe; SEAR, South East Asia; WPR, Western Pacific.
Model validation

Part of the process of validation is to show that the model can reflect well-known trends in TB decline in industrialised countries. In Europe, the rate of decline in the annual risk of infection before chemotherapy became widely available in the late 1940s was 4-5%/yr\textsuperscript{2}. Although the details differ from one country to another, the application of chemotherapy between 1950 and 1960 increased the decline in the annual risk of infection (ARI) up to about 12%/yr, and the decline in incidence rate of new cases (all forms of TB) to about 10%/yr\textsuperscript{3}. We have modelled control in the Netherlands by assuming that TB declined prior to 1940 as a result of reduced contact between infectives and susceptibles (achieved by isolation in sanatoria, for example), and that rates of 70% case detection and 95% cure were achieved gradually over the decade 1940-50. These assumptions give the line fits to the data shown in Figure 1. The observed ratio of ARI (%) to smear positive incidence (per 100,000 people) is about 1:50 when TB incidence is approximately steady\textsuperscript{2} (i.e. the risk of infection is 20 times the risk of disease); the ratio should decrease as TB declines because case finding and treatment shorten the duration of infectiousness, and ARI falls faster than incidence. Our model generates ratios between 1:50 and 1:60 before 1940, rising to 1:250 in 1975. The ratio of TB deaths : incidence : prevalence in the pre-chemotherapy era was roughly 1 : 2 : 4 (ref. 5), and the model generates ratios of 1 : 1.8 : 3.9.

![Graphs showing annual risk of infection and incidence rate over time.](image)

**Figure 1.** Model representation (line) of TB decline in Europe, illustrated by the fit to Dutch data (points) on the annual risk of infection (left) and incidence rate (new cases, right).
Uncertainty and sensitivity analyses

Forecasts of absolute numbers of cases and deaths are usually less certain than forecasts of relative numbers (e.g. the fraction of cases averted), so we place emphasis on the latter. All such comparative calculations were accompanied by multivariate uncertainty and sensitivity analyses. Sensitivity analysis was used to single out those parameters which most influence the results, but also to help identify the general principles of TB control set out below. Uncertainty analysis gave lower and upper bounds, or a 'range', on the estimates. All ranges are expressed as the interval between 5th and 95th centiles. These include the estimation errors and variation associated with parameter values, but not with variables such as the incidence rate of HIV. They therefore do not, and can not, embrace all the uncertainty in the system.
POTENTIAL IMPACT OF DOTS

General characteristics of tuberculosis control

Our analysis of DOTS impact has identified a series of general characteristics of TB control by chemotherapy. This section sets out these principles (Figures 1-3), whilst the next section presents specific forecasts. Seven of the characteristics relate to TB alone, and three to the relation between TB and HIV. We use two measures of the impact of control – the annual rate of decline in incidence, and the fraction of cases or deaths saved under DOTS.

(1) Incremental improvements in case detection, assuming 85% cure rate, cause (approximately) proportional increases in the rate of TB decline – the lines in Figure 2 (left) are nearly straight. The bold line indicates the rate at which the incidence of TB will fall from a steady state (averaged over 20 years; broken lines indicate 5th and 95th centiles), having increased case detection within one year from zero to any value on the x-axis. Assuming 85% cure, stable TB incidence prior to the introduction of a new programme, and a population with an age-structure typical of sub-Saharan Africa (to represent developing countries), 70% case detection will cause TB to decline at approximately 11%/yr (7-12%/yr). Clearly, incidence will fall more slowly when it takes longer to reach the target case detection rate.

![Graph showing the effects of case detection and cure rates on TB incidence decline.](image)

**Figure 2.** Effects of case detection (left) and cure rates (right) on the expected decline in TB incidence. Left: the fall in incidence generated by increasing case detection from zero to the value on the x-axis. The bold line gives the rate of decline of incidence from a pre-existing steady-state, assuming 85% cure; the dashed lines are 5th and 95th centiles. The light line is the fall in incidence starting from a situation in which the incidence is already declining by 4%/year. Right: the fall in incidence generated by increasing case detection from zero to 70% with different cure rates (x-axis); lines are drawn assuming that 25% (top) or 100% (bottom) of treatment failures remain infectious.
(2) The incidence rate will be less responsive to improvements in case detection when TB has already been in decline (light line with lower slope in Figure 2, left; intercept 4%/yr on the y-axis), as was the case in Europe prior to 1950. Case finding and cure reduce transmission, which first affects TB arising from recent infections. As TB incidence falls, a higher fraction of cases comes from temporally remote infections. Thus sensitivity analysis reveals that the rate of TB decline is directly related to the breakdown rate following (exogenous) re-infection, but inversely related to the rate of endogenous reactivation.

(3) The rate of decline in incidence is expected to decrease with time after the introduction of an improved control programme. The explanation is the same as in (2): the fraction of cases arising from remote infections steadily increases with years of control. Even when case detection and cure rates are held constant, the slowing of TB decline is inevitable. When this trend is seen in the number of reported cases\textsuperscript{19}, it need not therefore be explained by a slackening of control effort. The rate of decline in the Netherlands according to both model projections and data was about 10%/yr in 1955, falling to 8%/yr by 1975 (Figure 1).

