Prospects for worldwide tuberculosis control under the WHO DOTS strategy

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Summary

Background WHO advocates the use of directly observed treatment with a short-course drug regimen as part of the DOTS strategy, but the potential effect of this strategy worldwide has not been investigated.

Methods We developed an age-structured mathematical model to explore the characteristics of tuberculosis control under DOTS, and to forecast the effect of improved case finding and cure on tuberculosis epidemics for each of the six WHO regions.

Findings In countries where the incidence of tuberculosis is stable and HIV-1 absent, a control programme that reaches the WHO targets of 70% case detection and 85% cure would reduce the incidence rate by 11% (range 8–12) per year and the death rate by 12% (9–13) per year. If tuberculosis has been in decline for some years, the same case detection and cure rates would have a smaller effect on incidence. DOTS saves a greater proportion of deaths than cases, and this difference is bigger in the presence of HIV-1. HIV-1 epidemics cause an increase in tuberculosis incidence, but do not substantially reduce the preventable proportion of cases and deaths. Without greater effort to control tuberculosis, the annual incidence of the disease is expected to increase by 41% (21–61) between 1998 and 2020 (from 7·4 million to 10·6 million cases per year). Achievement of WHO targets by 2010 would prevent 23% (15–30) or 48 million cases by 2020.

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

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Introduction

Short-course chemotherapy is currently the most effective treatment for most patients with tuberculosis, and direct observation helps many patients to complete the 6–8 month treatment regimen.[1–3] Passive case detection is recommended because countrywide, active case finding would be prohibitively expensive in most countries, and because population surveys typically find that four in five cases have already sought medical attention at the time of detection by mass screening.[4] Moreover, evidence from more developed countries indicates that active case finding has only a limited impact on the transmission of infection. Passive case detection, coupled with treatment that ensured high cure rates, contributed to the rapid decline in rates of tuberculosis in more developed countries after 1950.[5] Preventive therapy, the main alternative to treatment of active cases, is recommended for people at high risk of developing tuberculosis (for example, contacts of known cases, HIV-1-positive individuals[6]), but not for entire populations, because incidence rates are lower than 0·2% per year in most parts of the world. For these reasons, WHO's DOTS strategy for worldwide tuberculosis control embraces passive case detection by means of smear microscopy, directly observed short-course therapy (DOTS) with the recording and reporting of treatment outcomes, together with mechanisms to ensure a regular drug supply.[7,8]

This partial justification for the DOTS strategy lacks two critical elements. First, we require a formal quantitative assessment of the likely worldwide effect of improvement in 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 used a mathematical model that brings together data from studies of the biology of tuberculosis, and from the history of successful tuberculosis control in industrialised countries, to assess the potential effect of DOTS in those developing countries where the disease is most prevalent.

Methods

Tuberculosis model

We developed an age-structured tuberculosis model framed in difference equations (discrete time). Our aim was to construct the simplest model able to answer the questions at hand, although the result is a moderately complex compartmental model.[9–11] Details of the model are in a technical appendix available from the investigators or *The Lancet*'s website (http://www.thelancet.com).

Tuberculosis arises as progressive primary disease in people who have been newly infected, or by endogenous reactivation (post-primary disease) or exogenous reinfection in those with remote (latent) infections. Cases of tuberculosis are infectious (pulmonary, sputum-smear positive) or non-infectious (pulmonary but sputum-smear negative, or extrapulmonary). People with any form of tuberculosis have a higher death rate than the general population if they are not treated—mortality from the infectious form is higher than from the non-infectious forms.

Our model did not distinguish between cases in men and women. Case detection was measured as the number of infectious cases diagnosed and treated per year divided by the estimated annual incidence of new infectious cases. According to convention, we refer to case detection as a rate even though it is actually a ratio. The case detection rate is also applied to a fraction of non-infectious cases, and that fraction varies between regions (table). This interpretation of case detection rate in terms of incidence corresponds with the WHO definition. An alternative is to define case detection as the rate of removal of prevalent infectious cases per head of population,[9] but this definition has different implications for the impact of tuberculosis control.

