THE GLOBAL TUBERCULOSIS SITUATION
Progress and Problems in the 20th Century, Prospects for the 21st Century

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“If the number of victims which a disease claims is the measure of its significance, then all diseases, particularly the most dreaded infectious diseases, such as bubonic plague, Asiatic cholera, etcetera, must rank far behind tuberculosis.” ROBERT KOCH, 1882

One hundred twenty years later, and nearly 60 years after the discovery of anti-tuberculosis drugs, how far has medicine advanced since the time of Koch? For the majority of the world's population, the answer clearly is, not far enough. Once called ‘the Captain of all these Men of Death,’ tuberculosis (TB)
remains a leading cause of mortality worldwide and the single leading cause among persons with HIV infection; however, 99% of the estimated 2 million deaths and 95% of the 8 million new cases each year occur in middle- and low-income countries of the world, which comprise 5.1 billion people, or 85% of the world's population. Focusing on these countries, this article describes the struggle between Mycobacterium tuberculosis and Homo sapiens, examines progress and problems in the 20th century, and discusses prospects for the 21st century. The article begins with an update on the global epidemiology of TB. The following sections concentrate on the factors responsible for resurgent TB in the past 20 years and on worldwide efforts to control TB. Subsequently, regional profiles spotlight the TB situation in Latin America, Africa, the former Soviet Union, India, and China in more detail. Prospects for the 21st century are introduced with a summary of predictive models of TB epidemiology based on factors driving the epidemic and global efforts to control it. Many of the past obstacles to TB control persist and will become challenges for the future. The article concludes with an update on global efforts for stopping TB before the 21st century ends.

GLOBAL DISTRIBUTION AND TRENDS

The epidemiology of TB can be viewed as an extended pandemic in which the time scale spans centuries. According to this model, once TB enters a susceptible population in which social and environmental factors favor its spread, an epidemic ensues, peaking in approximately 50 to 100 years, then declining over the next 200 to 300 years as natural selection affects the population's intrinsic resistance. These two phases of the epidemic correspond to two predominant clinical patterns of disease. In populations on the ascending limb, TB is predominantly an acute or subacute illness in young children, adolescents, and young adults, usually manifesting as progressive primary disease. Naturally, morbidity and mortality rates among youth curtails reproductive success. As susceptible individuals are removed from the population and resistant individuals survive to reproduce, the epidemic curve peaks and then begins to decline. On the descending limb, as more genetically resistant individuals predominate in the population, primary infection generally is controlled by the more effective immune response, and reactivation disease becomes more common. This manifests as the familiar subacute or chronic pulmonary disease affecting middle-aged and older adults in developed countries in the late 20th century.

This model is supported by accumulated observations from diverse sources suggesting that the present pandemic of TB began with the growth of crowded cities and widespread poverty in 17th century feudal Europe. Over the ensuing decades, TB became the “Great White Plague” in Europe, peaking in the late 18th century and causing 25% of all deaths in that period. With European exploration, then emigration, TB spread to the Americas and other parts of the world. By the 19th century, records show that TB mortality was declining not only in Europe, but also in the eastern United States, suggesting the population of European origin was on the descending limb of the epidemic curve. In contrast, the latter half of the 19th century saw rapid increases in TB in North America among indigenous people and among people of African descent. Likewise, the 19th and early 20th centuries saw rapid increases in TB in Africa, India, and China. Before then, TB appears to have been uncommon in Africa and Asia.

Once the indigenous peoples of Africa, Asia, and the Americas passed through the peak of their own epidemics, available data suggested a steady downward trend in TB morbidity and mortality rates throughout much of the world lasting into the 1980s, though rates were much higher in sub-Saharan Africa and Asia than in Western Europe. This trend accelerated in the 1950s because of the advent of effective chemotherapy. These trends could be assessed by the annual risk of TB infection (ARI) beginning in the early 20th century because of the development and standardization of tuberculin skin
testing. The ARI, based on skin test surveys in nonvaccinated populations, is independent of national reporting systems and can be compared with different countries. Between 1960 and 1990, the average annual risk of TB infection decreased worldwide (Table 1).

<table>
<thead>
<tr>
<th>Region</th>
<th>1960 ARI (%)</th>
<th>1990 ARI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Asia</td>
<td>6.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>4.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Middle East</td>
<td>3.5</td>
<td>0.5</td>
</tr>
<tr>
<td>India and China</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Latin America</td>
<td>1.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Europe</td>
<td>1.0</td>
<td>0.3</td>
</tr>
</tbody>
</table>


As a result, scientific and public health interest waned in countries with the resources to foster innovative research and programs. Optimism led to overconfidence and, eventually, to the dismantling of TB control programs. In the 1970s, US categorical federal funding for TB control and research evaporated. By the mid-1980s the TB program staff at the World Health Organization (WHO) had been reduced to one statistician and a secretary. As a consequence of these developments, \( M. \) \( tuberculosis \) staged a worldwide comeback, taking advantage of weakened defenses (incapacitated TB control programs and the HIV/acquired immunodeficiency syndrome [AIDS] epidemic) and bearing new weapons (drug resistance). This happened at different times in different places, but TB disease surged upward on a broad scale. This resurgence was difficult to quantify because of the inadequacies of surveillance in most countries, but the trends were documented by WHO. Averaged over 3-year periods, TB cases increased 28.7%, and case rates increased 20.8% worldwide from the 1984 to 1986 triennium to the 1989 to 1991 triennium. Cases and case rates increased throughout Asia, Africa, and the Middle East (Table 2).

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Number of Cases</th>
<th>Cases per 100,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>264,037</td>
<td>365,465</td>
</tr>
<tr>
<td>The Americas</td>
<td>227,277</td>
<td>207,790</td>
</tr>
<tr>
<td>Eastern</td>
<td>212,872</td>
<td>281,182</td>
</tr>
<tr>
<td>Mediterranean Europe (and</td>
<td>307,617</td>
<td>242,643</td>
</tr>
<tr>
<td>Soviet Asia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>1,338,896</td>
<td>1,874,950</td>
</tr>
</tbody>
</table>
WHO defines six geopolitical regions for surveillance and administrative purposes: (1) Africa, excluding Egypt, Libya, Tunisia, and Morocco; (2) the Americas; (3) the Eastern Mediterranean extending, eastward to Pakistan, and including Egypt, Libya, Tunisia, Morocco, but excluding Israel; (4) Europe, including Israel, Turkey, and the countries of the former Union of Soviet Socialist Republics; (5) Southeast Asia, including Indonesia and North Korea, but excluding Cambodia, Laos, Malaysia, and Vietnam; and (6) the Western Pacific Region including China, Cambodia, Laos, Malaysia, and Vietnam.

These data must be interpreted with caution, however, because case finding and reporting are poor in many national TB programs (NTPs). Moreover, during this period, China and India launched efforts to improve TB control, so increasing numbers in these countries (roughly half the world's TB morbidity rate) may reflect better case detection and reporting; however, this same report estimated the true incidence of TB in 1990 as 7.5 million new cases with 2.5 million deaths worldwide.[131]

In several affluent countries and in the few developing countries having stable, strong TB programs, and accurate surveillance data, these same trends were apparent beginning in the early to mid-1980s. In the United States, TB incidence increased 20% between 1985 and 1992. Case rates per 100,000 population per year increased 12% during this same period (9.3 to 10.5).[18] In 7 of the 14 major Western European countries with reliable data, TB incidence reached a nadir between 1986 and 1989, then increased to higher levels between 1990 and 1991.[60][130] For example, in Denmark, which reported the lowest rates in Europe, TB incidence per 100,000 increased 17% between 1986 and 1990 (5.8 to 6.8). Switzerland reported an increase of 33% between 1986 and 1990 (13.8 to 18.4), the largest increase in Europe. In four African countries with long-standing, reliable programs, the annual incidence per 100,000 of sputum smear-positive pulmonary TB increased 13% in Benin (from 30 in 1984 to 34 in 1992), 35% in Mozambique (from 37 in 1986 to 49 in 1992), 54% in Tanzania (from 32 in 1982 to 50 in 1992), and 77% in Malawi (from 31 in 1984 to 55 in 1992).

Because of the shortcomings in reporting systems, true TB morbidity and mortality rates may be reflected more accurately by scientific estimates than by surveillance data. Consequently, the true incidence of TB is estimated periodically by the WHO, the International Union Against TB and Lung Disease (IUATLD), and other agencies, based on the best available data.[131][151][154][188] The most comprehensive, detailed, and perhaps most accurate report provides data for 1997 and was issued by WHO in 1999.[53]

<table>
<thead>
<tr>
<th>Western Pacific</th>
<th>600,185</th>
<th>826,507</th>
<th>37.7</th>
<th>42.6</th>
<th>54.6</th>
<th>27.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Total</td>
<td>2,959,884</td>
<td>3,798,537</td>
<td>28.7</td>
<td>61.8</td>
<td>74.6</td>
<td>20.8</td>
</tr>
</tbody>
</table>


These data must be interpreted with caution, however, because case finding and reporting are poor in many national TB programs (NTPs). Moreover, during this period, China and India launched efforts to improve TB control, so increasing numbers in these countries (roughly half the world's TB morbidity rate) may reflect better case detection and reporting; however, this same report estimated the true incidence of TB in 1990 as 7.5 million new cases with 2.5 million deaths worldwide.[131]
Figure 1. Estimated worldwide incidence of tuberculosis per 100,000 population (A) and number of new cases (B) in 1997. (From Dye C, Scheele S, Dolin P, et al for the WHO Global Surveillance and Monitoring Project: Global burden of tuberculosis: Estimated incidence, prevalence, and mortality by country. JAMA 282:677–686, 1999, with permission).

### TABLE 3 -- ESTIMATES OF THE INCIDENCE, PREVALENCE, AND MORTALITY RATES OF TUBERCULOSIS IN 23 HIGH-BURDEN COUNTRIES IN 1997

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (millions)</th>
<th>Incidence</th>
<th>Prevalence</th>
<th>Mortality</th>
<th>Incidence</th>
<th>Prevalence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>960.2</td>
<td>1799</td>
<td>4854</td>
<td>437</td>
<td>187</td>
<td>505</td>
<td>46</td>
</tr>
<tr>
<td>China</td>
<td>1243.7</td>
<td>1402</td>
<td>2721</td>
<td>258</td>
<td>285</td>
<td>786</td>
<td>68</td>
</tr>
<tr>
<td>Indonesia</td>
<td>204.3</td>
<td>583</td>
<td>1606</td>
<td>140</td>
<td>246</td>
<td>508</td>
<td>55</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>122.0</td>
<td>300</td>
<td>620</td>
<td>68</td>
<td>181</td>
<td>405</td>
<td>44</td>
</tr>
<tr>
<td>Pakistan</td>
<td>143.8</td>
<td>261</td>
<td>583</td>
<td>64</td>
<td>214</td>
<td>383</td>
<td>58</td>
</tr>
<tr>
<td>Nigeria</td>
<td>118.4</td>
<td>253</td>
<td>454</td>
<td>69</td>
<td>314</td>
<td>693</td>
<td>68</td>
</tr>
<tr>
<td>Phillippines</td>
<td>70.7</td>
<td>222</td>
<td>490</td>
<td>48</td>
<td>392</td>
<td>604</td>
<td>166</td>
</tr>
<tr>
<td>South Africa</td>
<td>43.3</td>
<td>170</td>
<td>262</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russia</td>
<td>147.7</td>
<td>156</td>
<td>241</td>
<td>26</td>
<td>106</td>
<td>163</td>
<td>17</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>60.1</td>
<td>156</td>
<td>221</td>
<td>49</td>
<td>260</td>
<td>367</td>
<td>82</td>
</tr>
<tr>
<td>Vietnam</td>
<td>76.6</td>
<td>145</td>
<td>221</td>
<td>20</td>
<td>189</td>
<td>289</td>
<td>26</td>
</tr>
<tr>
<td>DR Congo</td>
<td>48.0</td>
<td>129</td>
<td>191</td>
<td>39</td>
<td>269</td>
<td>397</td>
<td>81</td>
</tr>
<tr>
<td>Brazil</td>
<td>163.1</td>
<td>122</td>
<td>188</td>
<td>19</td>
<td>75</td>
<td>115</td>
<td>11</td>
</tr>
<tr>
<td>Tanzania</td>
<td>31.5</td>
<td>97</td>
<td>125</td>
<td>31</td>
<td>308</td>
<td>396</td>
<td>99</td>
</tr>
<tr>
<td>Kenya</td>
<td>28.4</td>
<td>84</td>
<td>106</td>
<td>28</td>
<td>297</td>
<td>371</td>
<td>99</td>
</tr>
<tr>
<td>Thailand</td>
<td>59.2</td>
<td>84</td>
<td>180</td>
<td>17</td>
<td>142</td>
<td>305</td>
<td>29</td>
</tr>
<tr>
<td>Myanmar</td>
<td>46.8</td>
<td>80</td>
<td>163</td>
<td>19</td>
<td>171</td>
<td>348</td>
<td>40</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>22.1</td>
<td>74</td>
<td>167</td>
<td>23</td>
<td>333</td>
<td>753</td>
<td>104</td>
</tr>
<tr>
<td>Uganda</td>
<td>20.8</td>
<td>66</td>
<td>94</td>
<td>30</td>
<td>320</td>
<td>451</td>
<td>146</td>
</tr>
<tr>
<td>Peru</td>
<td>24.4</td>
<td>65</td>
<td>70</td>
<td>7</td>
<td>265</td>
<td>288</td>
<td>30</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>11.7</td>
<td>63</td>
<td>73</td>
<td>33</td>
<td>538</td>
<td>626</td>
<td>283</td>
</tr>
<tr>
<td>Cambodia</td>
<td>10.5</td>
<td>57</td>
<td>101</td>
<td>9</td>
<td>539</td>
<td>963</td>
<td>90</td>
</tr>
<tr>
<td>Total</td>
<td>3657.4</td>
<td>6367</td>
<td>13,728</td>
<td>1506</td>
<td>174</td>
<td>375</td>
<td>41</td>
</tr>
</tbody>
</table>