(4) Similarly, the fall in incidence under DOTS will be greater if the programme is applied to a population of younger average age. In younger populations, which are more typical of developing countries, a larger fraction of TB cases comes from recent infections.

(5) The fall in incidence after the introduction of DOTS will be greater if the current, ineffective programme achieves lower cure rates. Lower cure rates generate more treatment failures, which have a high rate of relapse to full TB. This increases the average breakdown rate from infection to disease, and therefore increases the short-term impact on incidence of reducing transmission.

(6) High case detection rates are counter-productive when accompanied by low cure rates\textsuperscript{30}. The cure rate interacts strongly with the infectiousness of treatment failures. If only 25% of failures remain infectious (Figure 2b, top line), incidence will always decline if the case detection rate is 70%, and if the cure rate exceeds 20%. Any improvement in the cure rate will cause incidence to fall faster. If 100% of treatment failures remain infectious, 70% case detection allows an \textit{increase} in incidence until the cure rate exceeds about 50% (Figure 2, right, bottom line).
The fraction of deaths saved under DOTS is expected to be greater than the fraction of cases. The first two bars in Figure 3 show the percentage of cases and deaths prevented over 23 years (between now and 2020) when 70% case detection is reached 10 years after the introduction of a new DOTS programme. The reasons for the difference are that non-curative treatment can prevent death without eliminating infectiousness, that prevalence is reduced sooner than incidence (prevalence is more directly linked to the death rate than incidence), and that a control programme will treat some non-infectious cases alongside the infectious ones. The difference will be greater when the pre-DOTS cure rate is lower, and when DOTS programmes treat a larger fraction of smear-negative cases.

**Figure 3.** TB cases (open bars) and deaths (filled bars) averted under DOTS, without (bars 1 and 2) and with HIV (bars 3-6). DOTS prevents a greater fraction of deaths than cases, and the difference is greater in the presence of HIV.

HIV can cause many more TB cases, but need not significantly reduce the preventable fraction of cases and deaths. The results in Figure 3 (bars 3 and 4) were obtained by introducing a model HIV epidemic in which HIV incidence rises from zero to 1.5% of the general population/year over 15 years. We have deliberately chosen a high rate of HIV incidence here – similar to current nationwide estimates for Botswana or Zimbabwe – because we want to investigate whether the preventable fractions of cases and deaths can be high despite high rates of HIV. The improved TB control programme begins in year 10 of the HIV epidemic, by which time 20% of TB cases are HIV positive. Fifteen years after the introduction of
HIV, the number of TB infections had increased by 40%, as compared with no HIV. The number of cases had increased more than threefold, and the number of deaths more than fourfold. But the fractions of cases and deaths saved were diminished by only 15% and 5%, respectively. The preventable burden of TB can in principle remain high because many of the excess cases, HIV-infected or not, arise as progressive primary disease from recent, preventable infection. This is not to say that good DOTS programmes will always reduce the incidence of TB; when HIV incidence rates are high, as in the above example, DOTS prevents cases merely by slowing the rise in TB incidence.

(9) The fraction of new TB cases which is HIV-positive will be greater when the case detection rate is higher. Better case detection reduces transmission more quickly, provided the cure rate is also high (see paragraph 6). Although a large fraction of TB cases in the HIV-infected population arises as progressive primary disease (see 8), the fraction of TB cases arising this way in the HIV-uninfected population is still larger. As a result, chemotherapy will have a bigger short-term effect on the incidence of TB in the HIV-uninfected population, assuming that the case detection rate is independent of HIV status. This differential impact will increase the proportion of all incident TB cases which is HIV-positive.

(10) The difference between cases and deaths prevented is greater in the presence of HIV. This can be seen in the aggregate results (Figure 3, bars 3 and 4), but is particularly striking among HIV-positive cases (bars 5 and 6). The reason is that DOTS cannot prevent TB arising in people who are already co-infected with Mtb and HIV, but cure rates are assumed to be equally high in HIV-positive and negative cases (though a proportion of cases under treatment dies of other AIDS-related conditions)²¹,²².

Taken together, results (2), (4) and (5) imply that, by improving case detection and cure in high burden countries now (especially where HIV is low), we could expect bigger incremental gains than were achieved in developed countries when drugs first became available 50 years ago.

**Regional and global forecasts**

These conclusions can now be applied in examining how improvements in case finding and cure could change the course of the TB epidemic in different regions of the world.
Figure 4. Number (top) and fraction (bottom) of cases (open bars) and deaths (filled bars) which could be prevented in different regions of the world by meeting WHO targets for case finding and cure by year 2010 (compared with maintaining current effort).

