Evolution of Tuberculosis Control and Prospects for Reducing Tuberculosis Incidence, Prevalence, and Deaths Globally

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Delegates to the World Health Organization’s (WHO’s) 1991 World Health Assembly (WHA) were presented with new estimates of the scale of the tuberculosis (TB) problem worldwide. They were told that 8 million people develop TB each year and several million die, that this enormous burden of disease was being reduced too slowly, if at all, and that the technology to control TB already existed but that it was generally underused. Some may already have been aware that chemotherapy programs to control TB are highly cost-effective. In response, they set 2 targets for TB control, to be reached by 2000: to detect 70% of all new sputum smear-positive cases arising each year (ie, a 70% case detection rate) and to successfully treat 85% of these cases. Although these are global targets, they have been adopted as national targets by individual countries.

During the early 1990s, the essential, basic methods for diagnosis and treatment became part of the DOTS strategy, which has become the internationally recommended approach to TB control. The term DOTS was at first an acronym referring to directly observed treatment (DOT) and short-course chemotherapy (SCC). The term was later expanded to include the following 5 elements:

1. Directly observed treatment
2. Short-course chemotherapy
3. Case notification
4. Case registration
5. Case recording

These elements are intended to ensure that patients are treated appropriately and to monitor the progress of the program. The DOTS strategy is designed to improve the detection and treatment of TB in low-resource settings. The strategy includes the following components:

- Directly observed treatment (DOT): Patients are observed by a health worker while they take their medications.
- Short-course chemotherapy (SCC): Patients are given a short course of antibiotics to treat their TB.
- Case notification: Patients with TB who have been cured or treated are recorded in a case register.
- Case registration: Patients with TB who have been diagnosed are registered in a national TB registry.
- Case recording: Patients with TB who have been notified are recorded in a national TB registry.

The DOTS strategy has been successful in many countries, and it has been adopted by many national TB control programs. However, the strategy is not without its challenges. One of the main challenges is the high cost of providing DOT and SCC. Another challenge is the low rate of case detection, which makes it difficult to identify all patients with TB. Despite these challenges, the DOTS strategy has been successful in reducing the incidence of TB and improving the survival rates of patients with TB.

The success of the DOTS strategy has prompted the World Health Organization (WHO) to focus on reducing the incidence of TB and improving the survival rates of patients with TB. The WHO has set targets for TB control, including a 70% case detection rate and an 85% treatment success rate. These targets are intended to help reduce the incidence of TB and improve the survival rates of patients with TB. The WHO has set up a Global TB Control Strategy to help countries achieve these targets.

The Global TB Control Strategy is intended to help countries achieve the following goals:

- Increase the case detection rate to 70% by 2005
- Increase the treatment success rate to 85% by 2005
- Reduce the incidence of TB by 50% by 2015
- Reduce the mortality rate from TB by 50% by 2015

The Global TB Control Strategy includes the following components:

- Strengthening national TB control programs
- Improving case finding and treatment
- Increasing funding for TB control
- Reducing the transmission of TB
- Increasing research on TB

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- Reduce the transmission of TB
- Increase research on TB

The success of the Global TB Control Strategy will depend on the willingness of countries to invest in TB control programs and to support the implementation of the strategy. The WHO has set up a Global TB Control Strategy Fund to help countries achieve the goals of the strategy. The fund is intended to provide financial support for countries that need help to implement the strategy.

The success of the Global TB Control Strategy will also depend on the development of new drugs and treatments for TB. The WHO is working with other organizations to develop new drugs and treatments for TB. The development of new drugs and treatments will help to reduce the incidence of TB and improve the survival rates of patients with TB.

The success of the Global TB Control Strategy will also depend on the development of new vaccines for TB. The WHO is working with other organizations to develop new vaccines for TB. The development of new vaccines will help to prevent the transmission of TB and reduce the incidence of TB.