Patients who complete short-course chemotherapy are cured of tuberculosis but remain infected; they move (back, for some) into the latent class, and the infection may later reactivate. The first

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Input data (1995 unless indicated)	WHO regions						
	Sub-Saharan Africa	Americas	Eastern Mediterranean	Western Europe	Eastern Europe	Southeast Asia	Western Pacific
Indicators							
Annual risk of infection (ARI %)	2·6	0·6	1·0	0·1	0·5	2·0	0·9
Incidence rates (new cases per 10^5 per year)							
All forms	215	62	102	13	61	188	94
Infectious cases	106	34	55	7	34	102	52
Ratio incidence rate infectious cases/ARI	40	63	57	86	65	49	58
Prevalence rate (infectious cases per 10^5 people)	201	55	101	8	55	184	83
Death rate (all forms per 10^5 people per year)	92	21	40	3	21	73	33
Change in annual risk of infection (% per year)	−0·3	−3·2	−2·9	−5·6	1·3	−0·9	−1·8
Change in incidence rate (% per year)	2·7	−2·5	−2·1	−5·0	1·1	−0·3	−1·2
Change in death rate (% per year)	2·9	−2·7	−2·2	−4·6	0·7	−0·7	−1·6
Change in contact rate (% per (year)	−0·7	−0·8	−1·0	−0·5	−0·9	−0·5	−0·6
HIV-1 infection in tuberculosis cases, 2020 (%)	21	2·5	0·2	0·5	0·5	4·0	1·4
Population growth (% per year)	2·8	1·4	2·7	0·4	0·4	1·7	1·1
Control variables							
Maximum 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
Old programme	40	60	50	75	60	50	60

Negative rates indicate decline.

Input data and indicators for regional calculations

aim of DOTS programmes is to achieve high cure rates. The second aim is to improve case detection. We therefore assumed that cases which would otherwise have received inferior treatment were 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.[7] These patients have the same death rate as other individuals without active tuberculosis, but a proportion remains infectious (those who fail, by definition, plus a proportion of the others), and all are more likely to redevelop full tuberculosis than those who have been cured. We use the term treatment failure to cover all three groups (fail, default, transfer out). In some patients tuberculosis will resolve without treatment (self-cured), but we assumed that these patients also have a higher chance of relapsing to full tuberculosis.

HIV-1/AIDS model

We used a separate HIV-1/AIDS model (modified from that of Garnett and Anderson[12]) to calculate the incidence rate of HIV-1 infection by age. HIV-1-positive individuals may be included in any of the above groups, except that we excluded self-cure from tuberculosis. People who have been infected with HIV-1 for longer than 6 years generally have higher rates of breakdown to tuberculosis when infected or reinfected with *Mycobacterium tuberculosis*. Further details of the HIV-1/AIDS model are in the technical appendix.

Projections of tuberculosis decline 1998–2020

Some previous studies explored the long-term effect of control (the transition from high to low endemicity, or to elimination).[9] By contrast, we focus on the potential decline in tuberculosis between 1998 and 2020. Numerical simulations were carried out with a time and age step of 1 year. We made projections for each of the six WHO regions (sub-Saharan Africa, Americas, eastern Mediterranean, Europe divided into east and west Europe, south-east Asia, western Pacific) beginning in 1910 for Europe and in 1950 for other regions, under the assumption that tuberculosis incidence was steady (in equilibrium) at these starting years. We used two measures of the effect of tuberculosis control: the annual rate of decline in incidence and the proportion of cases or deaths saved by DOTS.