We have calculated the number of cases and deaths which could be prevented over the next 23 years (up to 2020) in each of the 6 regions, compared with maintaining current effort, and assuming WHO targets for case finding (70%) and cure (85%) can be met by year 2010 (Figure 4, top). The greatest rewards for improved control effort, in terms of the absolute numbers of cases and deaths averted, will be in those regions which currently have the highest TB burdens: 18m cases in South East Asia (including India), 14m cases in Africa and 7m cases in the Western Pacific (including China). The numbers of
preventable deaths are 7.3m, 7.2m and 2.6m, respectively. Whilst the numbers of preventable cases and deaths vary dramatically between regions, the preventable fraction of the burden is relatively constant. That fraction lies between 16% (7-23%) for the Americas and 25% (15-35%) for SE Asia; the corresponding figures for deaths are 18% (9-27%) and 27% (16-38%) (Figure 4, bottom). Thus, despite the fact that a relatively large fraction of TB cases is HIV-positive in sub-Saharan Africa (conservatively, in the range 20-25% after 2010), the fraction of the TB burden preventable by DOTS is as high as in any other region.

The numbers of cases in the 6 regions are summed to give the global totals in Figure 5. If case finding and cure rates are maintained at present levels, estimated to be 63% and 57% respectively (based on ref. 8), we expect the annual global incidence of new cases to increase by 41% (21-61%) between now and year 2020. With current estimates of the global incidence, this is a rise from 7.4m to 10.6m cases/year, a total of 203m cases over the next 23 years. The increase in incidence will be greatest in Africa, where the growth rate of the young adult population is highest, where the HIV epidemic is largest, and where current control programmes are least effective.

**Figure 5.** Projected annual global incidence of TB assuming that WHO targets for case finding and cure are met in years 2000, 2010 and 2020, as compared with maintaining current control effort.
The impact of meeting WHO targets in the years 2000 (now highly unlikely), 2010 and 2020 are indicated by the areas between the lines in Figure 5: under these three different scenarios, 38\% (25-43\%), 23\% (15-27\%) and 14\% (8-16\%) of cases would be prevented, respectively, over the next 23 years. The fractions of deaths prevented are somewhat greater: 44\% (32-48\%), 26\% (17-29\%) and 15\% (7-17\%). These percentages correspond to 71m, 43m and 26m preventable cases, and 32m, 18m and 11m preventable deaths. For target year 2010, the maximum rate of decline in incidence would be 6-7\%/yr, after the targets had been reached.
DISCUSSION

A recent appraisal\textsuperscript{22} of best buys for research on major microbial diseases concluded that the development of strategies to extend DOTS coverage is one of the highest priorities. The results in this paper back that conclusion by quantifying the large numbers of cases and deaths that could be prevented by improving case detection and cure rates.

We have shown that the potential impact of DOTS on tuberculosis in many developing countries is even greater than the results achieved in industrialised countries when drugs became widely available 50 years ago. Whereas case detection rates above 70\% in Europe during the 1950s were associated with a fall in incidence rate of about 10\%/yr\textsuperscript{2}, it should be possible to generate such rates of decline with lower case detection rates in many developing countries with high TB burdens now. A new DOTS programme will have a bigger impact on incidence if it finds more cases sooner, if efforts are made to treat non-infectious as well as infectious cases, if it replaces a poor programme under which cure rates are low and the incidence rate has been falling slowly (or not at all), and if introduced to a relatively young population. The fraction of deaths prevented will generally be greater than the fraction of cases prevented, the more so if cure rates have been low in the past, and if the new programme treats smear-negative cases. We also find that the fraction of cases preventable by DOTS need not be markedly diminished by a large HIV epidemic. This is true provided case finding and cure rates can be maintained which, of course, is more difficult in an area of high HIV incidence which may have suffered a doubling or tripling of tuberculosis case rates.

The cure rate needs to be high in order to avoid prolonged transmission by those who fail treatment. Although treatment of any quality may reduce the number of TB deaths in the short-term, low cure rates could actually increase the rate of transmission, and hence the number of cases. This re-discovery of Styblo & Bumgarner’s\textsuperscript{23} result is particularly pertinent now that we have a better appreciation of the worldwide distribution of drug resistant TB\textsuperscript{24}. If the principal effect of drug resistance is to reduce the cure rate, further careful calculations are required of the cure rate threshold, below which case finding and treatment will make the tuberculosis epidemic progressively worse\textsuperscript{9}.