*Democratic Republic of Congo, formerly Zaire.
The most recent WHO annual report estimated that between 1997 and 1999 global TB incidence increased 12% to 8.4 million new cases (178 per 100,000 population). Of these, 3.7 million were sputum smear-positive (62 per 100,000 population). In other words, the global burden of TB has been increasing an average of 3% annually. If these trends continue, 10.2 million new cases are expected in 2005. Incidence trends are increasing fastest in African countries most affected by HIV (approximately 10%/year), followed by Eastern Europe and the former Soviet Union (approximately 8%/year) (Fig. 2). Smaller increases of approximately 1% to 3% per year are occurring in Latin America, African countries less affected by HIV, the Eastern Mediterranean, South and Southeast Asia, and the Western Pacific. These broad regional averages, however, conceal declining TB incidence in selected countries in these regions, for example, Argentina, Chile, Peru, Morocco, Croatia, Poland, and South Korea. In countries with established market economies, the collective TB incidence is decreasing by approximately 2% to 3% per year.

Why has TB resurfaced on such a broad scale? Clearly, epidemiological factors such as the pandemic of HIV infection and the extensive spread of drug-resistant TB play major roles. Political and economic developments also have contributed, such as the break-up of the Soviet Union; the Asian economic crisis; worsening poverty; and wars in the Balkans, the north Caucasus, and Africa. On the other hand, health authorities have been armed for over a decade with a highly cost-effective strategy to control TB, clearly articulated and vigorously promoted by WHO, IUATLD, and other organizations under the acronym, “DOTS” (directly observed treatment, short-course). Yet, NTPs have been too slow to implement DOTS, and most countries have not been able to contain the growth of TB.

To analyze the obstacles to DOTS implementation and develop recommendations to improve TB control, in 1998 WHO convened a meeting of international TB experts, public health officials, and NTP managers. This group delineated six principal constraints limiting the ability of health authorities to act: deficiencies of finances, human resources, health sector organization, antituberculosis drug supplies, public awareness, and most importantly lack of political will and government commitment. In simple terms, most governments have given TB control neither sufficient priority nor adequate resources to ease the burden of TB on their populations. Among developing nations, there are too few examples of the type of strong government commitment to TB control seen in Vietnam, Peru, Botswana, and Singapore. Government commitment is critical, because its absence results in inadequate financing for TB control, too few and insufficiently skilled personnel, inadequate physical infrastructure, and major problems with the health systems of the country. Examples of the problems within health systems include weak peripheral health services, lack of involvement and coordination with private practitioners, and poor coordination with vertical health services for specialized populations, such as those within the penal system and other institutionalized populations. Given these widespread shortcomings in government support for TB control, social forces and the epidemiological factors of HIV and multidrug-resistant TB have fueled the resurgence of TB worldwide.

**COEPIDEMICS OF TUBERCULOSIS AND HIV/ACQUIRED IMMUNODEFICIENCY SYNDROME**
From no recognized cases prior to 1980, to an estimated global prevalence of 34.3 million individuals with HIV by the end of the 1990s, the explosive spread of HIV/AIDS throughout the world constitutes one of the most devastating pandemics of recorded history. The Joint United Nations Program on HIV/AIDS (UNAIDS) estimated that 5.4 million persons became infected with HIV in 1999, and 2.8 million died. Africa and Southeast Asia have been affected by HIV/AIDS most heavily. An estimated 68% of persons with HIV worldwide live in sub-Saharan Africa, and 20% more live in Southeast Asia, 88% of the global total. Similarly, these two regions account for an estimated 90% of incident HIV infections and 89% of annual deaths. Although HIV/AIDS has affected the TB situation worldwide, its impact has been greatest in these two regions because of the high prevalence of TB infection in the populations and the high incidence of TB disease in these areas, even before the HIV epidemic. Of the estimated 15.3 million individuals coinfected with HIV and *M. tuberculosis* in 1997, 11.7 million were in sub-Saharan Africa, 2.8 million in Southeast Asia, 0.5 million in Latin America, and the remaining 0.3 million in the rest of the world combined, including North America, Europe, China, North Asia, and the Middle East. Figure 3 displays the distribution of estimated global HIV/TB coinfection by country. Although the proportion of people with HIV/TB coinfected was highest in many African countries, India had the highest number of HIV/TB coinfected individuals, about 2 million people.

The sharp increase in TB in countries most affected by HIV is related to the greatly increased risk of progression from primary or latent infection to active TB disease in persons infected with both pathogens, and the rapid spread of HIV infection in populations where ongoing transmission and latent infection with *M. tuberculosis* are common. The extent of ongoing transmission and the prevalence of latent TB infection in these populations can be estimated from the ARI. The ARI in Africa is approximately 1.5% to 2.5% (i.e., among 20-year olds, 30% to 50% are infected). In Southeast Asia, the ARI is 0.5% to 2.0%. In HIV-infected persons with a positive tuberculin skin test, the incidence of active TB disease ranges from 4.5% to 9.7% annually, or 4- to 26-fold higher than in HIV-uninfected, tuberculin skin test-positive individuals in the same studies. The potential for rapid spread of TB has been illustrated by outbreaks in residential facilities, hospitals, and prisons in which a high proportion of persons with HIV developed active TB within months or even weeks of exposure to an undiagnosed case of TB. In the United States, epidemiological evidence indicates that the HIV epidemic contributed substantially to the resurgence of TB between 1985 and 1992. A nationwide match of TB and AIDS case registries between 1981 and 1990 showed that the proportion of reported TB cases that matched cases in the AIDS registry increased steadily from 0.1% to 9.5%, and reported AIDS cases that matched cases in the TB registry increased from 1.9% to 5.8%. Thirty percent of the excess TB cases from 1985 through 1990 could be accounted for by identified TB-AIDS cases. Investigators compared the epidemiology of TB before 1980 and after 1985 in 10 countries in sub-Saharan Africa with relatively stable surveillance during the period of observation. The prevalence of HIV infection among TB cases in the later period averaged 44%. The excess incidence of TB after 1985 averaged 34% (i.e., 34% of the cases would not have occurred if the pre-1980 trends had continued). Moreover, in countries where over 50% of the TB cases were HIV-infected, the large majority of the excess TB cases could be attributed to HIV infection (would not have occurred in the absence of HIV infection). In northern Thailand, following the explosive spread of HIV infection in high-risk groups beginning in 1988 and 1989, the prevalence of HIV among TB cases jumped from 1.5% in 1990 to 45.5% in 1994, while the total number of TB cases increased 77%. Based on conservative assumptions, 36% of the total could be attributed to HIV infection. In summary, TB incidence increased sharply once HIV infection spread through these populations. HIV infection became...
increasingly common among TB patients, and most of the excess TB cases were attributable to HIV infection.

Fortunately, HIV-infected patients with pulmonary TB appear to be no more infectious to others than HIV-negative patients. Studies have shown that contacts of HIV-positive patients with pulmonary TB have approximately the same or, in some cases, lower frequency of TB infection and disease than contacts of HIV-negative patients. These findings likely are related to the lower frequency of cavitary lung disease and, in some cases, lower frequency of smear-positive pulmonary disease in patients with HIV infection. Thus, although the prevalence of HIV infection in a population increases TB incidence, it does not appear to increase incidence exponentially.

In addition to its effect on TB incidence, HIV hampers case detection and diagnosis in countries with limited diagnostic technology and human resources. The systemic symptoms and signs of HIV and TB overlap, making it difficult to distinguish between TB, HIV, and HIV-TB coinfection if laboratory tests are unavailable or unreliable. In addition, patients with HIV more commonly have extrapulmonary TB, unusual manifestations of TB, and unusual pathogens that may mimic TB such as nontuberculous mycobacteria (NTM), fungi, Nocardia, or rhodococcus. Chest radiographs may not be helpful, because HIV-infected persons with pulmonary TB less often have typical upper lobe cavitary disease and more often have lower lobe infiltrates, hilar and mediastinal adenopathy, or even normal radiographs, depending on the extent of immunosuppression. Patients with HIV are less likely to develop positive reactions to tuberculin skin testing. Furthermore, some studies have shown that sputum smears were less often positive among HIV-infected than among HIV-negative patients with pulmonary TB, again, especially as immune function declined. This is especially important in developing countries where sputum smears and, to a lesser degree, chest radiography are the principal diagnostic tools.

The treatment of TB also is complicated by HIV infection in less affluent countries. In many of these countries, the standard treatment for TB, until recently, was 12 months of isoniazid plus thiacetazone, supplemented by streptomycin for the first 2 months. More recently, a regimen of 2 months of isoniazid, rifampicin, pyrazinamide, and streptomycin, followed by 6 months of isoniazid plus thiacetazone has been used because of its better efficacy and modest cost. Severe cutaneous reactions to thiacetazone in HIV-infected patients have forced programs in HIV-prevalent countries to abandon thiacetazone and use much more expensive regimens. Problems with drug malabsorption and subsequent treatment failure also have been noted in patients with HIV infection, especially in areas of the world where gastrointestinal manifestations of AIDS are relatively common.

Considerable interest has focused on treatment outcomes in HIV-infected TB patients. Except early mortality, treatment of TB in patients with HIV infection can be as successful as in patients without HIV infection, in terms of resolution of symptoms and physical signs, radiographic abnormalities, bacteriological examination of sputum or tuberculous tissues, and cure rates. Outcome studies in Africa and Haiti have shown that relapses occur in 2% to 8% of HIV-positive patients, not significantly different from the 3% to 5% relapse rate in HIV-negative patients. A randomized, controlled trial in Zaire suggested that treatment for 12 months decreased the frequency of relapses compared with treatment for 6 months.

Early mortality is associated with delayed diagnosis or delayed initiation of treatment, extensive pretreatment disease, and unrelated complications of HIV infection. In New York City, early mortality (during treatment) in TB patients with HIV fell from 25% to 30% before DOTS was implemented, to 12% to 15% under DOTS but before treatment with combination antiretroviral drugs became standard (New York City TB Control Program, unpublished). Longer term mortality rates, on the other hand, are substantially higher in TB patients with HIV. In the era preceding highly active
antiretroviral treatment, the 1-year mortality rate for treated, HIV-associated TB ranged from approximately 20% to 35%. In a large South African study, after 6 months of followup, 14% of patients with HIV had died compared with 0.5% of HIV-negative patients. In Los Angeles County, after nearly 2 years of followup, the mortality rate was 54% despite apparent cures in 84 of 89 patients. In New York City, 3 years after the diagnosis of TB, the mortality rate was 77%, and in San Francisco, after 5 years of followup, the mortality rate exceeded 90%. Mortality was associated with lower CD4+ lymphocyte counts, drug-resistant TB, and nonadherence to treatment, though fewer deaths were caused by TB than by other HIV-associated diseases. On a broader scale, the estimated number of TB deaths attributable to HIV infection worldwide increased from 116,000 (4.6%) in 1990 to 500,000 (14.2%) in 2000. Africa and Southeast Asia accounted for 439,000 (12.5%) deaths in 2000.