In conclusion, the success of the Global TB Control Strategy will depend on the willingness of countries to invest in TB control programs and to support the implementation of the strategy. The WHO has set up a Global TB Control Strategy Fund to help countries achieve the goals of the strategy. The success of the Global TB Control Strategy will also depend on the development of new drugs and treatments for TB and the development of new vaccines for TB.
course chemotherapy but has become the term used to describe a broader public health strategy with 5 principal elements: political commitment; case detection by sputum smear microscopy, mostly among self-referring symptomatic patients; standard short-course chemotherapy with supportive patient management, including DOT; a system to ensure regular drug supplies; and a standard recording and reporting system, including the evaluation of treatment outcomes. Standard short-course regimens can cure more than 90% of new, drug-susceptible TB cases, and high cure rates are a prerequisite for expanding case finding. At 70% case detection, 85% cure, and in the absence of human immunodeficiency virus (HIV) infection, the TB prevalence rate is expected to decrease substantially, and incidence rate should decrease at about 5% to 10% per year.

Given the targets for case detection and cure and the WHA 2000 deadline, national TB control programs focused during the 1990s on DOTS implementation. The targets were not met by 2000, and the target year was deferred to 2005. However, 149 countries had adopted the DOTS strategy by the turn of the millennium, treatment success was reportedly 82%, and smear-positive case detection by DOTS programs was 28% and increasing. With this evidence of growing coverage, governments, donors, and other supporting agencies were beginning to ask for evidence that DOTS is having the expected epidemiologic impact.

Although the decline in TB has almost certainly been accelerated by good chemotherapy programs in countries such as Chile, Cuba, and Uruguay, there have been few recent, unequivocal demonstrations of impact in high-burden countries. Two examples come from Peru and China. In Peru, the incidence rate of pulmonary TB has decreased annually by 6% after the nationwide implementation of DOTS. In 13 provinces of China that implemented DOTS, the prevalence rate of culture-positive TB was cut by 30% between 1990 and 2000. In some other countries with good control programs, such as Vietnam, there has been no obvious reduction in incidence.

Since 2000, the United Nations Millennium Development Goals (MDGs) have provided a framework for evaluating implementation and impact under target 8 (among 18), which is to “have halted by 2015 and begun to reverse the incidence of malaria and other major diseases.” Although the objective is expressed in terms of incidence, the MDGs also specify that progress be measured in terms of the reduction in TB prevalence and deaths. The target for these 2 indicators, based on a resolution passed at the 2000 Okinawa (Japan) summit of G8 industrialized nations and subsequently adopted by the Stop TB Partnership, is to halve TB prevalence and death rates between 1990 and 2015.

The MDG framework for TB control therefore consists of 2 measures oriented toward DOTS implementation (case detection, treatment success) and 3 measures of impact (incidence, prevalence, deaths) that could be related to any method of TB control. This second set of measures serves not only to stimulate epidemiologic evaluation (beyond implementation) but also to allow a more comprehensive approach to TB control (beyond DOTS). A more inclusive approach to control might embrace methods for prevention, as well as methods for improving patient care by engaging all clinicians, public and private, taking notice especially of patients coinfected with HIV and carrying drug-resistant strains. It might also introduce new technology, as well as make better use of the tools that are already available.

In this analysis of progress and prospects in global TB control, we begin by reevaluating the scale and direction of the TB epidemic and by summarizing the progress made in DOTS implementation up to the end of 2003, which forms the background for a new evaluation of whether DOTS has reduced, and will continue to reduce, TB incidence, prevalence, and deaths worldwide. With the evidence at hand, we comment on the prospects for reaching the MDGs through DOTS expansion alone, through the implementation of a more comprehensive strategy, and through the introduction of new technology and procedures for TB control.