We have attempted to assess the potential rewards for introducing DOTS programmes around the world. If, instead of maintaining current effort, WHO targets for case detection and cure are reached by the year 2010, we would expect 23\% fewer cases and 26\% fewer deaths from TB over the next 23 years. With current and projected estimates of annual incidence, this amounts to 43m cases and 18m deaths. Most of these cases and deaths would be prevented in South East Asia (including India), sub-Saharan Africa, and the Western Pacific region (including China). The fraction of the burden alleviated in Africa is potentially as high as in any other region, despite the relatively high prevalence of HIV.
There are numerous uncertainties in making projections with mathematical models, and their effects are only partly reflected in the bounds on our estimates. Most of what we know about the natural history of tuberculosis – which determines model structure and parameter values – comes from studies in industrialized countries, and yet we are most interested here in the prospects for TB control in the developing world. Apart from the ranges attached to model parameter values, there are critical but unpredictable external variables. We do not know precisely how many TB cases arise each year, and how many are currently found and cured\textsuperscript{11,15}. Nor can we be sure of the course of HIV epidemics, which particularly affect projections for Africa and Asia. However, the principles of TB control revealed by our analysis do not depend on the exact results of model calculations. And, whilst predictions of the numbers of cases and deaths between now and 2020 are subject to great uncertainty, we can be more confident (roughly to the extent indicated by lower and upper bounds) about comparisons of the preventable fraction of the TB burden when control targets are met by different dates.

Even if WHO targets are met by year 2010, three-quarters of the global TB burden would not be averted over the next 23 years. Better diagnostics, drugs and vaccines, plus targeted preventive therapy, would undoubtedly help. But new control measures with the potential to have a major impact may not be available for years. Meanwhile, the most pressing tasks are to find ways of achieving higher cure rates, and reaching more cases, in the principal endemic countries of the world.

ACKNOWLEDGEMENTS

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TECHNICAL APPENDIX:
MODELLING TB CONTROL UNDER DOTS

MODEL
The structure resembles that of previous state-transfer compartmental models (Waaler 1968, Blower et al 1995, 1996), especially those which include age-structure and allow for exogenous re-infection (Vynnycky 1996, Vynnycky & Fine 1997). But the new model has emerged from a fresh appraisal of the data (Fig. 1). Definitions of variables and transition parameters are in Table 1.

![Flow diagram of the age-structured compartmental model for tuberculosis. Refer to Table 1 for definitions of variables and parameters, and to equations (1)-(9) for a formal description of the model.](image)

**Figure 1.** Flow diagram of the age-structured compartmental model for tuberculosis. Refer to Table 1 for definitions of variables and parameters, and to equations (1)-(9) for a formal description of the model.
The flow chart in Fig. 1 represents the following set of difference equations. Variables and parameters are defined in Table 1. For brevity, we write $S(t,a)$ as $S$, and $S(t+1, a+1) - S(t,a)$ as $S'$; with similar mappings leading to $L$ and $L'$, $T_i$ and $T_i'$, and so forth:

$$S' = -(\lambda(t) + m_a(a))S + m_a M$$

(1)

$$L' = \lambda(t)(1 - p(a))S - (v(a) + \lambda(t)p(a)x(a))L + dk(I_i + eI_s)$$

(2)

$$T_i' = \lambda(t)p(a)f(a)S + (v(a) + \lambda(t)p(a)x(a))f(a)L + wT_i + rF_i + r_a N_i - (n + \mu_a)T_i - dI_i$$

(3)

$$T_a' = \lambda(t)p(a)(1 - f(a))S + (v(a) + \lambda(t)p(a)x(a))(1 - f(a))L + rF_a + r_a N_a - (n + w + \mu_a)T_a - eI_a$$

(4)

$$F_i' = a(1 - k)I_i - rF_i$$

(5)

$$F_a' = a(1 - k)I_a - rF_a$$

(6)

$$N_i' = nT_i - r_a N_i$$

(7)

$$N_a' = nT_a - r_a N_a$$

(8)

$$M' = m_a(a)S - m_a M$$

(9)

The birth of susceptibles requires a boundary condition, $S(t,0) = 1$, and the maximum lifespan is taken to be 80 years, after which everyone dies. Equations (1)-(9) exclude deaths from causes other than TB because these have no influence on incidence and prevalence rates by age. However, population age structure is an important determinant of transmission, and is therefore included in the force of infection:

$$\lambda(t) = \beta(t) \sum_{a=0}^{80} \pi(t, a)(T_i + \phi F_i)$$

(10)