Sources of data

Key indicators and variables for the model (best estimates, with lower and upper bounds) were obtained by a comprehensive review of the published research, and by fitting to the number of incident tuberculosis cases in different age-groups of the Dutch population between 1951 and 1989 (see technical appendix). Current case-detection and cure rates for each of the six WHO regions were based on published data,[8,13] and on other data available to WHO. Rates of decline in tuberculosis since 1950 varied between regions (from 0·5% to 5·0% per year),[14,15] and we adjusted for these in the model by reducing the contact rate between infectious cases and others in the population. We estimated rates of HIV-1 infection at the time of our analysis and regional forecasts with data from UNAIDS[16] (plus unpublished data) and statistics from the United Nations Population Division[17] on population age structures and growth rates. The values of key indicators and input variables are shown in the table.

Model validation

Part of the process of validation is to show that our model can reflect well-known trends in tuberculosis decline in industrialised countries. In Europe, the rate of decline in the annual risk of infection before drug therapy became widely available in the late 1940s was 4–5% per year.[5] Although the details differ among countries, the use of chemotherapy between 1950 and 1960 accelerated the decline in the annual risk of infection (ARI) to about 12% per year, and the decline in incidence rate of new cases (all forms of tuberculosis) to about 10% per year.[5] To model control in the Netherlands, we assumed that tuberculosis declined before 1940 as a result of reduced contact between people who were infected or susceptible to infection (achieved by isolation in sanatoria, for example), and that rates of 70% case detection and 95% cure were achieved gradually from 1940 to 1950. 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 the incidence of tuberculosis is steady[5]—ie, the risk of infection is 20 times the risk of disease. This ratio should decrease as tuberculosis declines because case detection 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 tuberculosis deaths to incidence to prevalence before the 1940s was roughly 1/2/4,[5] and our model generates ratios of 1/1·8/3·9.

Uncertainty and sensitivity analyses

Forecasts of absolute numbers of cases and deaths tend to be less certain than forecasts of relative numbers (for example, the proportion of cases averted), so we focus on the latter. All such comparative calculations were accompanied by multivariate uncertainty and sensitivity analyses.[18] We used sensitivity analysis to single out those variables that most influence the results, but also to identify the general characteristcs of tuberculosis control. Uncertainty analysis gave lower and upper bounds, or a range on the estimates. All ranges are expressed as the interval between the 5th and 95th centiles. The ranges include the estimation errors

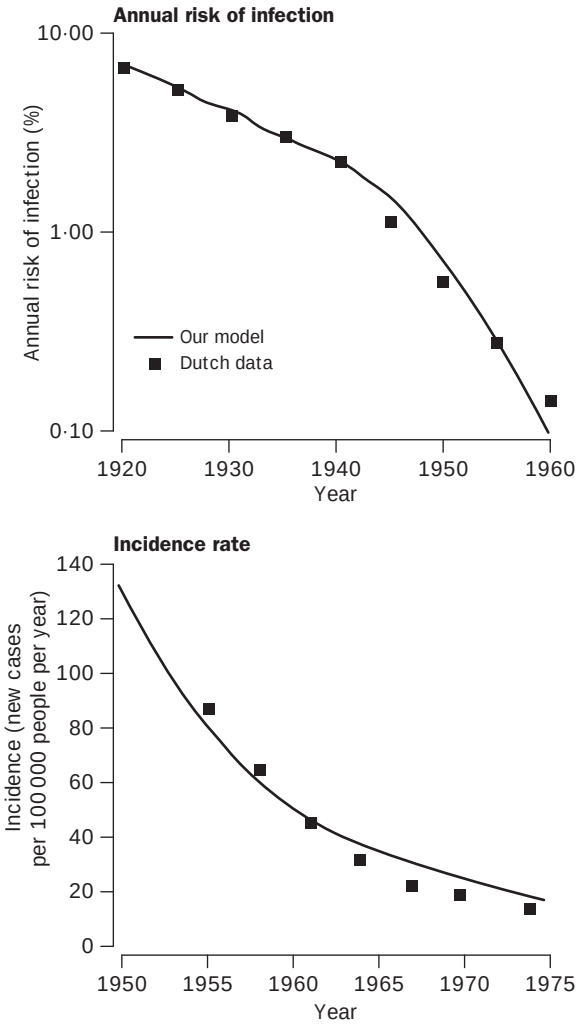

Figure 1: **Model representation of tuberculosis decline in Europe illustrated by fit to Dutch data for annual risk of infection and incidence rate**

and variation associated with indicator values, but not with variables such as the incidence rate of HIV-1 infection. They therefore do not, and cannot, embrace all the uncertainty in the system.