METHODS
Case Notifications, Case Detection, and Treatment Outcomes
Case definitions and the classification of treatment outcomes used by WHO are fully described elsewhere. Here, we distinguish between the incidence (new cases arising annually) and prevalence (cases existing at one point in time) of latent infection with Mycobacterium tuberculosis or of active TB disease and between numbers of cases and rates per 100 000 population. WHO has compiled TB case notifications from DOTS and non-DOTS programs for up to 200 countries and territories for 1980-2003 (not all countries reported every year). Since 1994, we have also received the results of treatment for patients registered in DOTS cohorts between 1994 and 2002. The principal measure of case detection for each country is the number of patients with new smear-positive sputum samples reported by the DOTS program in 1 year divided by the estimated annual incidence of smear-positive cases. TB incidence rates are rarely measured directly, so incidence is estimated from population-based surveys of the prevalence of M tuberculosis infection or TB disease or from independent assessments, often qualitative, of the performance of surveillance systems. The accuracy of these estimates is uncertain because, for example, even where disease prevalence surveys are done well, incidence cannot be calculated accurately from prevalence without precise measures of the duration of illness. Errors on the point estimates of incidence for high-burden countries typically range from −20% to 40%. Some low estimates of case detection are supported by independent research showing why patients are not detected by DOTS programs.
eral, however, estimates of incidence, and therefore case detection, should be considered approximate.

Treatment success under DOTS is defined as the percentage of smear-positive patients registered in an annual cohort who are cured (negative sputum-smear result at the end of treatment) plus the percentage who complete treatment. The other defined outcomes of treatment are: died, defaulted, failed (positive sputum-smear result at the end of treatment), transferred (outcome unknown after transfer to another treatment center), or not evaluated (no outcome reported). To obtain high rates of treatment success, DOTS programs must achieve high standards clinically, and they must provide comprehensive reports on patients in their care. By and large, DOTS programs follow recommended procedures for evaluating treatment outcomes, though this adherence does not exclude the possibility that cure rates are overestimated in some settings (underestimation is less likely, given that health workers are responding to performance targets). Cure rates outside DOTS programs are poorly known because recording and reporting often do not follow standard procedures.


For this analysis, countries are grouped into 9 epidemiologic regions: Africa, which is subdivided into 2 regions comprising countries with high HIV infection rates (≥4% in adults aged 15-49 years in 2003) and those with low rates of HIV infection (<4%); Central Europe; Eastern Europe; Eastern Mediterranean; established market economies (industrialized countries); Latin America; Southeast Asia; and Western Pacific. The countries in each region are listed in full elsewhere. When reporting from a country has been consistent through time (without large variations from year to year) and is unlikely to have been influenced by changes in case-detection effort, we take the trend in notifications to represent the true trend in incidence. Countries that do not provide reliable case notifications are assumed to follow the trend for their own epidemiologic regions, 1 of 9 in the world. The number of cases notified divided by the estimated proportion of cases detected gives the total incidence rate for any country in any year; hence, the time series of estimated incidence rates for 1990 to 2003.

We calculated the prevalence of TB from the product of incidence and duration and the TB mortality rate from the product of incidence and case fatality, as we have done previously. To carry out these calculations, the duration of disease and the case-fatality rate have been determined, country by country, for patients treated within or outside DOTS programs and for patients who receive no recognized TB treatment (Table 1). For patients treated under DOTS, the duration of an episode of TB consists mostly of the time between the onset of signs or symptoms and the start of treatment because treatment leads to rapid recovery. For example, patients diagnosed with smear-positive TB and given the appropriate combination of drugs usually become smear negative within 2 to 3 months, whereas the average total duration of illness is assumed to be 0.8 to 2.0 years, depending on the country.

Because the duration of illness is typically shorter for patients treated under DOTS than for patients who are treated elsewhere or untreated, the average duration of illness decreases as the proportion of patients treated under DOTS increases (higher case detection rate). And the prevalence of TB decreases as the average duration of an episode becomes shorter. By the same mechanism, the geographic expansion of DOTS reduces the case-fatality rate and the TB mortality rate in the whole population. To calculate the prevalence and mortality rates that would be associated with improvements in case detection up to 2015, we calibrated the relationships between detection, duration, and case-fatality rate by region by using the data and estimates compiled by WHO from 1995-2003. Thus, as an example for Southeast Asia, duration = -2.198 × (proportion treated under DOTS) + 2.826, with r² = 0.999, giving a duration that decreased from 2.8 to 1.8 years between 1995 and 2003 as case detection rate by DOTS programs increased from 2% to 45%.