where $\beta(t) = \beta(0)e^{-*}$. Numerical simulations of equations (1)-(9) were carried out for a population of constant, arbitrary size. Population age-structures for the 6 WHO regions were then used to convert rates (incidence, prevalence etc) to numbers; these
Table 1. Definitions of variables and parameters in the age-structured TB model.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S(t,a)$</td>
<td>Never before infected, susceptible to infection</td>
</tr>
<tr>
<td>$L(t,a)$</td>
<td>Latently infected, or cured of TB under good chemotherapy</td>
</tr>
<tr>
<td>$T_i(t,a)$</td>
<td>Infectious (smear positive) TB; primary, endogenous, exogenous or relapse</td>
</tr>
<tr>
<td>$T_n(t,a)$</td>
<td>Non-infectious (smear negative) pulmonary and extra-pulmonary TB</td>
</tr>
<tr>
<td>$N_i(t,a)$</td>
<td>Self-cured, from infectious TB; non-infectious</td>
</tr>
<tr>
<td>$N_n(t,a)$</td>
<td>Self-cured, from non-infectious TB; non-infectious</td>
</tr>
<tr>
<td>$F_i(t,a)$</td>
<td>Proportion of $T_i$ which is not cured under treatment (classed as having ‘failed’, ‘defaulted’ or ‘transferred out’ in cohort analysis)</td>
</tr>
<tr>
<td>$F_n(t,a)$</td>
<td>As $F_i$, but from $T_n$</td>
</tr>
<tr>
<td>$M(t,a)$</td>
<td>Immune to infection, naturally (MOTT) or following vaccination</td>
</tr>
<tr>
<td>$I(t,a)$</td>
<td>Incidence rate of infectious (sub $J$) or non-infectious (sub $N$) TB</td>
</tr>
<tr>
<td>$\lambda(t)$</td>
<td>Incidence rate (all rates per capita) or force of infection, or annual risk of infection (ARI)</td>
</tr>
<tr>
<td>$\beta(t)$</td>
<td>Per capita contact rate between $T_i$ and other individuals</td>
</tr>
<tr>
<td>$\theta$</td>
<td>Exponential rate of decline in $\beta$, reflecting ‘socio-economic improvement’</td>
</tr>
<tr>
<td>$\pi(t,a)$</td>
<td>Proportion of population in age class $a$ at time $t$</td>
</tr>
<tr>
<td>$m_+(a)$</td>
<td>Rate at which immunity is acquired by $S$ as a result of non-specific natural infection (age-independent) or vaccination (age-independent, or children $&lt; 1$ yr)</td>
</tr>
<tr>
<td>$m_-$</td>
<td>Rate at which protective immunity is lost</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Death rates; subscripts $i, n, HIV$ and $TB/HIV$ refer to different rates for $T_i, T_n, T_{HIV}$ and $T_{TB/HIV}$</td>
</tr>
<tr>
<td>$f(a)$</td>
<td>Proportion of progressive primary cases which becomes infectious</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Proportion of $F_i$ which is infectious</td>
</tr>
<tr>
<td>$n(a)$</td>
<td>Rate of natural cure for $T_i$ and $T_n$</td>
</tr>
<tr>
<td>$p(a)$</td>
<td>Proportion of infected $S$ which develop progressive primary TB (within 1 yr), infectious or non-infectious</td>
</tr>
<tr>
<td>$R$</td>
<td>Rate of relapse from $F$ to $T$</td>
</tr>
<tr>
<td>$r_n$</td>
<td>Rate of relapse after self-cure, from $N$ to $T$</td>
</tr>
<tr>
<td>$v(a)$</td>
<td>Rate at which $L$ progress to $TB$ by endogenous reactivation</td>
</tr>
<tr>
<td>$W$</td>
<td>Rate of smear conversion, from non-infectious to ($T_n$) to infectious TB ($T_i$)</td>
</tr>
<tr>
<td>$x(a)$</td>
<td>Proportion of (exogenously) re-infected $L$ which is susceptible to developing TB within 1yr</td>
</tr>
<tr>
<td>$D$</td>
<td>Rate at which TB cases are found and treated</td>
</tr>
<tr>
<td>$K$</td>
<td>Proportion of treated cases given curative chemotherapy</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>Relative case detection rate of non-infectious cases</td>
</tr>
</tbody>
</table>
Table 2. Estimates for transition parameters in Table 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value (range)</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_I$</td>
<td>0.3 (0.2-0.4)</td>
<td>Rutledge &amp; Crouch 1919, Berg 1939, Drolet 1938, Thompson 1943, Tatarsi 1947, Lowe 1954, Springett 1971, NTL 1974, Grzybowski &amp; Enarson 1978</td>
</tr>
<tr>
<td>$\mu_n$</td>
<td>0.21 (0.18-0.25)</td>
<td>Lindhart 1939, Murray et al 1993</td>
</tr>
<tr>
<td>$\mu_{TB/HIV}$</td>
<td>1.0 (0.75-1.0)</td>
<td>Styblo 1977, Murray et al 1993, Barnett &amp; Styblo 1991</td>
</tr>
<tr>
<td>$f(&gt;15)$</td>
<td>0.65 (0.5-0.65)</td>
<td>Springett 1971, Olakowski 1973, NTL 1974, Enarson &amp; Rouillon 1994, Grzybowski &amp; Enarson 1978</td>
</tr>
<tr>
<td>$p(&gt;15)$</td>
<td>0.14 (0.08-0.25)</td>
<td>DiPerri et al 1989, Daley et al 1992, Edlin et al 1992, Coronado et al 1993</td>
</tr>
<tr>
<td>$p(HIV)$</td>
<td>0.67 (0.36-0.8)</td>
<td>Springett 1961, Grzybowski et al 1965, Horwitz 1969, Fereebee 1970, Chan-Yeung et al 1971</td>
</tr>
<tr>
<td>$r$</td>
<td>0.3 (0-0.5)</td>
<td>Grzybowski et al 1965, Horwitz 1969, Fereebee 1970, Chan-Yeung et al 1971</td>
</tr>
<tr>
<td>$r_n$</td>
<td>0.03 (0.02-0.04)</td>
<td>Springett 1961, Grzybowski et al 1965, Fereebee 1970, Chan-Yeung et al 1971, Campbell 1974, Nakiela et al 1975, Styblo 1986</td>
</tr>
<tr>
<td>$\nu(&gt;15)$</td>
<td>1.13×10^{-4} (10^{-4}-3×10^{-4})</td>
<td>Sutherland 1968, Sutherland et al 1982, Vynnycky 1996, Vynnycky &amp; Fine 1997, this study</td>
</tr>
<tr>
<td>$w(HIV)$</td>
<td>0.17 (0.04-0.2)</td>
<td>Schulzer et al 1992</td>
</tr>
<tr>
<td>$x(\leq 15)$</td>
<td>1.0 (0.5-1.0)</td>
<td>Assumed (no data)</td>
</tr>
<tr>
<td>$x(&gt;15)$</td>
<td>0.35 (0.1-0.6)</td>
<td>Assumed (no data)</td>
</tr>
<tr>
<td>$x(HIV)$</td>
<td>0.75 (0.5-1.0)</td>
<td>Assumed (no data)</td>
</tr>
<tr>
<td>$\phi$</td>
<td>0.5 (0.25-0.75)</td>
<td>Assumed (no data)</td>
</tr>
<tr>
<td>$w$</td>
<td>0.015 (0.007-0.02)</td>
<td>Fereebee 1970, HKCS 1974</td>
</tr>
<tr>
<td>$m_{+}(a)$</td>
<td>0.2 (0-0.5)</td>
<td>Colditz et al 1994, Fine 1994, 1995</td>
</tr>
<tr>
<td>$m_{-}$</td>
<td>0.15 (0.06-0.2)</td>
<td>MRC 1972, Hart &amp; Sutherland 1977, BTTA 1975</td>
</tr>
</tbody>
</table>