The increasing numbers of cases and high mortality rates have led many programs to consider treating latent TB infection in individuals with HIV. Although treatment of latent infection must be a lower priority than diagnosing and treating active disease, it should be considered in developing countries where the risks of TB and HIV are high, because there is near certainty that HIV/TB coinfected individuals will go on to develop active TB disease. Studies in Latin America, Haiti, Africa, and Thailand have documented the efficacy of preventive treatment in tuberculin skin test-positive persons with HIV and, to a varying degree, in anergic persons with HIV, over follow-up periods of 4 months to 3 years. WHO and UNAIDS suggest that preventive treatment may be offered to persons with HIV/AIDS in settings of high TB prevalence, while at the same time ensuring full implementation of DOTS for the diagnosis and treatment of active TB disease. Numerous issues remain unresolved, however. Should preventive treatment be extended or continued indefinitely? Will patients accept and adhere to treatment for latent infection? How will it affect the occurrence of drug-resistant TB? For national HIV and TB control programs, where is the balance in cost-effectiveness between treatment of latent TB infection in persons with HIV/AIDS versus optimizing DOTS implementation and AIDS prevention nationwide? Pilot projects and controlled studies in developing countries are needed.

**DRUG-RESISTANT TUBERCULOSIS**

Another major threat to global TB control is the emergence of mycobacterial resistance to antituberculosis. Drug-resistant TB results in higher morbidity and mortality rates, greater difficulty in treatment, and much higher costs than drug-susceptible TB. Drug-resistant TB was identified initially in the 1940s soon after the first antituberculosis drugs were developed. Drug resistance became less important, however, once the principles of combination chemotherapy were established in the 1950s. In more recent years, reports of problems with multidrug-resistant TB, defined as TB resistant to at least isoniazid and rifampin, have been increasing rapidly from many different areas of the world. An in-depth treatise on the global impact of multidrug-resistant TB summarized published reports up to 1999 and presented detailed case studies from Russia, Azerbaijan, Peru, and South Africa. Many of the reports cited, especially from less affluent countries, were limited by problems with laboratory quality and epidemiological methods, however. Consequently, in 1994, the WHO and the IUATLD launched the global project on antituberculosis drug resistance surveillance to determine the levels of resistance to isoniazid, rifampin, ethambutol, and streptomycin in nationally representative populations using standardized methods. The approach was epidemiologically and microbiologically rigorous but flexible enough to allow the participation of any country.

By 2000, two rounds of the global survey were completed, the first covering 1994 to 1996 and the second covering 1996 to 1999. Seventy-two countries or regions within large countries (e.g., state,
province, or oblast) were included, and isolates from over 118,000 patients were tested. In addition, 28 areas provided data at two or more points in time enabling trends to be determined. Including both rounds, the data covers geographic areas representing 33% of the world population and 28% of reported TB cases worldwide. A network of top laboratories provides quality assurance and validates the susceptibility data, so the results can be trusted.

**New Tuberculosis Cases**

The results show that drug-resistant TB is ubiquitous, occurring in every country, although the problem is only a fraction of the total TB pandemic. The median prevalence of resistance to any of the four drugs was 11%, with a range of 1.7% to 41%. Eleven countries or regions exceeded 20%, while 18 were below 5%. Resistance was highest to isoniazid or streptomycin, with rifampin and ethambutol resistance much lower. Across all sites, approximately 60% of new patients with any resistance had resistance only to a single drug. With respect to multidrug-resistant TB, the median prevalence was 1%, with a range of 0% to 14.1% (Fig. 4). Seven sites were “hot spots” for primary multidrug-resistant TB, with prevalence exceeding 5% (four sites in the former Soviet Union), while eight sites had no detectable MDRTB (four in western Europe). In aggregate, approximately 38% of new patients with resistance to two, three, or four drugs had multidrug-resistant TB.

![Figure 4. Prevalence of multidrug resistance (defined as resistance to at least isoniazid and rifampin) among new tuberculosis cases from 1994 to 1999.](https://home.mdconsult.com/das/article/body/1/jorg=journal&source=&sp=12347508&sid=)

Among new cases, drug resistance was associated strongly with migration. Levels of resistance to at least one drug were significantly higher among foreign-born residents in 9 of 17 countries providing data. These included the United States, Canada, six western European countries, and Iran. In most sites, the ratio was approximately two- to fourfold, although a sevenfold disparity was noted in Norway. Levels of multidrug-resistant TB were also significantly higher among the foreign-born in Iran, nearly fourfold.

Twenty-eight sites provided data on new cases from at least 2 years between 1994 and 1999. Analysis of trends from these sites revealed that resistance to at least one antituberculosis drug increased significantly in two middle-income countries, Estonia and Peru, but also in three high-income, low-incidence countries, Denmark, Germany, and New Zealand. These increases were mostly in streptomycin and isoniazid resistance, while resistance to rifampin and ethambutol remained stable. In many countries, mainly in Europe, increases may be caused by an influx of immigrants from countries with a higher prevalence of drug-resistant TB. Fortunately, these countries did not observe an upsurge of multidrug-resistant TB. Only Australia experienced a statistically significant rise in multidrug-resistant TB, from 0.7% in 1995 to 2.0% in 1996. In contrast, the Netherlands, Spain, and Switzerland observed significant decreases in the frequency of patients with resistance to at least one drug, while France and the United States observed significant decreases in multidrug-resistant tuberculosis TB. No significant changes in drug resistance levels were detected in 16 countries or regions.

There is an alarming public health problem in the former Soviet Union. The Baltic countries of Latvia and Estonia and the Russian oblasts of Ivanovo and Tomsk have unusually high levels of multidrug-resistant TB in new and retreatment patients. In these areas, the first priority must be sound basic TB control, because high levels of multidrug resistant TB reflect poor TB control program performance in past years. A poor TB control program can create multidrug-resistant TB much faster than even the best...
program can manage it, especially in resource-limited settings. At the same time, prevention of multidrug-resistant TB is synonymous with sound basic TB control (i.e., curing new patients the first time they are treated). Clinical laboratory services for rapid drug susceptibility tests (DST) of *M. tuberculosis* are limited in much of the former Soviet Union, however. On a population level, most patients do not have significant drug resistance and can be cured without DST results, using standard WHO/IUATLD DOTS treatment regimens.[62] In contrast, in countries with a high prevalence of multidrug-resistant TB, new patients in whom standard DOTS treatment fails have high likelihoods of significant drug resistance. Such patients need rapid evaluation and possibly treatment with second-line antituberculosis drugs. International collaborations can provide resources and technical expertise in the short term, while sustainable solutions are being developed.

**Previously Treated Cases of Tuberculosis**

Prior treatment is a consistent, strong risk factor for drug resistance. In global surveillance projects, prior treatment was associated with any drug resistance (odds ratio [OR] = 4.2, 95% confidence interval [CI] 3.7, 4.7) and multidrug-resistant TB (OR = 10.5, CI 8.5, 12.9). Moreover, the duration of prior treatment showed a dose-response effect. Prior treatment for longer than 12 months had a stronger effect on the prevalence of multidrug-resistant TB (OR = 13.7, CI 4.5, 41.6) than prior treatment for 6 to 11 months (OR = 7.6, CI 2.6, 22.4). Data from 58 countries or regions showed a median prevalence of resistance to at least one drug of 33.4%, with a range of 0% to 93.8% among those previously treated (Fig. 5).[62] [119] [179] [180] Again, isoniazid resistance was highest, but, unlike in new patients, rifampin resistance was second. Regarding multidrug-resistant TB, the median prevalence was 9.1%, with a range of 0% to 48.2%. In six sites, over one third of the retreatment patients had multidrug-resistant TB, including two in China and two in Baltic countries. The problem in previously treated cases is worrisome, because such cases are likely to carry strains of *M. tuberculosis* resistant to many antituberculosis drugs. Fortunately, previously treated cases comprised a small proportion of the total cases (median 9.9%, range 0.5% to 24.7% in the 1996 to 1999 survey). Once sound TB control practices are implemented, retreatment cases are the first to decline substantially.

![Figure 5. See legend on opposite page](http://home.mdconsult.com/das/article/body/1/jorg=journal&source=&sp=12347508&sid... 22/12/2002)
In response to the crisis of high or increasing levels of multidrug-resistant TB in many countries, WHO and several partners have launched the “DOTS-Plus” initiative to evaluate the feasibility and cost-effectiveness of using second-line drugs in developing countries. This initiative is spearheaded by WHO’s *Working Group on DOTS-Plus for MDRTB*, an open group of stakeholders in TB control, experts in TB, leaders in public health, and representatives from the pharmaceutical industry. The concept behind DOTS-Plus is that management of multidrug-resistant TB must be based on the foundation of a solid DOTS program. If a program cannot treat new patients with drug-susceptible TB successfully in nearly all cases, then it will be much less successful treating multidrug-resistant TB patients and risks creating (and spreading) incurable TB. Recognizing that the high cost of second-line antituberculosis drugs is a major barrier for less affluent countries, this initiative enables pilot projects to benefit from large reductions in the cost of second-line drugs that a subcommittee of the working group negotiated with pharmaceutical companies. Pilot projects wishing to procure drugs at these concessional prices apply to the WHO’s Green Light Committee, which evaluates the application and the proposed project site. Applications are approved if the basic TB program and the proposed services for multidrug-resistant TB meet explicit standards established by the working group, and the project is monitored periodically to provide technical assistance as needed.

Although the optimal approach to multidrug-resistant TB from a clinical perspective would be to select treatment based on rapid, accurate, and current DST results, this is unrealistic in many regions of the world. Therefore, pilot projects and national programs are evaluating various ways to achieve the best possible results with resources that are often grossly inadequate, taking practical considerations into account. In South Africa, a standardized regimen was devised based on drug resistance surveillance. It will be administered to a large cohort of patients with multidrug-resistant TB without further DSTs to evaluate the costs, feasibility, and outcomes of this approach. In a Peruvian pilot project, patients in whom the standardized retreatment regimen has failed are treated with a standardized empiric regimen based on DST results from prior case series until new DST results become available. DSTs are repeated at a reference laboratory in the United States. Clinical specimens and results are shuttled back and forth as rapidly as possible. In the Baltic republics, only patients with confirmed multidrug-resistant TB are enrolled in the DOTS-Plus program, and they are treated with an individualized regimen based on DST results. Based on critical evaluation of the results of such pilot projects, more informed recommendations can be issued regarding the management of retreatment cases, chronic cases, and multidrug-resistant TB cases in resource-limited countries where real-time DST results may not be available.

**GLOBAL EFFORTS TO CONTROL TUBERCULOSIS**

Because of the worldwide resurgence of TB, complicated by HIV infection and multidrug resistance, in 1993, WHO declared TB a global public health emergency, the first time any disease received this designation. At about the same time, WHO, IUATLD, and many other international, national, and nongovernmental organizations began developing strategies and mobilizing resources for improving TB control worldwide. Most important, WHO formalized the strategy developed by Karel Styblo of the IUATLD for TB control at the national and local program levels. The DOTS strategy includes five crucial elements: sustained government commitment to TB control, bacteriological diagnosis of TB primarily by sputum smear microscopy (as opposed to radiographic or clinical diagnosis), an uninterrupted supply of quality-assured antituberculosis drugs distributed under strict control, standardized short-course (i.e., rifampin-containing) chemotherapy administered under direct observation, and a system of monitoring and accountability that includes a standard recording and reporting format to monitor program performance by accurately quantifying case notifications and treatment outcomes on a regular basis. Sputum microscopy is emphasized as the only feasible means
to detect most infectious cases in low- and middle-income countries accurately and rapidly. Culture and
drug-susceptibility testing are implicit for countries with adequate resources and infrastructure. The call
for a stable supply of quality-assured drugs refers to frequent shortages encountered in many countries
because of inadequate drug policies, poor management, and inadequate financial reserves. These
conditions create a market ripe for counterfeit or substandard drugs produced in countries without strict
controls. Controlled distribution is important to prevent over-the-counter abuse of antituberculosis drugs
by lay people or unqualified medical practitioners.