Estimates of duration and case fatality are made with greater or less precision, according to the source of data. The duration of TB is estimated most accurately from the ratio of prevalence to incidence obtained from population-based surveys. Because these quantities have rarely been measured in the same place, the evaluations for most countries are based on expert opinion. Estimates of case fatality are most reliable for patients treated under DOTS (data submitted to WHO) or for those who are not treated at all (data from natural history studies in the

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**Table 1. Case-Fatality Rates and Durations of Different Forms of Tuberculosis Used to Calculate Mortality and Prevalence Rates From Estimated Incidence Rates**

<table>
<thead>
<tr>
<th>Case-fatality rate, proportion</th>
<th>DOTS</th>
<th>Non-DOTS</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV uninfected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear positive</td>
<td>0.05-0.15</td>
<td>0.05-0.30</td>
<td>0.70</td>
</tr>
<tr>
<td>Smear negative</td>
<td>0.03-0.08</td>
<td>0.03-0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>HIV infected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear positive</td>
<td>0.05-0.15</td>
<td>0.05-0.38</td>
<td>0.83</td>
</tr>
<tr>
<td>Smear negative</td>
<td>0.05-0.15</td>
<td>0.08-0.50</td>
<td>0.74</td>
</tr>
</tbody>
</table>

| Duration of condition, y†   |      |          |           |
| HIV uninfected              | 0.75-2.0 | 1.0-3.5 | 2.0 |
| HIV infected                | 0.5    | 0.5     | 0.5     |

Abbreviation: HIV, human immunodeficiency virus.

*Ranges indicate minimum and maximum values used across all countries. Adapted from Dye et al.17
†Both smear positive and smear negative.
The data are least reliable for patients treated with various drug regimens that are not recommended by WHO. The uncertainties associated with these methods are discussed more fully elsewhere.13,17,18

Forecasting TB Trends, 2003-2015

To be conservative in the first instance about the outlook for TB control, we assume that the trends in incidence to 200313 will continue until 2015 (FIGURE 1). Four methods of extrapolation have been used and are based on the case notification series for each region: incidence rate unchanging from year to year (Eastern Mediterranean and Southeast Asia), incidence rate changing exponentially (1.5% per year for African countries with low rates of HIV infection, −4.6% per year for Central Europe, −4.0% per year for Eastern Europe, and −0.8% per year for the Western Pacific), decline in incidence rate slowing linearly (−5.1% per year for countries with established market economies and −2.9% per year for Latin America), and increase in incidence rate slowing exponentially (−10.5% per year for African countries with high rates of HIV infection). Projections for the region comprising African countries with low rates of HIV infection and for the Eastern Mediterranean region are based on estimated incidence rates since 1995 and 2000, respectively.

This approach to forecasting supposes, in the first instance, that DOTS and other forms of TB control will have no additional impact on transmission (and allows us to avoid the complexities and uncertainties of transmission modeling8). It also assumes that there will be no rapid reduction in the prevalence of HIV infection in Africa.

TB prevalence and death rates between 2003 and 2015 are calculated as for 1990-2003, from projected incidence rates, and from the predetermined durations and case-fatality rates. The average durations and case fatality rates for any region in any year are again governed by the proportions of cases treated in or outside DOTS programs or not treated at all. Notwithstanding targets for TB control, we did not know what these proportions would be, so we examined 3 scenarios that embrace the likely range of outcomes (FIGURE 2). The baseline forecast is that trends in smear-positive case detection observed in each region from 1995-2003 will continue up to the 70% target and remain steady thereafter. In a more optimistic scenario that satisfies the WHA target, 70% of new cases would be detected annually in each region by 2005. In a more pessimistic scenario, the case detection rate never increases above 50% in any region. More details about these methods, forecasts, and scenarios can be found on the WHO Web site.25

Figure 1. Trajectories of the Tuberculosis Epidemic for 9 Epidemiologically Different Regions of the World