Results

We identified a series of general characteristics of tuberculosis control by DOTS.

Decline in tuberculosis incidence from steady state

Figure 2 shows that incremental improvements in case detection, under the assumption of an 85% cure rate, cause proportional increases in the rate of tuberculosis decline—the lines for case detection (top) in figure 2 are nearly straight. The bold line shows the rate at which the incidence of tuberculosis will fall from a steady state (averaged over 20 years), having increased case detection within 1 year from zero to any value on the *x* axis. Assuming an 85% cure rate, stable incidence of tuberculosis before the introduction of a new DOTS programme, and a population with an age distribution typical of that in sub-Saharan Africa (to represent developing countries), 70% case detection will cause tuberculosis to decline at about 11% (range 7–12) per year. Clearly, incidence will fall more slowly when the time taken to reach the target case detection rate is longer.

Decline in tuberculosis incidence when disease is already in decline

The incidence rate will be less responsive to improvements in case detection when tuberculosis has already been in decline (light line with lower slope in figure 2 [top]; intercept 4% per year on the *y* axis), as was the case in Europe before 1950. Case detection and cure reduce transmission, which first affects cases of tuberculosis that arise from recent infections. As the incidence of tuberculosis falls, a greater proportion of cases arises from temporally remote infections. Thus, sensitivity analysis reveals that the rate of decline in tuberculosis is directly related to the rate of breakdown that follows (exogenous) reinfection, but is inversely related to the rate of endogenous reactivation.

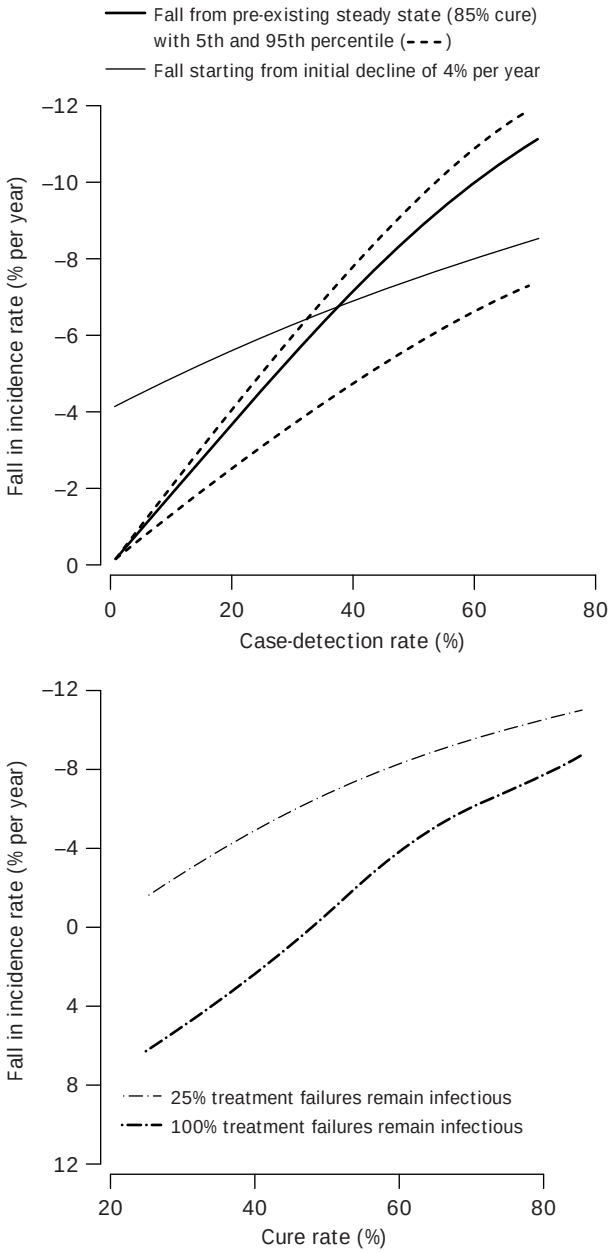

Figure 2: **Effects of case detection (top) and cure rates (bottom) on expected decline in tuberculosis incidence**

Top: fall in incidence generated by increasing case detection from zero to value on *x* axis. Negative numbers indicate a fall, positive numbers a rise.