The DOTS strategy has been called one of the most cost-effective health interventions of the late 20th
century. Where it has been implemented assiduously, DOTS-type programs have demonstrated
considerable success. “Implemented assiduously” is an important proviso, because nominal DOTS
programs reporting poor outcomes do not, on closer examination, ensure adherence to treatment. The
tenational TB programs of Botswana, Peru, and Vietnam, the expanding DOTS programs in China
and India, and demonstration projects in Tomsk and Orel, Russia, exemplify the DOTS strategy and
provide quantitative data that support claims of its efficacy. Tanzania is the oldest example of the (de facto) DOTS strategy, because it was the first IUATLD-supported NTP (beginning in
1979). Once standardized short-course chemotherapy was introduced in 1982, treatment completion
increased from 55% to 80% or 85%. Between 1983 and 1998, case notifications increased from
approximately 12,000 per year to 51,000 per year, and annual incidence rates increased from 58 to 160
per 100,000 population because of improved case registration and increasing HIV/AIDS. Despite
this near-tripling of TB morbidity rates, the annual risk of TB infection, determined by serial skin test
surveys in nonvaccinated school children, remained essentially the same. The ARI was 0.011 between
1983 and 1987 and 0.009 between 1993 and 1999, and the estimated number of new infections per
notified case decreased from 36 to 19 over the same period. These impressive results likely reflect the
effectiveness of the Tanzanian NTP.

Global implementation of DOTS is monitored by WHO and has been published annually since 1996 in
the “Global Tuberculosis Control” series of WHO reports. To compile these reports, WHO requests
information from all 212 member countries on case notifications for the previous year, treatment
outcomes for patients registered 2 years before, and the national TB control program policy. WHO
categorizes countries that have accepted DOTS based on the degree of DOTS implementation: less than
10% (pilot phase), 10% to 90% (expansion phase), and greater than 90% (routine implementation). Non-
DOTS countries, in contrast, are subdivided according to their incidence rates: low is less than 10 per
100,000, while high is greater than or equal to 10 per 100,000. NTP performance is assessed on case
detection, treatment outcomes, and trends in a standard cohort analysis format. Because case notification
data are subject to the limitations discussed previously, these reports include estimates of true TB
incidence, case detection, control program effectiveness, and country-by-country analyses of progress in
TB control.

The most recent DOTS data refer to program status at the end of 1999, case notifications in 1999, and
treatment results for cases registered in 1998. These data include 171 (81%) of the 212 countries
representing 98% of the world's population. Nominally, 127 countries had implemented DOTS in 1999
(Fig. 6), compared with 70 in 1995 and a small handful of IUATLD countries in 1990. In total, 82% of
the world's population was living in countries adopting the DOTS strategy to some degree, but only 71
of the 127 DOTS countries reported covering greater than 90% of the country's population. Another 47
countries covered 10% to 90%, and eight countries, covered less than 10% of the population.
Consequently, 45% of the world's population had access to DOTS in 1999, compared with 23% in 1995.
Among the 22 high-incidence countries, by 1999 all but one had adopted the DOTS strategy. Population
coverage in these countries varied between 5% and 100%, and 46% of their cumulative population was
described by DOTS. Thus, effective DOTS expansion and self-sustainability, especially in these high-
incidence countries, is the most pressing priority in terms of global TB control. Progress in global DOTS
expansion to date is displayed in Figure 7.

**Figure 6.** Proportion of 211 countries implementing the directly observed short-course treatment (DOTS) tuberculosis control strategy in 1999 categorized according to different levels of DOTS coverage. (From WHO: Global tuberculosis control, WHO Report 2001. Geneva, Switzerland, WHO/CDS/TB/2000. 275, 2001.)

**Figure 7.** Progress in the global implementation of the directly observed short-course treatment (DOTS) tuberculosis control strategy between 1995 and 1999 shown by changes in the categorization of countries according to the levels of DOTS coverage. (From WHO: Global tuberculosis control, WHO Report 2001. Geneva, Switzerland, WHO/CDS/TB/2000. 275, 2001.)

The stated targets for TB control under the DOTS strategy are to detect 70% of sputum smear-positive cases and cure 85% of cases detected. These were calculated as the targets required to decrease TB transmission.[150] Thus, to evaluate DOTS, the two primary measures are the proportion of estimated cases detected and the proportion of cases treated successfully. The proportion of cases detected is established by comparison with the best estimates of true TB incidence based on all sources of information. Because recording and reporting of cases are basic components of DOTS, for purposes of analysis, case detection and reporting are considered synonymous. The proportion cured is based on cohort analyses of the outcomes of all patients registered for treatment with standard definitions of six outcome categories: cured, treatment completed, failed, defaulted, died, and transferred out. In 1999, in six high-incidence countries with full coverage (>95%) for at least 2 years, detection of new sputum smear-positive cases ranged between 51% and 59% of the estimated total number in four countries, to 80% in Vietnam, and to 95% in Peru.[122] Overall, in the 22 high-incidence countries, case detection under the DOTS programs increased from 9% in 1995 to 23% in 1999 relative to the estimated total TB incidence in those countries (DOTS programs only covered 46% of their populations in 1999). In these 22 countries, patients registered and treated in DOTS regions fared considerably better than those in non-DOTS regions. Of patients treated in DOTS programs, 84% had successful outcomes (range, 58% to 97%); 8.8% had poor outcomes, and 4.9% had unknown outcomes. In contrast, in non-DOTS regions, only 31% of patients had successful outcomes (range, 20% to 85%); 7.9% had poor outcomes, and 60% had unknown outcomes. Only two countries, Vietnam and Peru, met the explicit targets for both case detection and treatment success. Brazil, China, and Cambodia exceeded 80% treatment success but fell short of case detection targets. The remaining countries did not meet either target.[122]

Critics of the DOTS strategy express concern that standardized chemotherapy with isoniazid, rifampin, pyrazinamide, and ethambutol may lead to treatment failures and amplify drug resistance among patients with pre-existing resistance to one or more of these drugs.[66] From a clinical perspective, it clearly would be preferable to know the drug susceptibility pattern of a patient's *M. tuberculosis* prior to treatment. Patients with any rifampin resistance and especially with multidrug resistance should be treated with a different combination of drugs for a longer period of time. From a public health perspective, however, routine drug susceptibility testing is out of reach for most TB control programs, and the large majority of patients have fully drug-susceptible TB. Even in regions with high levels of rifampin resistance (including multidrug resistance), the majority of patients will have rifampin-susceptible disease and would likely be treated successfully with the standard four-drug regimen. A cohort review of more than 6400 patients in six countries that use the DOTS strategy demonstrated that 5.4% of new patients and 23.6% of retreatment patients had resistance to rifampin, including 3.3% and 19.3% with multidrug resistance. Among new patients, treatment succeeded in fewer multidrug-resistant TB patients (52%) and in fewer patients with any other form of rifampin-resistant TB (73%) than in patients with drug-susceptible TB (85%). Among retreatment patients, the differences in
treatment success were even greater (29% with multidrug resistance and 53% with any other rifampin resistance compared with 67% with no drug resistance). Overall, treatment succeeded in 79% of patients, including 83% of new patients and 57% of retreatment patients (retreatment patients constituted 14% of the total). In contrast, recent work in Chennai, India, showed that rifampin resistance emerged in only 2% of patients overall, even though initial isoniazid resistance was detected in 18% of patients. Rifampin resistance emerged in only 1% of patients with drug-susceptible TB and 11% of patients with baseline isoniazid resistance. Of note, 3.4% of patients had baseline rifampin resistance. From a programmatic point of view, sputum smear microscopy and completion of standard short-course treatment should be higher priorities than drug susceptibility testing and treatment with prolonged courses of second-line drugs, considering the cost and resources required. The same resources would benefit many more patients. Once a program has firmly established the basic TB services and consistently achieves the WHO-recommended targets for case detection and cure, additional resources could be directed to optimizing services for high-risk patients. For example, drug susceptibility testing might be offered to retreatment patients in whom the risks of multidrug-resistant TB are much higher.

The challenge now is to strengthen and expand DOTS coverage worldwide as rapidly as possible while continually improving the quality of existing DOTS programs. Under the leadership of WHO, the global movement to improve TB control in less affluent countries through DOTS has become an important positive force in public health. It continues to gain momentum, high-level commitment, and increasing resources from governments, national and international agencies, non-governmental organizations, and private partners. Although some decry the acronym, DOTS, or find fault with technical elements of the strategy, it works and is growing. In essence, DOTS means quality diagnosis, treatment, and follow-up. Thus, it behooves all concerned to contribute to these far-reaching and highly successful efforts. Even critics can engage in constructive dialogue. In short, if the goal is to reduce global morbidity and mortality rates from TB, supporting this initiative appears to be the straightest path.

LATIN AMERICA: MOVING FROM GOOD POLICIES TO GOOD PUBLIC HEALTH PRACTICE

Tuberculosis remains a major public health problem throughout most of Latin America and the Caribbean, but the disease incidence and the control programs vary widely, reflecting the political, geographic, and socioeconomic diversities of the region (see Fig. 1). Over the past 50 years, public health in the region has benefited from social and economic progress, especially the development of primary care systems, specialized referral services, and laboratory networks. In many countries, national policies have been based on WHO and IUATLD recommendations for more than 20 years. Economic crises in the 1980s weakened public health infrastructures, however, and prevented paper policies from being translated into practice, except in a few countries with established, strong primary care systems.

In the 1990s, national TB control programs were reorganized and reinvigorated following the WHO and Pan American Health Organization (PAHO)-recommended DOTS strategy. With renewed economic growth and global mobilization against TB, more resources are becoming available for TB control in lower-income nations in the region. Some high-incidence countries have expanded DOTS coverage and improved patient outcomes. Other countries need to intensify and expand their programs.

Epidemiology

The World Health Organization (WHO) estimated 390,000 new TB cases occurred in the Americas in 1997, excluding the United States and Canada, but only 228,000 cases (58%) were reported.
Estimated annual incidence rates were highest for Haiti, Peru, and Bolivia, exceeding 250 per 100,000, and high also in Ecuador and the Dominican Republic, exceeding 100 per 100,000. Cuba, Costa Rica, and some nations of the English-speaking Caribbean have the lowest rates, under 20 per 100,000. Brazil and Peru are in the dubious elite of 22 WHO-designated high-incidence countries, with an estimated 120,000 and 65,000 new cases of TB in 1997. Case reporting has remained steady over the decade in Brazil, with frequent problems of incomplete reporting to the federal level. In Peru, on the other hand, reported incidence has fallen at an average of 7.5% per year, believed to indicate true trends. Although aggregate indicators based on reported cases must be interpreted with caution in such a diverse region, average incidence rates in Latin America declined from 141 per 100,000 between 1981 to 94 per 100,000 in 1991, but then jumped to 116 per 100,000 between 1994 and 1995. TB incidence has since declined, albeit erratically, to 102 per 100,000 by 1999. Case detection rates for smear-positive pulmonary cases are high compared with other regions, with over 70% of all incident cases reported in 2001, according to WHO.

**HIV/Acquired Immunodeficiency Syndrome**

The World Health Organization (WHO) and PAHO estimate that the proportion of HIV/TB coinfected patients ranged between 0% and 7% in South and Central American countries in 1997. In contrast, the Caribbean Islands were very diverse in this respect, ranging from 0% in 13 nations to greater than 20% in 5. For comparison, 20% of TB patients in the United States were estimated to have HIV. HIV seroprevalence studies among representative groups of TB patients have not been conducted in Latin America in recent years, however. Some countries recommend offering HIV testing and counseling to all diagnosed TB patients. Application of such guidelines has been sporadic, however, and results may not be representative. Systematic surveillance is needed, especially in countries with high TB and HIV incidences, such as Haiti, the Dominican Republic, Honduras, and Brazil. As HIV care programs improve, voluntary testing may ensure that patients have access to treatment for other opportunistic infections, and in some countries like Brazil, to antiretroviral therapy. Expanded HIV testing, which is very low at present, can increase treatment of latent TB infection among those coinfected with both pathogens.