Points mark trends in incidence rates, derived from case notifications for 1990-2003. Dashed lines project incidence rates beyond 2003 to 2015. The 2 panels separate regions with estimated incidence rates above (A) or below (B) the global average in 1990 (solid line). Groupings of countries are based on the World Health Organization (WHO) regions of Africa, which is subdivided into countries with high human immunodeficiency virus (HIV) infection rates (≥4% in adults aged 15–49 years in 2003) and those with low HIV rates (<2%), Central Europe, Eastern Europe (former Soviet countries plus Bulgaria and Romania), Eastern Mediterranean, established market economies (all 30 Organization for Economic Cooperation and Development countries, except Mexico, Slovakia, and Turkey, plus Singapore), Latin America, Southeast Asia, and Western Pacific. The countries in each region are listed in full elsewhere.15 Lines were fitted by nonlinear least squares regression to the notification data for countries within regions, and the fitted lines aggregated to generate the regional trend. Aggregation of fits to country data explains why regional trends do not always look smooth.
RESULTS
Dynamics of the Global TB Epidemic
Although the incidence rates of TB disease have been increasing most quickly in eastern and southern African countries with the highest rates of HIV infection, there is evidence that the rate of increase is slowing (Figure 1A). The trajectories of the TB epidemics in these countries will depend on the dynamics of HIV infection; however, if the trend from 1990-2003 persists, the estimated TB incidence rate will exceed 500 per 100,000 by 2015 (≈3.3 million cases). In other parts of Africa that have lower rates of HIV infection, the rate of increase in TB has been much slower (1%-2% per year), but the case notifications give no indication of when or at what level TB incidence will reach its peak.

Since 1990, TB incidence has also increased in Eastern Europe (mostly in the countries of the former Soviet Union), but the time series of notifications suggests that incidence rate peaked around 2001 (Figure 1B). The downturn is clear in data from Russia, Belarus, and the Baltic States of Estonia, Latvia, and Lithuania, whereas incidence rates appear still to be increasing in the central Asian republics of Kazakhstan, Kyrgyzstan, Tajikistan, and Uzbekistan. Our projections assume that, from 2003 onward, the incidence rate will continue to decrease at 4% per year in eastern Europe at the same rate as observed from 1980-1990 before the collapse of the Soviet Union.

In all other regions, the incidence rate was stable or decreasing continuously between 1990 and 2003 and relatively quickly in Latin America, Central Europe, and the established market economies. Summing across the 9 regions depicted in Figure 1 gives the global trend in incidence rate, which was increasing most quickly at 1.5% per year in 1995 but has since been decelerating. If the trends suggested by the case notifications are correct, and if these trends persist, the global incidence rate will reach about 150 per 100,000 in 2015, generating more than 10 million new cases in that year (Figure 1).

Implementation of the DOTS Strategy
More than 17 million TB patients were treated in DOTS programs between 1994 and 2003. The case detection rate by DOTS programs increased almost linearly from 11% globally in 1995 to 28% in 2000 and then accelerated to 45% in 2003 (Figure 2). If the 7% global increase in detection between 2002 and 2003 is maintained, detection will reach approximately 60% by 2005, 10% below target. Comparing different parts of the world in 2003, case detection was highest in the Latin American (48%) and Western Pacific regions (50%) and lowest in Eastern Europe (22%). The recent acceleration has been mostly due to rapid implementation in India, where case detection increased from 1.7% in 1998 to 47% in 2003, and in China, where case detection increased from 30% in 2002 to 43% in 2003. India and China together accounted for 63% of the increase in case notifications by DOTS programs between 2002 and 2003.