Bottom: fall in incidence generated by increasing case detection from zero to 70% with different cure rates (*x* axis).

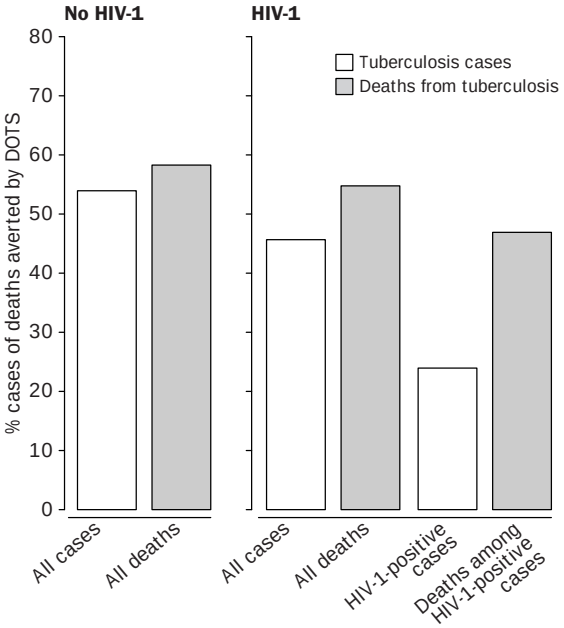

Figure 3: **Tuberculosis cases and deaths averted by DOTS, with or without HIV-1**

Decline in tuberculosis incidence after introduction of control programme

The rate of decline in incidence is expected to decrease with time after the introduction of an improved control programme, since the proportion of cases caused by remote infections steadily increases with years of control. Even when case detection and cure rates are constant, the slowing of the decline in the incidence of tuberculosis is inevitable. When this trend is seen in the number of reported cases,[19] it need not, therefore, be explained by a slackening of control effort. The rate of decline in the Netherlands according to our model projections and data was about 10% per year in 1955, and fell to 8% per year by 1975 (figure 1).

Decline in tuberculosis incidence under DOTS

The fall in incidence under DOTS will be greater if the programme is applied to a population of younger than of older average age. In younger populations, which are more typical of developing countries, a larger proportion of tuberculosis cases comes from recent infections.

The fall in incidence after the introduction of DOTS will be greater if the previous ineffective programme achieved low cure rates. Low cure rates lead to more treatment failures, which have a high rate of relapse to full tuberculosis. This situation increases the average breakdown rate from infection to disease, and therefore increases the short-term effect on incidence of a reduction in transmission of infection.

High rates of case detection are counter-productive when accompanied by low cure rates.[20] The cure rate interacts strongly with the infectiousness of treatment failures. As shown in figure 2, if only 25% of treatment failures remain infectious, 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 increase in incidence until the cure rate exceeds about 50% (figure 2).

The proportion of deaths saved by DOTS is expected to be greater than the propotion of cases. Figure 3 (left) shows the percentage of cases and deaths prevented during 23 years (between 1998 and 2020) when 70% case detection is reached 10 years after the introduction of a DOTS programme. The reasons for this difference are that: non-curative treatment can prevent death without eliminating infectiousness; prevalence is decreased sooner than incidence (prevalence is more directly linked to the death rate than to incidence); and a control programme will treat some non-infectious cases alongside the infectious ones. This difference will be greater if the pre-DOTS cure rate is low, and if DOTS programmes treat a greater proportion of smear-negative cases.