**Drug-Resistant Tuberculosis**

As of 2000, 11 countries had conducted representative national surveys of antituberculosis drug resistance among new and retreated cases, and several more plan to survey their own populations. Only Argentina, the Dominican Republic, and Peru reported rates of multidrug-resistant TB among new cases exceeding 1% (with Brazil at 0.9%) (see Fig. 4). The Dominican Republic reported the highest rates, with 41% of tested cases having resistance to one or more drugs, and 6.6% having resistance to both rifampin and isoniazid. Because of widespread use of isoniazid and streptomycin over several decades, single and multiple resistance to these drugs runs high.

The conditions that hasten emergence of drug-resistant strains vary across the region. In Brazil, the public supply of drugs has been relatively steady. Fixed-dose combinations are used, and access to TB drugs in private pharmacies is very limited. DOTS remains the exception rather than the rule, and the quality of laboratory services needs improvement. Additionally, the reporting systems do not track all patients started on treatment. In some nations, TB drugs are sold widely in the private market, and coverage with DOTS-type standards of care is limited. Peru has documented relatively high rates of multidrug resistance, attributed to poor drug supplies and insufficient case management practices over a decade ago prior to the implementation of DOTS. In the past decade, however, as a result of decisive political commitment and program leadership, Peru has developed one of the most effective TB control programs in the developing world and has surpassed global targets for case detection and successful treatment. With a strong DOTS foundation and international partnerships, Peru has made the treatment
of drug-resistant disease national policy to eliminate residual multidrug-resistant TB. Peru is serving as a global testing ground to determine whether individualized or standardized regimens will be required to control epidemic multidrug-resistant TB. Studies in Peru, the Dominican Republic, Mexico, and elsewhere suggest that multidrug resistance compromises the effectiveness of DOTS regimens and therefore must be urgently contained. A study reviewing national trends in Nicaragua suggests that the increase in multidrug-resistant disease can be prevented with full DOTS application, especially if implemented before a marked emergence of multidrug-resistant TB. Outbreaks of drug-resistant disease in Colombia were shown to be caused by poor program performance and mismanagement, rather than clonal transmission of multidrug-resistant TB. Although basic laboratory networks and quality control of smear microscopy exist, access to culture and DST is limited. In 17 large Latin American countries, only 49 laboratories were capable of carrying out DST, including national reference laboratories.

Control Program Strategies and Results

Tuberculosis control programs in several countries in the region have been using directly observed treatment models for more than a decade with relatively high treatment success rates. These include Cuba, Chile, Uruguay, Nicaragua, and Peru. In some of the countries, success may be attributable to full application of DOTS. A recent study has examined the epidemiological impact of Peru's success this last decade. Before DOTS was implemented in 1991, the TB incidence rate was probably (or nearly) steady. From 1990 to 1992, reported cases increased as a result of improved case detection. From 1993 onward, the incidence of new pulmonary TB cases declined in every region of Peru, despite continued increases in diagnostic efforts. The national rate of decline ranged from 1.9% to 9.7% per year (average 5.8%). Over this period, 158,000 cases and 91,000 deaths were prevented among smear-positive patients with pulmonary TB. In addition, programmatic successes may be attributed in part to improvements in the primary health infrastructure in general and additional case management strategies. In Cuba, for example, patients are supervised by family physicians in the community and continue to receive their regular incomes while on full disability leave during treatment. In Uruguay, patients receive pensions. In Peru, TB patients receive a food basket at the completion of each month of treatment, and health education campaigns stimulate effective passive case finding. Nicaragua's results may be moderated because of serious economic problems the country has faced over the last decade.

In low-income countries that have adopted the DOTS package more recently, progress has been seen, but obstacles remain. Program assessments suggest that lack of access to health services remains an obstacle in countries such as Haiti, Ecuador, Bolivia, Guatemala, Brazil, and Mexico. This limits case detection and holding. Cultural barriers also may be a factor for some at high risk, such as indigenous populations. Poorly motivated primary health care staff and lack of community health workers also limit opportunities for DOTS, although each of these countries has local success stories in which communities and/or health services rose to the challenge. In Brazil, a major new family health program is scaling up and aims to provide a network reaching most of the nation's 5000-plus municipalities with teams to handle prevention and patient care at the community level, including TB control services. The “Stop TB” initiative is sponsoring opportunities for high-incidence TB control programs to join donors, nongovernmental partners, social security institutes, and specialists in defining new operational strategies to improve quality and coverage. Donor commitments, from agencies such as the World Bank, the US Agency for International Development (USAID), the UK Department for International Development (DFID), and others have risen in Latin America over the past 5 years, but the vast majority of resources still come from the governments themselves.

Challenges for the Future

Major challenges to further strengthen TB control in Latin America include adapting TB control to
health sector reform,[164] reducing default and undocumented transfer rates, involving specialists and referral centers, coordinating control efforts across borders,[128] [93] [165] and building local capacity in operations research.

The TB control success stories in Latin America have shown that much more rapid progress is feasible than has been demonstrated in a majority of countries. The DOTS framework provides a strong strategy on which to build. The health infrastructure, human capacity, and epidemiological conditions are sufficient to expect that high levels of nationwide DOTS coverage and program performance can be achieved. The risks associated with failing to extend and improve quality services, as seen through avoidable morbidity, mortality, and emerging drug resistance, are great. With explicit targets in mind, and higher-level political commitment, high-incidence countries can ratchet up case detection and cure rates, while medium- and lower-incidence countries can focus on preventing TB among high-risk groups.

AFRICA: THE IMPACT OF RAMPANT HIV INFECTION

Of the 48 countries in sub-Saharan Africa, 41 are classified by the World Bank as low-income countries, the rest being in the middle income group. The level of economic development in Africa shapes the region's ability to respond to the epidemiological circumstances. Sub-Saharan Africa was suffering severely from TB before HIV/AIDS; now the region is severely affected by HIV/AIDS. The dual epidemic has been devastating to the people and economic development of the region.

Epidemiology

After years of decline in many countries, TB case rates in Africa began to rise dramatically in the mid-1980s.[127] The 1997 WHO report on the global incidence of TB indicated sub-Saharan Africa had the highest regional incidence rate in the world, 259 cases per 100,000 population.[53] Africa contains 9 of the 10 countries in the world with the highest incidence rates, 8 of the 22 high-incidence countries, and 33 of the 48 countries with incidence rates exceeding 200 cases per 100,000 population. The rates in some of these countries are staggering, averaging more than 500 cases per 100,000 population in Botswana, Namibia, Zambia, and Zimbabwe, and more than 400 cases per 100,000 population in Lesotho, Malawi, and Swaziland. In addition, the highest rates of TB-specific mortality occur in Africa, 34% overall, ranging from less than 10% in Algeria to 50% or more in Zimbabwe, the Central African Republic, and Zambia, more than twice the global average.[53]

Studies on the transmission of M. tuberculosis in Africa based on molecular genetic techniques indicate that a much higher-than-expected proportion of patients may have disease related to recent infection. Results from Botswana, in settings with very high HIV prevalence, show that isolates from 42% of study patients with pulmonary TB fell into genetic clusters, suggesting disease resulting from recent infection.[101] Analogous data from rural South Africa, with much lower HIV prevalence, show 45% of patients had genetically clustered isolates.[185] Furthermore, the results suggest that congregate settings such as prisons, mines, hospitals, and workplaces (including farms) account for the majority of recent transmission, not household exposures.

HIV infection was not associated with genetic clustering of isolates. These results suggest that active transmission in the community accounts for a much larger proportion of incident cases than previously believed (approximately 10% to 20%), similar to results from affluent countries.
**HIV/Tuberculosis Coepidemics**

Rising TB incidence rates in sub-Saharan Africa have been attributed largely to the escalating HIV epidemic. In 18 African countries with consistent TB reporting, estimated TB incidence rates correlate closely with independently estimated HIV prevalence rates (Fig. 8). In some sub-Saharan African countries, HIV seroprevalence in young adults is as high as 30%. The WHO African region has the highest proportion of persons with TB/HIV coinfection, approximately 1.2% of the population, or 8 million Africans. Africa also had the highest fraction of TB cases with HIV (32%). In addition to explaining the high rates of TB, high HIV prevalence may explain partly the low treatment success and high case mortality rates in Africa (Table 4). For the cohort of new patients who entered treatment in 1997, treatment succeeded in 63% of DOTS areas in the WHO-defined African region, compared with 78% worldwide. The mortality rate for the same cohort in the same region was 6.5%, compared with 3.8% worldwide.


<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Registered (number)</th>
<th>Cured (%)</th>
<th>Completed (%)</th>
<th>Died (%)</th>
<th>Failed (%)</th>
<th>Default (%)</th>
<th>Transferred (%)</th>
<th>Unknown (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>227,207</td>
<td>57</td>
<td>13</td>
<td>6.0</td>
<td>1.1</td>
<td>11</td>
<td>6.9</td>
<td>5.1</td>
</tr>
<tr>
<td>AMR</td>
<td>63,173</td>
<td>65</td>
<td>15</td>
<td>4.4</td>
<td>1.0</td>
<td>6.0</td>
<td>2.6</td>
<td>5.6</td>
</tr>
<tr>
<td>EMR</td>
<td>39,311</td>
<td>64</td>
<td>10</td>
<td>3.5</td>
<td>2.1</td>
<td>10</td>
<td>5.2</td>
<td>4.9</td>
</tr>
<tr>
<td>EUR</td>
<td>12,487</td>
<td>62</td>
<td>15</td>
<td>5.8</td>
<td>4.5</td>
<td>4.9</td>
<td>3.2</td>
<td>4.4</td>
</tr>
<tr>
<td>SEAR</td>
<td>114,355</td>
<td>66</td>
<td>6.0</td>
<td>3.9</td>
<td>1.2</td>
<td>6.4</td>
<td>1.7</td>
<td>15</td>
</tr>
<tr>
<td>WPR</td>
<td>268,742</td>
<td>94</td>
<td>1.1</td>
<td>1.6</td>
<td>0.9</td>
<td>1.2</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Total</td>
<td>725,275</td>
<td>73</td>
<td>7.6</td>
<td>3.8</td>
<td>1.2</td>
<td>6.0</td>
<td>3.2</td>
<td>4.9</td>
</tr>
</tbody>
</table>


**Drug-Resistant Tuberculosis**

The prevalence of multidrug resistance in Africa is relatively low. Of 35 countries in the first round of the WHO/IUATLD Global Drug Resistant Surveillance, eight were in sub-Saharan Africa. The global median prevalence of multidrug-resistance TB was 1.4%. Although the Ivory Coast was a hot spot, with 5.3% prevalence of multidrug resistance, five of the seven remaining countries had less than 1.0%
multidrug-resistant TB, and only one other exceeded the median (Zimbabwe, 1.9%). In the second round of this surveillance, 7 of 56 countries or regions were in sub-Saharan Africa.\[181\] Compared with the global median of 1.0%, only Mozambique was substantially higher, with 3.5% multidrug-resistant TB. Three countries had values near the median of 0.9% to 1.5%, and the remaining three had less than 0.5% multidrug-resistant TB. This was attributed in part to the relatively late introduction of rifampin and the unavailability of antituberculosis drugs outside national programs. Resistance to isoniazid was relatively common, however, significantly exceeding the median in 9 of the 15 African countries.

An important observation coming from sub-Saharan Africa is that, despite sharp increases in TB incidence, well-run DOTS programs apparently prevent the growth of resistance to antituberculosis drugs, even with the use of rifampin-based short-course treatment.\[21\] In a nationwide survey in Botswana conducted in 1995 and 1996, resistance to at least one drug was found in only 4% of new cases and 15% of retreatment cases. More importantly, multidrug resistance was found in less than 1% of new and 6% of retreatment cases.\[22\] A repeat survey in 1999 showed no significant change in these rates, even though TB incidence increased from 444 cases per 100,000 population to 537 cases per 100,000 population.\[159\] Given the mechanisms that create drug resistance, the effectiveness of DOTS against the growth of multidrug-resistant TB is expected in a population with low baseline levels of drug resistance.