The global treatment success rate under DOTS has been high since the first observed cohort in 1994 (77%) but has remained above 80% since 1998, even though the cohort size had increased 6-fold to 1.4 million patients (Figure 3). There is, however, much variation between regions. Treatment success exceeded the 85% target in the Western Pacific region, largely be-
cause China reported a 93% success rate. Treatment results were especially poor in African countries with high rates of HIV infection (71% success) and low rates of HIV infection (74%), the established market economies (77%), and Eastern Europe (75%) (Table 2). In African countries most affected by HIV, 8% of patients died during treatment, and 20% were lost to follow-up (defaulted, transferred to other treatment centers, or not evaluated). Both of these findings could be related to the high rates of HIV infection among TB patients (estimated to be 40% in 2003). In the established market economies, the death rate is higher than in any other region (10%) because a large proportion of patients is elderly.13 In Eastern Europe, 9% of cases failed treatment and 7% died during treatment. These poor outcomes are likely to be associated with the relatively high rates of drug resistance in this region (eg, more than 10% of previously untreated TB patients carry multidrug-resistant TB strains, multidrug-resistant TB resistant to at least isoniazid and rifampicin, in parts of the Russian Federation, Uzbekistan, and Kazakhstan14).  

**Epidemiologic Impact of DOTS**

Most of the impact DOTS had on transmission up to 2003 is reflected in the trends in incidence rates (Figure 1). To evaluate the impact of TB control beyond 2003, we first assumed that these trends in incidence would persist to 2015 and investigated the way in which better case detection and treatment could reduce prevalence and death rates by cutting the duration of illness and case fatality. Data reported for 1990-2003, calculations, and projections through 2015 of incidence, prevalence, and death rates are available elsewhere.23 Summing across the 9 regions gives the trends in global prevalence and deaths shown in Figure 4A. In our assessment, the global TB prevalence rate has been decreasing since 1990 and more rapidly with the accelerated implementation of DOTS since 2000 (Figure 4A). By 2003, the prevalence rate was decreasing in 7 of 9 regions and globally at 5% to 6% annually, the exceptions being the 2 regions of Africa. Assuming no additional impact on transmission, the 3 scenarios for improving case detection generate prevalence rates of 190 to 230 per 100 000 population in 2015, which represents less than a halving of prevalence since 1990. Prevalence will decrease sooner if case detection by DOTS programs (and hence the quality of treatment) can be improved more quickly, thus reducing the burden of illness during this period. Prevalence will decrease farther than indicated in Figure 4A if case detection rates exceed 70%. Notice that, after any improvements in case detection have had their maximum effect, the prevalence rate increases again in line with the incidence rate. To meet the MDG targets, control programs around the world must have at least a small additional effect on transmission so that, between the best and worst scenarios for DOTS implementation (Figure 1), the incidence rate also decreases by 2% (for the best scenario) or 4% (for the worst scenario) per year from 2003-2015. Even if the target of halving prevalence is achieved globally, it is unlikely to be reached in Africa. Even though prevalence is not expected to increase as much as incidence in Africa (because HIV infection is associated with a shorter duration of illness),26 the prevalence in parts of Africa with high rates of HIV infection is projected to be much higher in 2015 (609 per 100 000) than it was in 1990 (288 per 100 000). An additional problem is that Eastern Europe is not expected to have recovered fully from the resurgence of TB during the 1990s. We estimate that the prevalence rate was 84 per 100 000 in Eastern Europe in 1990, increasing to a maximum of 156 per 100 000 in 2001 and, in the baseline scenario, decreasing to 73 per 100 000 in 2015. If Africa and Eastern Europe are excluded from the global statistics, the prevalence rate in 2015 would be about half that in 1990 (Figure 4A). Although the target for reducing global prevalence appears to be within reach, the target death rate is not (Figure 4B). Our calculations indicate that the death rate in 2003 was about the same as in 1990 (29 per 100 000 per year), and the number of deaths was higher in a larger global population (1.8

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**Table 2. Adverse Outcomes of Treatment and Overall Treatment Success for Patients Registered in DOTS Cohorts in 2002**