Decline in tuberculosis incidence under DOTS in relation to HIV-1

HIV-1 can cause an increase in tuberculosis cases, but need not substantially reduce the preventable proportion of cases and deaths. Figure 3 shows the effect of a model HIV-1 epidemic in which HIV-1 incidence rose from 0 to 1·5% of the general population per year over 15 years. We deliberately chose a high rate of HIV-1 incidence—simlar to nationwide estimates for Botswana or Zimbabwe—because we wanted to investigate whether the preventable proportion of tuberculosis cases and deaths can be high despite high rates of HIV-1.

In our model, the improved DOTS control programme begins in year 10 of the HIV-1 epidemic, by which time 20% of tuberculosis cases are HIV-1 positive. 15 years after the introduction of HIV-1, the number of tuberculosis infections increased by 40%, compared with a setting without HIV-1. The number of cases increased more than three-fold and the number of deaths by more than four-fold. However, the corresponding proportion of cases and deaths averted fell by only 15% and 5%, respectively. The preventable burden of tuberculosis can, in principle, remain high because many of the excess cases, whether or not they have HIV-1 infection, arise as progressive primary disease from new preventable infection. This is not to say that good DOTS programmes will always reduce the incidence of tuberculosis; when HIV-1 incidence rates are high, as in figure 3, DOTS prevents cases merely by slowing the rise in the incidence of tuberculosis.

The proportion of new tuberculosis cases that are HIV-1-positive will be greater if the case-detection rate is high. Better case detection reduces transmission rapidly, provided the cure rate is also high. Although a large proportion of tuberculosis cases in the HIV-1-infected population arises as progressive primary disease, the proportion that arises this way in the population without HIV-1 infection is still larger. As a result, chemotherapy will have a greater short-term effect on the incidence of tuberculosis in the population without HIV-1 than in those with HIV-1, on the assumption that the case-detection rate is independent of HIV-1 status. This differential effect will increase the proportion of all incident cases of tuberculosis that are HIV-1-positive.

The difference between cases and deaths prevented is greater in the presence of HIV-1 (figure 3), particularly among HIV1-positive cases. The explanation is that DOTS cannot prevent tuberculosis in people who are already coinfected with *M tuberculosis* and HIV-1, but cure rates are assumed to be equally high for cases positive and negative for HIV-1 (although some cases under DOTS will die of other AIDS-related disorders).[21,22]

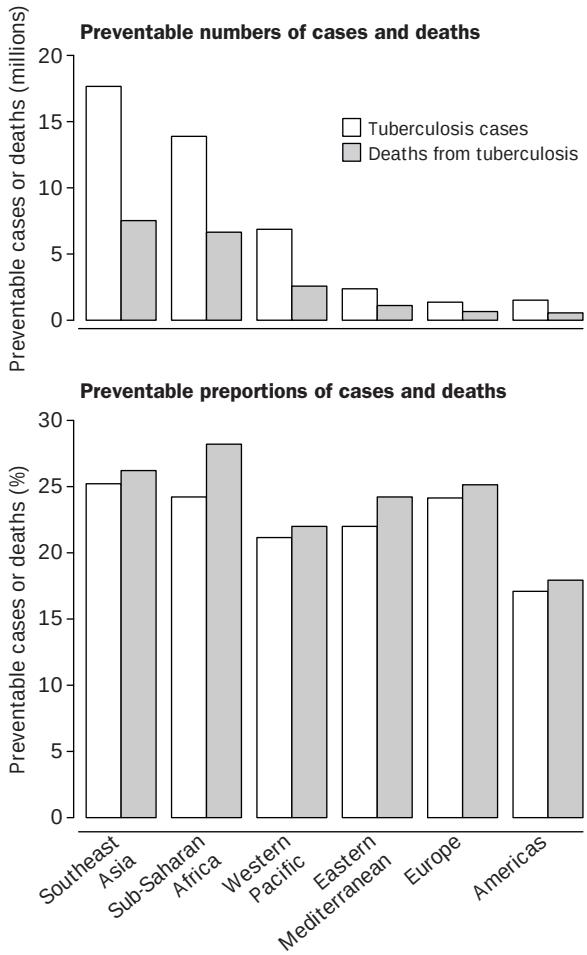

Figure 4: **Number and proportion of cases and deaths that could be prevented in different regions of the world if WHO targets for case finding and cure are achieved by 2010 (compared with maintaining current control effort)**