Note: All rates are per capita per year; ranges are bounds used for uncertainty analysis.
different age-structures reflect births and deaths (all causes, including TB).

For developing countries we used 1996 population age-structures (assumed to be invariable over the period of interest) to calculate weighted incidence rates which, together with projections of total population size, provided the total numbers of incident cases through time (UNPD 1996).

Equation (9) represents immunity in the simplest way. The justification is that we are not primarily concerned with the effect of acquired immunity on TB incidence, but rather with the way in which immunity might influence the impact of DOTS.

CASE DETECTION AND CURE

The case detection ‘rate’ \(d\) is the ratio of the treated cases/yr to incident cases/yr. From equations (1)-(9), for example, the incidence rate of infectious cases at age \(a\) is:

\[
I = \lambda(t)p(a)f(a)S + (v(a) + \lambda(t)p(a)x(a))f(a)L + wT_n + rF_i + r_iN_i
\]  

(11)

Equations (1)-(9) express the pre-DOTS case detection rate only. We assume that a new DOTS programme provides cure rates of 85% for everyone treated (the same for HIV-positive and negative; Grosset 1992, Harries 1997), and that case detection increases from zero to 70% (except for W Europe) over a variable number of years (Table, main text). It is recommended that new programmes concentrate on improving the cure rates of patients already seeking treatment, so we assume that no additional cases are found until the cure rate reaches 85%.

PARAMETER ESTIMATES

Most estimates were obtained from the literature (Table 2). However, we obtained further estimates of \(v(a), f(a)\) and \(x(a)\) by fitting a 3-compartment \(SLT\) sub-model (susceptible, latent, TB cases) to data describing the incidence of TB in the Netherlands (Styblo et al 1997). TB incidence in different birth cohorts is driven by the force of infection \(\lambda\), or annual risk of infection (ARI), which is measured by tuberculin skin testing. The Netherlands data include both age- and time-specific ARI since 1910, and age-specific incidence rates (new indigenous cases, excluding relapses, as 3-year averages) from 1951 to 1989. Parameters \(v(a), f(a)\) and \(x(a)\) determine the rates at which people develop primary, exogenous and endogenous disease, and can therefore be estimated by matching infection and incidence data. Although it is known that individuals have a high risk of developing disease for the first few years (average 1.8 yr; Sutherland 1968) after acquiring infection, we assume here that this high risk applies only in the first year (thus avoiding a third dimension in the model, besides age and time).