<table>
<thead>
<tr>
<th>Region</th>
<th>Died</th>
<th>Failed</th>
<th>Defaulted</th>
<th>Transferred</th>
<th>Not Evaluated</th>
<th>Treatment Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa: high HIV rate</td>
<td>8.0</td>
<td>1.0</td>
<td>9.7</td>
<td>6.8</td>
<td>3.5</td>
<td>71.1</td>
</tr>
<tr>
<td>Africa: low HIV rate</td>
<td>3.8</td>
<td>3.1</td>
<td>14.4</td>
<td>3.6</td>
<td>0.7</td>
<td>74.4</td>
</tr>
<tr>
<td>Central Europe</td>
<td>5.0</td>
<td>3.5</td>
<td>6.0</td>
<td>1.0</td>
<td>4.7</td>
<td>79.7</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>6.7</td>
<td>8.8</td>
<td>6.4</td>
<td>2.7</td>
<td>0.5</td>
<td>74.9</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>3.2</td>
<td>1.4</td>
<td>7.8</td>
<td>2.6</td>
<td>1.5</td>
<td>83.5</td>
</tr>
<tr>
<td>Established markets</td>
<td>9.7</td>
<td>2.4</td>
<td>2.6</td>
<td>4.1</td>
<td>4.8</td>
<td>76.5</td>
</tr>
<tr>
<td>Latin America</td>
<td>4.3</td>
<td>1.2</td>
<td>6.0</td>
<td>3.4</td>
<td>1.7</td>
<td>83.4</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>3.9</td>
<td>2.5</td>
<td>6.4</td>
<td>1.5</td>
<td>0.6</td>
<td>85.1</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>2.2</td>
<td>0.9</td>
<td>2.2</td>
<td>2.1</td>
<td>3.6</td>
<td>89.0</td>
</tr>
</tbody>
</table>

Abbreviation: HIV, human immunodeficiency virus.

*Data are the percentages of smear-positive patients with different outcomes, among all those registered for treatment.15 Regions are defined in Figure 1. Bold numbers identify principal causes of treatment failure.
million). Although the TB death rate, like prevalence, was decreasing in 7 of 9 regions by 2003 and globally at 2% to 3% annually, the rate forecast for 2015 is only fractionally lower than in 1990 for all 3 scenarios. To halve the death rate by 2015, the incidence rate would also have to decrease by 5% to 6% per year from 2003 onward. Again, the principal obstacle to meeting the MDG target is that the number of TB deaths has increased significantly in Africa and Eastern Europe since 1990. Not allowing for any reduction in transmission, the TB death rate will be 97 to 118 per 100,000 in African countries most affected by HIV compared with 40 per 100,000 in 1990. However, excluding Africa and Eastern Europe from the global trend, the TB death rate decreases from 28 to 18 per 100,000 between 1990 and 2015 in the baseline scenario. The MDG target for the rest of the world could therefore be reached with a more modest reduction in incidence rate of about 2% annually from 2003.

**COMMENT**

Although the global incidence rate of TB was, in our assessment, still increasing slowly in 2003 (∼1% per year), this increase could be reversed by further reductions in transmission in high-burden countries. With small additional reductions in the incidence rate, the MDG objective of halving prevalence would also be achieved globally. The more difficult challenge is to halve the TB death rate. The mortality statistics illuminate the important regional variations in failure to control TB, primarily in Africa and Eastern Europe. But the difficulty of preventing deaths is not confined to these regions; where anti-TB drugs have been used for many years, it will not be easy to reduce TB mortality further because most of the work in preventing deaths has already been done.

The difficulties of managing TB in Africa and Eastern Europe are closely linked to HIV/AIDS and drug resistance, and specific solutions will be needed for these problems in these regions. But the numerous agencies that now operate under the umbrella of the Stop TB Partnership must adopt a broader agenda for TB control worldwide, which includes more vigorous application of the basic package of care under DOTS, making use of clinicians in public and private sectors; the development of an enhanced DOTS strategy based on current technology; and the introduction of new evidence-based technology and innovative procedures arising from new research, including studies on the social, economic, and political environment in which new and current methods are used. All interventions that aim to improve care, as distinct from prevention, must adopt patient-supportive approaches that lead to high compliance and the best possible outcomes of treatment.