Expected impact of DOTS in highly endemic areas

Taken together, these results suggest that through improvements in case detection and cure in high-burden countries (especially where the incidence of HIV-1 is low), we could expect bigger incremental gains with DOTS than were achieved in industrialised countries when drugs first became available 50 years ago.

Regional and worldwide forecasts

Figure 4 shows the number of cases and deaths that could be prevented in the next 23 years (up to 2020) in each of the six WHO regions, compared with maintaining current efforts. For this calculation, we assumed that WHO's targets for case finding (70%) and cure (85%) can be achieved by 2010. The greatest benefit of improved tuberculosis control, in terms of the absolute number of cases and deaths averted, will be in the regions that currently have the highest burdens of disease: 18 million cases in southeast Asia (including India), 14 million in Africa, and 7 million in the western Pacific (including China). The corresponding numbers of preventable deaths are 7·3 million, 7·2 million, and 2·6 million. Although the numbers of preventable cases and deaths vary substantially between regions, the preventable proportion of the burden is fairly constant. That proportion lies between 16% (7–23) for the Americas and 25% (15–35) for southeast Asia; the corresponding figures for deaths are 18% (9–27) and 27% (16–38). Thus, although a large proportion of

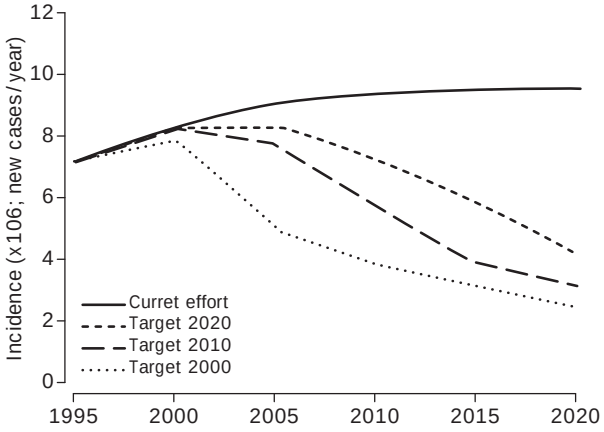

Figure 5: **Projected annual worldwide incidence of tuberculosis under assumption that WHO targets for case finding and cure are met in 2000, 2010, and 2020, compared with maintenance of current control effort**

tuberculosis cases in sub-Saharan Africa are HIV-1 positive (a conservative estimation is about 20–25% after 2010), the fraction of the tuberculosis burden that can be prevented by DOTS is as high as in any other region.

The numbers of cases and deaths in the six regions are summed to give the global totals in figure 5. If case detection and cure rates are maintained at present levels, estimated to be 63% and 57%, respectively,[8] we expect the annual incidence of new cases worldwide to increase by 41% (21–61) between 1998 and 2020. This increase in incidence is a rise from 7·4 million to 10·6 million cases per year, a total of 203 million cases in the next 23 years. This increase will be greatest in sub-Saharan Africa, which has the highest rate of growth of the young adult population, the most widespread HIV-1 epidemic, and the least effective control programmes.

The effects of WHO targets being met in 2000 (now highly unlikely), 2010, and 2020 are indicated by the areas between the lines in figure 5. Under these circumstances the proportion of tuberculosis cases that would be prevented are 38% (25–43), 23% (15–27), and 14% (8–16); the proportions of deaths prevented are greater: 44% (32–48), 26% (17–29), and 15% (7–17). These percentages correspond to 71 million, 43 million, and 26 million preventable cases, and 32 million, 18 million, and 11 million preventable deaths. For the target year 2010, the maximum rate of decline in incidence of tuberculosis would be 6–7% per year, after the targets have been reached.