The \(SLT\) sub-model was used to generate incident cases in 7 cohorts born at 10-year intervals since 1880, and best estimates of the above parameters (with standard deviations) were obtained both by maximum likelihood and least squares (which gave
almost identical results). We assumed that there are just two age-specific rates for each parameter, to distinguish adults from children. Trying 15, 18 and 20 years as cut-off ages, the best results were obtained by defining children as $\leq 15$ years old, and we used this threshold age in all calculations. The resulting fit to Dutch incidence data is shown in Fig. 2. The goodness of fit tested the form of the sub-model, and contributed to our assessment of parameter estimates in Table 2. Estimates of $p$ ($\leq 15$ yr, 0.14 sd 0.0055; $>15$ yr, 0.25 sd 0.0038) are higher than obtained from most other studies in other countries (and therefore used as upper estimates), but agree with similar analyses of the Dutch data by Sutherland (1982) and Vynnycky (1996). (Note that these earlier models were formulated in a different way from ours, and do not give precisely comparable results.) Overdiagnosis of TB may be the explanation for the high values. Preferring the lower estimates obtained for England & Wales (Vynnycky 1996, Vynnycky & Fine 1997) we opted to use $p$ ($\leq 15$) = 0.04 and $p$ ($>15$) = 0.14 as point estimates for all the analyses described in this paper (Table 2).

Our estimates of $x$ ($>15$ yr, 0.21 sd 0.009) and $v$ ($>15$ yr, $1.13 \times 10^4$ sd $3.23 \times 10^4$) were lower than implied by the results of Sutherland et al (1982) and Vynnycky (1996). For $x$, we have chosen to compromise with a point estimate of 0.35, and for $v$ we have used our own estimated value. However, estimates for both $x$ and $v$ are accompanied by ranges sufficiently large to embrace the previous estimates made from various sets of data (Table 2). This choice of values for $p$, $x$ and $v$ yields a ratio of smear-positive incidence/10$^5$/yr : annual risk of infection (%) of about 50 when TB incidence is stable, conforming with Styblo’s (1991) well-known rule of thumb (see ‘Model validation’, main paper).

Whilst we are primarily interested in this study in the potential impact of control in highly endemic areas (poor countries), we must note that most of the data on TB natural history comes from developed countries. Where estimates of the same parameter have been derived from studies in both developed and developing countries, such as $\mu_1$ and $n$, they have not markedly differed. But this need not always be so - further data from developing countries may yield estimates which are systematically different, implying that our current forecasts are biased.

SIMULATIONS

To make projections, we first established equilibrium rates by age (0-80 years) in year zero by dropping the time dependence in equations (1)-(9), and then solving numerically. The equilibrium value of $\beta$ was calculated from the relation between force of infection and the prevalence of smear positives (equation 10). The choice of year zero varied according to the history of TB epidemiology and control in particular countries. We chose 1910 for Western Europe (although the TB decline began earlier than this, events before 1910 do not significantly affect projections from 1995), and 1950 for developing countries (approximately when drugs became widely available). Each projection simulated the change from equilibrium (steady state with respect to time), accounting for (a) the initial incidence rate in each country, (b) the duration and background rate of decline in TB (based on ARI data and modelled by reducing $\beta$) (Cauchan et al 1988, Murray et al 1993), (c) the recent history of, and prospects for improving, case finding and cure rates, (d) demography (Table, main text).
Figure 2. Least squares fit of the age-structured TB model (lines) to incidence (points, all TB cases in Dutch people/yr) in the Netherlands, 1951-1989. The maximum likelihood fit is almost identical. Parameter estimates (LSE and MLE) contribute to the estimates and ranges in Table 2.
SENSITIVITY AND UNCERTAINTY

Uncertainty refers to the imprecision of forecasts, whilst sensitivity analysis indicates which parameters and variables are most responsible for the imprecision. A parameter could be important because outcome variables are relatively responsive to unit change in its magnitude, or because a lack of information leads to an estimate with wide confidence limits. We used sensitivity analysis to find out which parameters and variables need to be measured with greatest care, but also to gain some general insights into TB control by DOTS.

For each calculation we generated 100 sets of parameters using Latin Hypercube Sampling (Blower & Dowlatabadi 1994), assuming that variables and parameters were independent, and rectangularly distributed between lower and upper limits. For sensitivity analysis, we present $2 \times 2$ groups of results: that is, for each of 2 y-variables (annual rate of fall in incidence, fraction of cases prevented under DOTS), given a fixed percentage $\pm 33\%$ change in variables, and for parameters between the limits in Table 2. The importance of each x-variable is measured by its partial rank correlation coefficient (PRCC). The statistical significance of associated t-tests depends on sample size (number of simulations); $p < 0.05$ is therefore necessary for, but does not assure, epidemiological significance.

TB incidence will decline faster under short-course chemotherapy when infections are converted more quickly into cases, and when these cases are more quickly removed. PRCCs for $r$ and $x(>15)$ are positive, and $v(>15)$ and $\theta$ are negative, because these changes increase the fraction of cases that arises quickly from the pool of infected individuals (Table 3a). The rate of removal of cases under DOTS is determined, above all, by the case detection ($d$) and cure rates ($k$), which compete with the TB death rate ($\mu_{TB}$). Poor pre-DOTS programmes (with lower $k$ especially) create the potential to reduce incidence more quickly by generating a greater number of treatment failures, which relapse at rate $r$. Low cure thereby increases the average rate at which infections become cases.

Table 3. Sensitivity analysis of the tuberculosis model. Partial rank correlation coefficients (PRCC) of key x-variables for each of two y-variables (a) the annual rate of fall in incidence (without HIV), and (b) the fraction of cases prevented under DOTS (with HIV).