**Botswana's Experience**

The experience in Botswana illustrates several important features of the TB epidemic in Africa. Starting in 1975, Botswana has had one of the finest TB control programs in the developing world.\[31\] The program adheres strictly to all five elements of the DOTS strategy. In spite of this, TB incidence more than doubled during the 1990s, from 202 cases per 100,000 population in 1989 to 537 per 100,000 population in 1999.\[14\] In 2000, UNAIDS estimated that 36% of persons 15 to 49 years of age in Botswana were living with HIV, among the highest prevalence figures in the world.\[159\] The strong association of TB morbidity and mortality rates with the HIV epidemic dominates the epidemiological picture in Botswana. Approximately 85% of TB inpatients in Gaborone and Francistown in 1997 and 1998, and 73% of TB outpatients in Gaborone between 1997 and 1999, were HIV seropositive (unpublished data, Centers for Disease Control and Prevention [CDC]). Preliminary results from an autopsy studies in Francistown in 1997 and 1998 found that TB caused 36% of deaths of hospitalized adults with AIDS.\[4\]

**Tuberculosis Control Strategies**

In Africa, as elsewhere in the developing world, the basis of TB control remains case finding and treatment in accordance with the WHO DOTS strategy. In 2000, more than half the population in Africa (61.0%) had access to DOTS programs.\[122\] This is the highest percentage of all the WHO reporting regions and higher than the 1997 figure of 57.5%. In stable African societies, national and regional governments provide TB services to the population at no charge to patients, although convenient access to diagnostic and therapeutic services is not universal. In regions with military conflicts, public health services are disrupted, and TB spirals out of control. Even in societies at relative peace, however, the HIV epidemic has rendered many TB control programs unable to cope with sharply increased case loads. Moreover, TB control programs may be unable to respond adequately to the challenges of diagnosing HIV-associated TB because of the increased frequency of sputum smear-negative and extrapulmonary cases.\[44\]

One potentially important control strategy being evaluated in Africa is treatment of latent TB infection in persons with HIV. Generally, latent infection is not treated in developing countries, except in children of infectious patients in some areas. Clinical trials in Africa have demonstrated that treatment of latent
TB infection prevents active TB disease in persons with HIV in settings of high TB prevalence.\textsuperscript{[85]} \textsuperscript{[113]} \textsuperscript{[168]} The efficacy of preventive therapy is approximately 50% for all patients with HIV regardless of tuberculin skin test status, and 70% in those with a positive tuberculin skin test.\textsuperscript{[186]} Based on these results and the safety profile of isoniazid, UNAIDS issued guidelines in July 1998 recommending preventive therapy for HIV-infected persons with a positive tuberculin skin test or, where skin testing is not done, in settings with high TB prevalence (>30%).\textsuperscript{[183]} After excluding active TB, isoniazid (5 mg/kg) is recommended as daily, self-administered therapy for 6 months. In spite of these guidelines, the optimal regimen and duration for preventive therapy have yet to be conclusively determined,\textsuperscript{[85]} and there have been difficulties implementing the guidelines on a wide scale.\textsuperscript{[1]} \textsuperscript{[77]} In addition, access to HIV testing and methods for excluding patients with active TB must be addressed for preventive therapy to have an impact on TB case rates in sub-Saharan Africa.

**Challenges for the Future**

Africa suffered disproportionately from TB prior to the AIDS epidemic. Now it is disproportionately affected by AIDS, and it will be burdened increasingly by the coepidemic of HIV-associated TB.\textsuperscript{[44]} TB and HIV/AIDS services must be integrated to improve advocacy, education, surveillance, and case management. Ensuring access to voluntary, confidential HIV testing among TB patients and offering TB preventive therapy to persons diagnosed with HIV infection are prime examples. From a broader perspective, improved inexpensive diagnostic techniques, more rapidly effective drugs, and, especially, an effective vaccine may have a greater impact on TB in Africa than elsewhere.

**THE FORMER SOVIET UNION: SOCIAL UPHEAVAL AND EPIDEMIC MULTIDRUG-RESISTANT TUBERCULOSIS**

The TB situation in countries of the former Soviet Union reflects the abrupt and complex political and social changes that have taken place there since 1991. These transitions have disrupted the former public health and social services infrastructures. The stuttering transition to a market-based economy resulted in economic collapse, with high inflation and shrinking government budgets that have profoundly affected all aspects of the health system. Sharply reduced financial support led to the disruption of TB control activities. The region is struggling with rapid increases in incidence, mortality, drug resistance; incomplete and inconsistent surveillance data; outdated medical knowledge; and an aging physical infrastructure. These same political and economic circumstances created social conditions that fueled the growth of TB: unprecedented poverty, unemployment, homelessness, drug abuse; sharp increases in alcoholism, malnutrition, and crime; and overcrowded prisons. In addition, armed conflicts created mass migration and great numbers of refugees, and asylum seekers.\textsuperscript{[129]} \textsuperscript{[177]} \textsuperscript{[192]} \textsuperscript{[194]} Contrary to the situation in high- and low-income countries, where immigration and HIV/AIDS, respectively, are major causes of resurgent TB, the deteriorating TB situation in Russia and surrounding countries is caused by the dismantling of former political and socioeconomic structures.

**Epidemiology**

Tuberculosis has increased tremendously in the countries of the former Soviet bloc since the beginning of the 1990s.\textsuperscript{[129]} \textsuperscript{[177]} \textsuperscript{[192]} \textsuperscript{[194]} Of 374,000 new TB cases in WHO's European Region in 1999 (the highest figure in two decades), 81% occurred in Eastern Europe and the former Soviet Union.\textsuperscript{[129]} In 1998, all of the former Soviet countries except Armenia and Tajikistan reported more than 50 cases per 100,000 population, while Georgia, Lithuania, Romania, the Russian Federation, and Turkmenistan reported more than 80 cases per 100,000 population.\textsuperscript{[129]} In the Russian Federation, after decades of decline,
reported TB cases more than doubled from a nadir of 34 cases per 100,000 population in 1991 to 82.4 cases per 100,000 population in 1998 (121,434 cases).

Over the same period, case numbers doubled in Latvia, and, according to the official statistics, there is a dramatic epidemic of the disease in Kyrgyzstan and Kazakhstan: 122.9 and 126.4 cases per 100,000 population, respectively, in 1998, the highest figures in the region. In other Central Asian republics, the TB situation is also very serious, but, because of underreporting, the real figures are unknown. The majority of cases in all these countries are in persons 20 to 49 years of age, the most economically productive years.

**HIV/Acquired Immunodeficiency Syndrome**

The TB/HIV coepidemic is still not widespread in this region; however, HIV is growing rapidly. In the past 3 years, steep increases have brought the number of cases from a few dozen to several thousands in Belarus, Russia, and Ukraine (Dr. A. Gromyko, WHO European Regional Office, personal communication). There has been an alarming increase in the number of patients with HIV reported in the Russian Federation: 23 cases in 1987, 26,054 in 1999, 52,000 in June 2000, and 70,000 in December 2000. Today, HIV/AIDS does not have an important impact on TB, but the rising levels of HIV will fuel a TB/HIV coepidemic. With this rapid spread of HIV and the overlap with people infected with *M. tuberculosis*, a major public health disaster can be anticipated, especially because of the high levels of multidrug-resistant TB. Urgent, concerted action is needed.

**Multidrug-Resistant Tuberculosis**

Without hyperbole, regions of the former Soviet Union face an unprecedented epidemic of multidrug-resistant TB. Four of the top five “hot spots” in both global surveys (in terms of the proportion of cases) were Estonia, Latvia, and two oblasts of the Russian Federation (Fig. 9). In these settings, such patients are practically incurable because of the high cost and unavailability of needed drugs and laboratory support. In these areas, multidrug-resistant TB among new pulmonary cases ranged from 4.0% to 14.4% and, among retreatment cases, from 19.2% to 54.4% between 1994 and 1996. Between 1997 and 1999, the corresponding prevalence was 9.0% to 14.1% among new cases (four of the top five) and 23.7% to 37.8% among retreatment cases (four of the top five, and four of the top six, respectively). These results should be compared with the Czech Republic and Poland, where less than 0.6% to 1.6% of new patients have multidrug-resistant TB, a sign of good TB control. Indeed, these countries have among the best programs in the world. The main cause of multidrug-resistant is the poor management of TB patients, inadequate choice of chemotherapy regimen and followup, frequent lack of drugs, and poor compliance of patients.

where there is substantial existing multidrug-resistant TB. Cure rates for multidrug-resistant TB using the standard DOTS regimen were extremely low in a number of countries, in the range of 50% to 55% in the strongest programs like those of Korea and Peru, but as low as 10% in weak programs. Therefore, management of multidrug-resistant TB using second-line drugs becomes essential in such settings to prevent primary multidrug-resistant TB caused by transmission from existing cases. To this end, an international consortium of experts and agencies is developing DOTS-Plus to add specific treatment of multidrug-resistant TB in programs that have built a foundation of a solid DOTS program. DOTS-Plus pilot projects have been initiated in Estonia, Latvia, and Russia recently. It must be stressed, however, that the first priority is the implementation of DOTS to prevent multidrug-resistant TB.

Prisons in the former Soviet Union have been spotlighted as breeding grounds for TB, especially multidrug-resistant TB. TB spreads easily in prisons because of overcrowding, poor ventilation, malnutrition, and poor hygienic conditions. Patients frequently are transferred between pretrial detention centers and prisons and may be housed with otherwise healthy persons in crowded, poorly ventilated cells. Prisoners are affected by other diseases, poor nutrition, HIV, and alcohol and drug abuse, which all favor TB. Drug shortages and weak laboratory services result in inadequate treatment, which has generated extensive multidrug-resistant TB in the penal system. One Siberian prison reported a TB prevalence of 7000 cases per 100,000 prisoners. The prison in Baku, Azerbaijan, between 1995 and 1997 had a huge multidrug-resistant TB prevalence. Among all TB cases, 23% were multidrug-resistant TB. The same situation exists in Mariinsk prison (Siberia) and the prison of the Republic of Georgia (22.6% and 13%, respectively). Furthermore, TB control in prisons is integrated poorly with civilian TB control programs. Prisoners with TB are released once their sentences are finished or because of mass amnesties (to reduce crowding) without appropriate follow up in civilian society. Once outside of prison, these people are highly mobile and tend to avoid authorities. Serious operational problems hamper the completion of care for released prisoners.

*Tuberculosis Control: Challenges in Implementing the Directly Observed Short Course Therapy Strategy*

At the first meeting of NTP managers from Eastern Europe and the former Soviet Union in 1994, participants from 25 countries agreed to adopt WHO's DOTS strategy, because DOTS had proved to be cost-effective and efficient in high-incidence, low-income countries. In 1995, in collaboration with many national and international partners, WHO started DOTS pilot projects in several countries in this region. Between 1995 and 2000, there was a dramatic change in the number of countries adopting sound national TB control strategies based on the essential elements of DOTS. In the 27 countries in Central/Eastern Europe and the former Soviet Union, only two have not adopted DOTS. Four countries are in the preparatory phase of implementing DOTS. Eight countries are piloting DOTS, including Russia; four are in the expansion phase covering between 10% and 90% of the population, and nine have implemented DOTS fully, covering greater than 90% of the population (Armenia, Czech Republic, Estonia, Hungary, Latvia, Kyrgyzstan, Romania, Slovenia, and Slovakia). In the Czech Republic, Slovenia, and Slovakia, progress has been sustained, and at present, the epidemiological situation is similar to that of many Western European countries. Overall, 16% of the population of the region have access to DOTS.

Analysis of the TB control programs suggests that their performance increased progressively, achieving a cure rate today of approximately 75%. The pilot areas in Kyrgyzstan and Orel Oblast (Russia) exemplify good program performance with low default rates and high treatment success in DOTS compared with non-DOTS areas.