By 2003, DOTS had almost fully exploited the limits of public notification systems, which compile statistics on TB patients diagnosed and treated in clinics and hospitals run by government health ministries. The next phase of DOTS expansion must therefore adapt the basic package of care so that it can move beyond the limits of public notification systems, which means forging better links between DOTS programs and other, nonparticipating public clinics and hospitals, as is now being done in Indonesia, among other places. It also means engaging medical services in prisons and the armed forces, private clinicians, nongovern-
mental organizations, mission hospitals, and clinics in the corporate sector. All medical practitioners must be encouraged to adopt, as a minimum, the basic package of care. Most difficult of all, DOTS programs must participate in the expansion of health services to serve populations where no professional health care is yet available. For example, half the population of Ethiopia has no access to health services and therefore no access to TB diagnosis and treatment.

In some places where DOTS has already been implemented, the basic tools are plainly inadequate. Where a high proportion of patients carry drug-resistant bacilli, first-line drugs give unacceptably low cure rates. For TB patients who are HIV-positive, the risk of death during and after treatment is much higher than for patients who are not infected with HIV. Some improvements to DOTS could be instituted immediately. All patients suspected of carrying drug-resistant, and especially multidrug-resistant, bacilli (eg, those who have already failed treatment) should be tested for resistance to first-line drugs and receive standardized or, where possible, individualized regimens, including second-line drugs.

TB patients and individuals suspected of having TB should be tested for HIV infection and offered cotrimoxazole and antiretroviral drugs in appropriate combination with anti-TB drugs. There should be active searching for TB cases among HIV-infected people. Individuals who do not have active TB should be offered isoniazid preventive treatment.

The DOTS approach to TB control is comparatively cost-effective but its implementation is complex and has limitations. It is not difficult to imagine a set of tools that would improve the efficiency of TB control. The first new tools to reach field application will probably be diagnostics. A new drug could improve cure rates by shortening the duration of treatment to 2 to 3 months to improve compliance by increasing the cure rate among patients carrying bacilli resistant to present drugs or perhaps by reducing the relapse rate among patients coinfected with HIV. The ultimate tool, yet to be created, is a vaccine that has consistently high efficacy against pulmonary TB, whether or not vaccinated individuals are already infected.

In any discussion of TB control, it is vital to remember that incidence and death rates are not governed simply by drug treatment. Among other determinants of the slow dynamics of TB epidemics are cofactors such as nutritional status, tobacco and alcohol use, other infectious agents, and susceptibility genes that warrant additional study.

All forecasts of health trends are surrounded by uncertainties. Although we have eschewed transmission modeling, thereby avoiding some strong epidemiologic assumptions, there are weaknesses in the data on which our calculations are based. For example, TB incidence is estimated by various indirect methods because incidence is rarely measured directly in longitudinal field surveys. Similarly, TB death statistics would ideally come from reliable vital registration systems, but many of the poorest countries do not systematically or accurately record deaths by cause. In addition, the assessment of regional trends in incidence requires judgments about the reliability of case notifications reported by individual countries. With these limitations, the data and forecasts reported herein should be interpreted with caution.

In summary, although investment in TB control is comparatively cost-effective but its implementation is complex and has limitations, it is not difficult to imagine a set of tools that would improve the efficiency of TB control. The first new tools to reach field application will probably be diagnostics. A new drug could improve cure rates by shortening the duration of treatment to 2 to 3 months to improve compliance by increasing the cure rate among patients carrying bacilli resistant to present drugs or perhaps by reducing the relapse rate among patients coinfected with HIV. The ultimate tool, yet to be created, is a vaccine that has consistently high efficacy against pulmonary TB, whether or not vaccinated individuals are already infected.

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In summary, although investment in the development of technology for TB control is comparatively greater than ever before, the new tools that emerge during the next decade are likely to facilitate rather than replace the DOTS strategy. DOTS will also be strengthened by further research on risk factors and by the development of human resources and primary health infrastructure. With the vigorous implementation of an enhanced strategy for TB control, it should be possible to satisfy the Millennium Development Goals in most countries by 2015. The mission to control tuberculosis in Africa and Eastern Europe will be more challenging, but until that task has been accomplished, TB will remain a major concern for public health worldwide.
EVOLUTION OF TUBERCULOSIS CONTROL

Life is infinitely more stubborn than theory, it goes its way independent of it and silently conquers it.
—Alexander Hersen (1812-1870)