<table>
<thead>
<tr>
<th>Control variables</th>
<th>PRCC</th>
<th>Parameters</th>
<th>PRCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$(DOTS)</td>
<td>0.90*</td>
<td>$R$</td>
<td>0.65*</td>
</tr>
<tr>
<td>$d$(DOTS)</td>
<td>0.57*</td>
<td>$v(&gt;15)$</td>
<td>-0.33*</td>
</tr>
<tr>
<td>$k$(pre-DOTS)</td>
<td>-0.16</td>
<td>$\mu_{TB}$</td>
<td>0.29*</td>
</tr>
<tr>
<td>$\theta$</td>
<td>-0.09</td>
<td>$x(&gt;15)$</td>
<td>0.22*</td>
</tr>
</tbody>
</table>

(b) fraction of TB cases saved (with HIV)

<table>
<thead>
<tr>
<th>Control variables</th>
<th>PRCC</th>
<th>Parameters</th>
<th>PRCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$(DOTS)</td>
<td>0.89*</td>
<td>$r$</td>
<td>0.46*</td>
</tr>
<tr>
<td>$d$(DOTS)</td>
<td>0.69*</td>
<td>$v(&gt;15)$</td>
<td>-0.24*</td>
</tr>
<tr>
<td>$k$(pre-DOTS)</td>
<td>-0.34*</td>
<td>$\mu_{TB}$</td>
<td>0.23*</td>
</tr>
<tr>
<td>$\theta$</td>
<td>-0.32*</td>
<td>$f(HIV)$</td>
<td>0.22*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$p(&gt;15)$</td>
<td>0.20*</td>
</tr>
</tbody>
</table>

Note: Asterisks denote significant t-tests at $p < 0.05$.  

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There is a strong relationship between the rate of TB decline and the fraction of cases saved, so Table 3b is similar to Table 3a. However, TB control is now taking place against the backdrop of an HIV epidemic. There is considerable doubt surrounding the value of $f_{HIV}$, which increases the number of infectious cases. The second most influential HIV-related parameter is $\mu_{TB/HIV}$ (PRCC = 0.18), which adds to $\mu_{TB}$; increasing the total rate at which cases are removed.

Notably absent from Table 3 is parameter $m_{+}(a)$. This means that the rate of acquisition of immunity, for example by vaccination, has little influence on the impact of TB control by chemotherapy.

The results of uncertainty analysis were used to attach confidence limits (CL) to estimates in the main text. These are bounds, between 5th and 95th centiles, within which 90% of simulation results lie. They under-estimate the uncertainty of forecasts because they do not allow for errors in estimating current incidence rates, or the size of the HIV epidemics. On the other hand, rectangular distributions of parameter values are more conservative than, say, triangular distributions, generating wider confidence limits. For these reasons, we do not attempt to assess uncertainty in the absolute numbers of cases and deaths, only in comparative indicators such as the two $\gamma$-variables in Table 3.

HIV/AIDS

We used a separate HIV model to generate epidemics appropriate to each of the six WHO regions of the world. Exact details of the HIV model can be found in Garnett and Anderson (1994) and in Gregson et al (unpublished MS available on request). The model has been used by Surasiengsunk et al (in press) to investigate the demographic impact of HIV in Thailand.

HIV is assumed to spread by heterosexual transmission through a population stratified according to age, sex and sexual activity. Susceptibles are exposed to HIV infection with a risk that depends upon their rate of sexual partner change, the probability that each partner is of a particular age from a particular activity group, the proportion of such partners that are infectious, and the transmission probability from those partners, which depends upon their sex and the stage of their HIV infection. HIV infection is assumed to have four stages: stage 1 is short but viraemia and transmissibility are high; stage 2 is long, viraemia is low and cases are asymptomatic; stage 3 is short with high viraemia and deteriorating immunity; stage 4 is AIDS. Stages 1 and 2 take 6 years on average. For those infected with M. tuberculosis, the risk of TB is high during stages 3 and 4. We therefore use the HIV model to generate incidence rates of stage-3 HIV infection by age, and apply these rates to each of the 9 classes of individuals in Fig. 1. We then have a parallel 9-class TB/HIV model, with the different transfer rates indicated in Table 2.
AIDS epidemics in developing countries were assumed to peak 8-13 years after the introduction of infection, sooner in Africa, later in Asia and Latin America. Demographic, behavioural and biological parameters, which determine the shape of the HIV epidemic, were derived from data for Zimbabwe (Garnett and Anderson, 1994) and Thailand (Surasiengsunk et al, 1998). Incidence rates were adjusted so as to reflect, approximately, UNAIDS projections of the HIV epidemic (UNAIDS/WHO 1997), and to generate plausible rates of HIV infection among TB cases (Raviglione et al 1997, Harries 1997, Cantwell & Binkin 1996, 1997; Table, main text). HIV incidence was assumed to remain constant through time in Western Europe.
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