In contrast, the programs in Ivanovo and Vladimir oblasts (Russian Federation) reveal some of the
challenges to DOTS implementation. In Vladimir, political tensions have hampered broad, energetic DOTS implementation despite a relatively favorable economic situation and the best efforts and intentions of the TB program and international partners. In Ivanovo, the TB control program was reputed to be one of the finest in Russia prior to 1991 (Alexander Khomenko, personal communication). WHO fostered a DOTS pilot project in Ivanovo in late 1995. Between 1995 and 1999, however, treatment success stagnated between 60% and 65% for several reasons. First, the oblast's economy, based largely on a single industry (textiles), collapsed in 1991, and funding for TB control was curtailed. Drug shortages led to inadequate treatment, and lack of transportation led to inadequate follow-up. This led to high failure rates (approximately 15%), partly because of high levels of multidrug-resistant TB in new patients, increasing from 3.8% in 1996 to 8.9% in 1998. At the same time, unemployment, homelessness, poverty, alcoholism, and imprisonment (crime) increased sharply. These social circumstances did not favor adherence to treatment, and default rates remained too high, approximately 10% or higher. Difficult socioeconomic circumstances led to delays in diagnosis and treatment initiation, which, combined with relatively high levels of default, drug resistance, and treatment failure, led to mortality rates of approximately 12% (Ivanovo TB Control Program, unpublished). Intensification of efforts by the oblast TB control program, CDC, WHO, and the Russian Central Tuberculosis Research Institute, combined with renewed commitment by the local government, have led to significantly improving outcomes for TB patients in Ivanovo since 1999. Ivanovo is a good example of the pitfalls, challenges, and potential solutions for TB control in the former Soviet Union in general.

Challenges for the Future

Implementation of sound TB control programs based on the DOTS strategy is the first priority in the current social and economic situation. Further expansion of DOTS in the region is vital. The multidrug-resistant TB crisis in “hot spots” in the region must be addressed as an international public health emergency. Drug resistance surveillance needs to be strengthened and expanded. Once DOTS is established to prevent the creation of even more multidrug-resistant TB among patients with initially drug-susceptible disease, DOTS-Plus implementation should follow closely behind. TB epidemics in prisons are out of control. It is crucial to link prison programs, often administered by Ministries of Justice or Ministries of Internal Affairs, with the civilian NTPs, generally under the Ministries of Health. TB control systems are vertical and not connected well with general medical services. Consequently, health sector reforms should include closer relationships between the TB control system and the general medical services. Lastly, although HIV-associated TB is not a major problem yet in terms of the numbers of coinfected individuals, it is a major concern, because efforts to prevent this future calamity have been sluggish at best. As with so many other countries, the newly independent nations of the former Soviet Union are in the denial phase of the HIV epidemic, which ends when AIDS becomes a leading cause of death and disease. Without increased national commitment, bolstered by international partnerships, however, the countries of Eastern Europe and the former Soviet Union will not be able to solve these problems. The future of TB control depends very much on health authorities working with and mobilizing new partners.

INDIA: TUBERCULOSIS CONTROL IN THE COLOSSUS OF TUBERCULOSIS

India's vast population of more than 1 billion people experiences 23% of the total global TB incidence each year and carries the burden of 30% of all prevalent cases of TB in the world. At the same time, India remains one of the poorest countries. Of 127 countries studied by the World Bank, India ranked 19th from the bottom in terms of per capita gross domestic product. There are large disparities in health status and in TB rates between males and females, between urban and rural areas, and different
states in the country. Although key principles of the DOTS strategy were demonstrated first in India—case detection by sputum microscopy among patients attending health care facilities, home-based treatment, intermittent dosing, and the importance of direct observation of treatment—until recently, India had applied these principles on only a very limited basis.[71]

**Epidemiology and Socioeconomic Dimensions**

With an estimated incidence of new smear-positive TB of 84 cases per 100,000 population, there are over 800,000 new smear-positive cases of pulmonary TB per year and about 1.8 million total new cases.[52] TB deaths are estimated to be at least 437,000 per year. Furthermore, TB is a major barrier to economic development, costing India approximately $3 billion per year.[132] TB has devastating social costs as well; data suggest that each year, more than 300,000 children are forced to leave school because their parents have TB. Additionally, more than 100,000 women with TB are rejected by their families.[128]

**HIV/Acquired Immunodeficiency Syndrome**

An estimated 4 million people with HIV live in India.[159] In 1997, approximately 3% of all TB patients in India had concomitant HIV infection, and 188 persons per 100,000 population had HIV/M. tuberculosis coinfection.[52] Although serial surveillance data are limited, trends may be deduced to some extent from studies of HIV prevalence in sentinel populations. In some of the major urban areas, HIV prevalence among women seeking antenatal care increased from 0% through 1991 to a median 2.0% in 1999, while outside of urban areas, from 0.1% in 1987 to a median 0.25% in 1999.[159] Given increasing trends and a high prevalence of latent M. tuberculosis infection, efforts aimed at controlling TB and HIV are critical to avoid the explosive coepidemic seen in Africa.

**Drug-Resistant Tuberculosis**

Drug resistance surveillance in several areas of India suggests rates of multidrug-resistant TB in new patients in the range of 0% to 3%.[129] The first global survey included the state of Delhi, but did not separate new and retreatment patients. Resistance to any of the four drugs was detected in 32.4% of patients, and 13.3% had multidrug-resistant TB. The second global surveillance included the state of Tamil Nadu. Among new patients, resistance to any of the four drugs was detected in 18.8%, and 3.4% had multidrug-resistant TB.

**Control Efforts, Directly Observed Short Course Treatment Implementation**

Following a program review in 1992, India revised its NTP, and pilot implementation of DOTS began in 1993. Between 1993 and 1998, India gradually increased the coverage of the DOTS program, pilot testing, and finalizing policy materials and training modules. India has rapidly expanded coverage with the DOTS program since 1998 (Fig. 10).[29] By 1999, India accounted for more than one-third the global increase in the number of patients treated in DOTS programs, and in 2001, India treated more patients under DOTS than any other country. By mid-2002, more than 400 million people in the country will have access to the program.

![Figure 10](http://home.mdconsult.com/das/article/body/1/jorg=journal&source=&sp=12347508&sid...)
The quality of diagnosis has remained good, even with rapid expansion. As in well-performing programs all over the world, more than half of all patients with pulmonary TB are documented to have positive sputum smears. In the previous NTP, treatment of large numbers of nontuberculosis patients with nonspecific abnormalities on chest radiographs was common. The quantity of diagnostic effort is also impressive. By mid-2001, the program was examining more than 150,000 patients for TB every month, performing more than 20,000 sputum smears for acid-fast bacilli every day.

Treatment results also have been good. Treatment success has increased from less than 40% in the previous program to more than 80%. Treatment results are displayed in Table 5.

### Table 5 -- Outcomes of Treatment for Tuberculosis in the Revised National Tuberculosis Control Program, India, 1993 to 1999

<table>
<thead>
<tr>
<th></th>
<th>Evaluated</th>
<th>Cured</th>
<th>Completed</th>
<th>Died</th>
<th>Failed</th>
<th>Defaulted</th>
<th>Tr</th>
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</thead>
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<tr>
<td>New smear-positive</td>
<td>82,401</td>
<td>66,125</td>
<td>1615</td>
<td>3569</td>
<td>2533</td>
<td>7421</td>
<td>1</td>
</tr>
<tr>
<td>New smear-negative</td>
<td>69,359</td>
<td>58,437</td>
<td>2417</td>
<td>949</td>
<td>6765</td>
<td>7421</td>
<td>9</td>
</tr>
<tr>
<td>New extrapulmonary</td>
<td>24,399</td>
<td>22,062</td>
<td>437</td>
<td>63</td>
<td>1593</td>
<td>7421</td>
<td>6</td>
</tr>
<tr>
<td>Relapsed smear-positive</td>
<td>12,036</td>
<td>8288</td>
<td>782</td>
<td>718</td>
<td>1553</td>
<td>7421</td>
<td>12</td>
</tr>
<tr>
<td>Other retreatment</td>
<td>24,557</td>
<td>12,465</td>
<td>1614</td>
<td>1329</td>
<td>4309</td>
<td>7421</td>
<td>17</td>
</tr>
</tbody>
</table>

The impact of the program on case fatality rates has been dramatic. A systematic evaluation of the previous NTP, even in a relatively wellperforming district, indicated a 29% mortality rate in smear-positive patients. In the current program, the mortality rate is less than 5%. The weighted differential mortality rate (including smear-positive and -negative patients) between the old and new programs is at least 18%. Therefore, by treating nearly 1 million patients by early 2002, the program will have saved nearly 200,000 lives.

Not all patients with TB seek care through the national TB program, however. A 1997 WHO report indicates that 50% to 80% of people with TB-like chest symptoms seek help first from the nearest trusted health care provider, usually a private for-profit practitioner. Poorly qualified private providers abound, especially in rural settings. Overdiagnosis (based largely on chest radiography) and overtreatment (with allopathic and traditional remedies) are common; the practitioner's goal as an entrepreneur is to alleviate patients' symptoms before they decide to switch providers. As patients
“shop” for a diagnosis among several health care providers, the diagnosis of TB generally is delayed by weeks. For patients treated for TB by private practitioners, the average out-of-pocket costs are estimated at between $100 and $150. (The annual income of a daily wage earner may be $200.) As their funds are depleted, poorer patients tend to discontinue one or more drugs or take them less regularly, with no provisions for direct supervision of treatment. Eventually, many patients switch to government health care providers, so patients with more difficult or advanced forms of TB crowd government health care facilities. Care is free, but long waiting times may result in lost wages. Coordination among private and government health care services for TB management is a major challenge facing TB control in India.

**Challenges for the Future**

The main challenges to implementing the revised NTP are intensification, coordination, and patient-friendly services. In terms of intensification, not all health care providers are involved; therefore not all patients receive the benefits of the new program. To increase case detection rates and decrease use of nonstandard treatment, an increasing proportion of government-, private-, and donor-supported health providers must be involved in the program. Coordination is also a major challenge, especially in urban areas, some of which lack primary health care systems, TB control infrastructure, or both. As the proportion of the population in urban areas continues to increase, effective coordination and service provision become even more important. Finally, DOTS often is not sufficiently convenient to patients. Ideally, no patient should pay for transportation or lose wages to participate in DOTS. Greater involvement of community resources can ensure that DOTS is accessible and acceptable to patients. A model for government–private partnership for TB control was pilot tested in a poor area of the city of Hyderabad, where there were no government health services. A charity hospital set up a free-of-charge DOTS program including 30 microscopy and DOT points at small private hospitals throughout the area. Physicians from the hospital visited all 358 private practitioners in the area and encouraged them to refer patients with symptoms suggestive of TB. As a consequence, 213 private providers referred 2244 TB suspects over 4 years. Of these, 43% were diagnosed with TB; those with TB excluded were referred back to their original private practitioners for further evaluation and treatment. Treatment succeeded in 92% of new patients and 74% of retreatment patients. As a consequence of this program, TB patients were diagnosed sooner (8 versus 10 weeks), paid less for diagnosis and treatment ($6 versus $31), and lost less income because of illness (1.4 versus 2.8 months of wages). Clearly, testing and extending innovative public–private partnerships such as these will be necessary to ensure that all (or nearly all) TB patients are diagnosed and treated with adequate standards of care.

On World TB Day 1997, the Director General of WHO declared “The DOTS strategy represents the most important public health breakthrough of the decade, in terms of lives which will be saved.” Nowhere is the potential of DOTS more apparent than in India. Full implementation throughout India would result in an increase of more than one million complete treatments per year and, in the short term alone, would prevent more than 200,000 deaths per year. The pace of effective expansion will determine the number of cases and deaths from TB and the magnitude of drug resistance. If India expands the revised national TB control program to cover the entire country by 2005 and meets global targets for TB control, then, over the next 20 years, the best estimates are that the program will cumulatively:

- Cure more than 25 million cases of TB,
- Prevent more than 15 million additional cases of TB,
- Prevent nearly 6 million deaths, and
- Save more than $27 billion.

In contrast, if effective expansion of DOTS does not occur in India, then there will be substantial global ramifications in terms of case detection rates, deaths from TB, and spread of drug resistance.
CHINA: THE WORLD'S LARGEST DIRECTLY OBSERVED SHORT-COURSE TREATMENT PROGRAM

Epidemiology

In 1997, WHO estimated that China had the second highest number of TB cases in the world: 1.4 million new TB cases per year, including 630,000 new smear-positive pulmonary cases. In addition, an estimated 258,000 persons died from TB annually, accounting for 17% of the global TB mortality rate. These estimates were based partly on data from the 1990 National TB Prevalence Survey in China, which found 33% of the population with \( M. \text{tuberculosis} \) infection, 0.5% of the population with active TB, and 134 of 100,000 persons with smear-positive pulmonary TB.