Discussion

WHO's 1996 appraisal[23] of best buys for research on major microbial diseases concluded that the development of strategies to extend DOTS coverage is a priority. Our findings lend support to that conclusion by quantifying the large numbers of cases and deaths that could be prevented through improvements in case detection and cure rates.

We found that the potential effect of DOTS on tuberculosis in many developing countries is even greater than the results achieved in industrialised countries when drugs became widely available in the 1940s. For example, case-detection rates above 70% in Europe during the 1950s were associated with a fall in incidence rate of about 10% per year; generation of similar rates of decline with lower case-detection rates should now be possible in developing countries with high tuberculosis burdens. A new DOTS programme will have greater effect on

incidence if it detects cases of infectious and non-infectious tuberculosis as soon as possible, if it replaces a poor programme under which cure rates are low and the incidence rate has been falling slowly (or not all), and if it is introduced in a young population. The proportion of deaths prevented will generally be greater than the proportion of cases prevented, especially if cure rates have been low in the past and the new programme treats smear-negative cases. We also found that the proportion of cases that can be prevented by DOTS need not be substantially diminished by a large HIV-1 epidemic. This finding is possible provided case-detection and cure rates can be maintained; we recognise that such efforts are difficult in a population with a high incidence of HIV-1 and which may have had a doubling or tripling of rates of tuberculosis.

The cure rate needs to be high to avoid long-term transmission by those people who are classified as treatment failures. Although treatment of any quality may reduce the number of deaths from tuberculosis in the short-term, low cure rates could actually increase the rate of transmission, and hence the number of cases. This rediscovery of Styblo and Bumgarner's finding[20] is particularly pertinent now that we have a better appreciation of the worldwide distribution of drug-resistant tuberculosis.[24] The main effect of drug resistance is to lower the cure rate, and further careful calculations of the cure-rate threshold are needed to identify the point below which case finding and treatment will make the tuberculosis epidemic progressively worse.[9]

We calculated that if, instead of maintaining current strategies of tuberculosis control, WHO targets for case detection and cure are reached by the year 2010, we would expect 23% fewer cases and 26% fewer deaths from tuberculosis in the next 23 years, which amounts to 43 million cases and 18 million deaths. Most of these cases and deaths would be prevented in Southeast Asia, sub-Saharan Africa, and the western Pacific region. The fraction of the burden alleviated is potentially as high in Africa as in any other region, despite the high prevalence of HIV-1.

Uncertainty is inescapable in projections with mathematical models, and its effect is only partly reflected in the bounds on our estimates. Most of what we know about the natural history of tuberculosis comes from studies in industrialised countries, and yet we are most interested here in the prospects for tuberculosis control in the developing world. Apart from the ranges attached to variables in our model, there are critical but unpredictable external factors. We do not know precisely how many tuberculosis cases there are each year, and how many are found and cured.[8,13] Nor can we be sure of the course of HIV-1 epidemics, particularly with our projections for Africa and Asia. However, the principles of tuberculosis control that we have identified do not depend on the exact results of model calculations. And, although the predictions of the numbers of cases and deaths between 1998 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 proportion of the tuberculosis burden if WHO targets are met by different dates.

Even if the targets are achieved by 2010, three-quarters of the worldwide tuberculosis burden would not be averted in the next 23 years. Better diagnostic techniques, drugs, and vaccines, plus targeted preventive therapy, would undoubtedly help, but may not be available for many years. The most pressing task is to improve cure rates and reach more cases of tuberculosis in the main endemic countries of the world.

Contributors

The mathematical model for tuberculosis was developed jointly by all the investigators. Geoffrey Garnett collated estimates of HIV-1-related model variables and constructed the model HIV-1 epidemics. Karen Sleeman reviewed estimates of all other variables. Brian Williams wrote computer programs for, and carried out, model fitting to European data. Christopher Dye did all other programming and wrote the paper.

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