HIV/Acquired Immunodeficiency Syndrome

There is very little information on HIV-associated TB in China, in part because the magnitude of the HIV/AIDS epidemic in China is unknown. Authorities believe China is in an early stage of the epidemic. The Ministry of Health (MoH) estimates about 500,000 persons have HIV infection, mostly caused by intravenous drug use. Limited data from a few locations suggest the HIV/AIDS epidemic may worsen dramatically over the next decade, however. From 1.5 to 10 million HIV infections are projected by 2010. As HIV spreads in China, the impact on TB could be substantial. The Chinese government hopes to keep the prevalence of HIV infection at less than 0.5% through 2010. If 6 million Chinese (0.5% of the population) become infected with HIV, there could be over 1 million new HIV-associated cases of TB (assuming 50% of those coinfected with HIV and \( M. \text{tuberculosis} \) will develop active TB). Thus, even if the spread of HIV infection can be contained according to the government's goal, there would still be a substantial increase in the number of TB cases attributed to HIV infection.

Drug Resistance

The most reliable estimates of drug-resistant TB in China come from the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance, which has surveyed 4 of China's 31 provinces and has ongoing studies in several others. In these four provinces, the prevalence of resistance to any of the first-line TB drugs was 1.5 to four times higher than the global median, and the prevalence of combined resistance to isoniazid and rifampin was 2.5 to nine times the global median. New and retreatment cases are included in these figures. Although there may have been methodological problems with the survey in Hunan province, which reported the highest rate of drug-resistant TB, these data nevertheless suggest that China has a serious problem with drug-resistant TB, including multitherapy-resistant TB.

Control Efforts, Directly Observed Short-Course Therapy Implementation

In response to the seriousness of the TB situation, China implemented two major TB control projects in the 1990s based on the WHO-recommended DOTS strategy. The World Bank provided major funding for the first project, and the MoH provided funds for the second project. Local governments also provided substantial counterpart funding. DOTS was implemented in 1991 and expanded to 12 provinces, including 573 million people by 1994. By 1997, these projects had covered 50% and 14% of the country's population, respectively.

Results from treatment of the first 112,000 patients, published in 1996, showed 89.7% cure rates among...
new cases and 81.1% cure rates among retreatment cases. Case detection and reporting is eightfold higher in these project areas, accounting for 89% of TB cases reported in China. Cure rates have ranged from 94% to 97% among new cases, since 1994, compared with 84% to 86% in non-DOTS areas. The program's impact is suggested by the results of the 2000 nationwide TB prevalence survey, which found the incidence of smear-positive TB had decreased 21%, to 122 cases per 100,000 population nationwide. The TB death rate had decreased 53% to 9.8 per 100,000; this totals 56,000 deaths averted in 2000. These results validate estimates of the impact of DOTS based on mathematical modeling. More importantly, TB incidence decreased 37.7% in DOTS areas compared with 3.2% in non-DOTS areas.

The current NTP is implemented primarily through the two aforementioned TB control projects. Through these projects, China has gained substantial experience in implementing the DOTS strategy. These projects have incorporated all key elements of DOTS into the NTP. These include a standard diagnostic algorithm for evaluating symptomatic patients emphasizing sputum smear microscopy to identify the most infectious TB patients, standard treatment regimens for new and retreatment TB cases, DOTS administered by village doctors, use of WHO's recording and reporting systems to provide sound data for program evaluation, training of tens of thousands of staff, and a stable supply of quality drugs.

The foci of the NTP are detecting infectious cases and ensuring completion of treatment for all cases detected. Infants are given BCG vaccines at birth through the Expanded Program of Immunization. Other activities such as contact investigation or treatment of persons with latent TB infection, however, are not part of the NTP. Second-line TB drugs are used to treat patients with drug-resistant TB, generally in specialized hospitals and not as part of the NTP.

Challenges for the Future

The paradox in this success story is that DOTS coverage has not increased since 1997, and the number of cases enrolled also has not increased significantly. Furthermore, the percentage of the total estimated cases treated through these programs was relatively low. Less than 25% of the estimated new smear-positive pulmonary cases are treated through these programs. The most important challenge is to sustain and expand the successful DOTS program to the entire nation (i.e., to secure the political commitment and financial resources for this purpose). To further reduce TB morbidity and mortality rates, prevent the development of multidrug-resistant TB, and minimize the impact of HIV/AIDS on the TB epidemic in China, increased case detection and expansion of DOTS to the entire country are essential. The TB projects in the 1990s raised the awareness of governmental leaders of the importance of TB as a public health problem. They also showed China can control TB successfully, so government officials emphasize TB control more than in the past. International partners are working to provide new funds for TB control in China. The future of DOTS expansion depends largely on whether these developments can secure the needed funding.

THE FUTURE OF GLOBAL TUBERCULOSIS CONTROL

The resurgence of TB in the United States and Western Europe alerted health care professionals and policy makers to the global public health emergency of TB. In the last decade of the 20th century, TB control efforts and TB research responded. In 1991, a rational, systematic, and highly cost-effective approach to TB control for both national and local levels was formalized, packaged under the acronym, DOTS, and started being promoted by WHO. By 1999, 127 countries, representing 82% of the world's population, had adopted DOTS in theory, covering 23% of global TB cases. Large-scale programs such as those in India and China have had dramatic success. Major advances in basic and applied science hold
tremendous promise for the future. Nucleic acid amplification techniques have transformed both epidemiological and genetic research and promise to transform diagnostic testing for TB.[75][87][90][161][187]
The complete genome of *M. tuberculosis* was sequenced in 1998. The functions of the 4000 plus genes in the mycobacterial genome are being studied systematically through computer-assisted analysis and oligonucleotide microarrays that allow large numbers of genes or gene segments to be compared simultaneously.[6][9][46][103][142] Molecular genotyping techniques have enabled individual strains to be identified and traced, prompting major advances in epidemiological understanding of the transmission dynamics of TB.[4][7][161] Advances in cellular immunology have pushed the understanding of the pathogenesis of TB to new levels.[58] Fluoroquinolones have proved effective in TB, and new oxazolidinone derivatives appear promising in vitro.[10][22]

Given these developments, there can be no question that advances in basic and applied science and technology hold potential for the future. Most importantly, fast diagnostic tools, more rapidly effective therapeutics, and highly effective vaccines seem realistic during the 21st century. What happens, however, until such possibilities become realities? Estimates of future TB morbidity and mortality rates, based on various assumptions and contingencies, have been developed by mathematical modeling. Work at WHO suggests that without further change in TB control, the annual incidence of TB will increase to approximately 10.6 million cases in the year 2020.[52] In contrast, widespread implementation of effective DOTS programs (i.e., achieving WHO targets for case detection [70%] and cure [85%] by 2010), will reduce global TB incidence by % to 7% per year in the first years after the targets are reached. This will prevent 23% of cases and 26% of deaths, or, in absolute numbers, 43 million cases and 18 million deaths. In relation to HIV infection, in settings with rapid increases in the prevalence of HIV infection in the general population such as Botswana or Zimbabwe, TB cases and deaths will continue to rise, although at a substantially slower pace. DOTS will prevent 15% of cases and 5% of deaths. Higher levels of case detection and cure will be needed to decrease incidence. The work of other investigators, using different models and strategies, supports or extends the results noted, taking into account the possibilities of other interventions and the impact of multidrug-resistant TB.[12][110]

Tuberculosis control programs must be strengthened to ensure that effective treatment becomes accessible to all and that such treatment remains available in the foreseeable future. This will require strengthening of health care systems and increased community contribution to TB care and control. A more integrated and rational approach to patients with respiratory symptoms is also a priority to increase detection and facilitate treatment. Cost-effective clinical tools for primary care health workers need to be tested and implemented. The involvement and oversight of private practitioners in TB control efforts, especially in Southeast Asia, will be crucial to improving access to optimal care at all levels. TB control in prisons must be strengthened and coordinated with the TB control in the general population because of the huge numbers of prisoners with TB or at high risk for TB in many countries, especially those of the former Union of Soviet Socialist Republics. An effective model is needed for both medical and administrative measures that would enable services to detect and manage TB, including smooth transitions between the correctional system and civilian society or between private practitioners and public health care systems. New approaches are needed to control the spread of HIV infection and prevent the morbidity and mortality caused by TB among persons with HIV. This will require a broader perspective than just DOTS, with integration between TB control and HIV care systems. Lastly, nascent efforts to control multidrug-resistant TB in resource-poor countries, such as DOTS-Plus pilot projects, must be accelerated to generate the evidence and experience that can serve as a solid basis for policy.[81][82]

With current priorities, tools, and constraints firmly in view, a global partnership has been launched linking health, social, and economic sectors in the fight against TB, called the “Stop TB” initiative.[148] Stop TB is hosted by WHO and includes an expanding list of international, governmental, nongovernmental, and private partners. This partnership has introduced a revised framework for global...
TB control that extends the basic DOTS package with strategies for strengthening the capacity of the public health care system to sustain and expand DOTS; integration with general medical and primary care health care services; community involvement and patient-centered approaches to care; collaboration across public, private, and voluntary sectors; integration with HIV prevention and control programs; specific attention to diagnosis, treatment, and prevention of multidrug-resistant TB in the context of strong basic TB control; and, most importantly, advocacy to generate and sustain the political commitment for human and financial resources to make TB control a priority and an essential part of each nation's health care system. [147]

To advance the process of global TB control in this context, in March 2000, Stop TB convened the ministers of health and finance from the top 22 high-incidence countries, together with global leaders from TB control organizations, donor countries, international development agencies, and nongovernmental organizations in Amsterdam, the Netherlands. [3] The resulting Amsterdam Declaration called for accelerated expansion of control measures and for increased political commitment and financial resources to reach targets for global TB control. In response, NTP managers from the 22 high-incidence countries, technical and financial partners, and the global network of WHO developed a Global DOTS Expansion Plan based on expanding DOTS at the country level and on building partnerships to mobilize the needed resources. [147] This plan provides the template for these activities, identifies country-specific needs, and quantifies the deficit in resources needed to implement the full DOTS program in an integrated and sustainable manner.

For the 22 high-incidence countries, the annual cost of TB control is estimated at $700 million to $900 million per year. [146] The gap between resources currently available and those needed is approximately $100 million to $300 million per year, assuming current levels of aid are sustained. Globally, the cost would be between $900 million and $1.1 billion, excluding higher-income countries funding their own TB control efforts, and the gap would be $150 million to $400 million per year. Current donor funds and bank loans provide $50 million per year for the 22 high-incidence countries and $200 million per year globally. Therefore, it is vital that these financial contributions be sustained. In short, worldwide TB control in terms of WHO global targets could be implemented for an additional $400 million per year. [146]

Direct programmatic costs aside, the indirect costs of TB are enormous and represent a major loss to the economies of the affected countries. Three-fourths of TB patients are adults between 15 and 54 years of age, economically the most productive years. Data from India and Bangladesh indicate that working adults spend an average of $100 to $150 for diagnosis and treatment, more than half their annual incomes. [148] In addition to out-of-pocket costs, in Bangladesh and Uganda, adult TB patients lost 9 to 14 months of work. Typically, TB costs a family 20% to 30% of the annual household income in direct cash outlays, plus 3 to 4 months of work time. As a result, families often go into debt and/or take their children out of school to earn income, perpetuating the cycle of poverty. In India alone, the indirect costs of TB total over $3 billion, largely as a result of premature deaths.

In addition to the economic costs, the social and emotional costs, including stigmatization and discrimination, especially against women, are enormous.

Still, DOTS is highly cost effective, decreasing the cost per patient cured in Uganda from $646 under conventional treatment to $280 under DOTS, mostly in savings to the patient. [148] The World Bank calls DOTS one of the most cost-effective health care interventions of the past 50 years. [188] In India, the economic benefits of investing in DOTS would far outweigh the costs. Based on highly conservative assumptions, the economic savings from DOTS implementation would amount to $4.6 billion to $8.3 billion equivalent to between 1993 and 1994 (2.1% to 4.0% of gross domestic product between 1993 and 1994). [45] In other words, investing in sound TB control by the DOTS strategy would result in a significant net gain and effectively boost India's economic growth.
The question is not whether the world can afford to invest the needed money in TB control, but whether it can afford not to. Without additional financing, the global incidence of TB morbidity and mortality will only increase, as noted previously by approximately 134,000 cases and 32,000 deaths per year (averaged over 20 years), making TB control even more expensive in the future than it is now. The specter of multidrug-resistant TB compounds this problem, because poor TB control creates multidrug resistance and multidrug-resistant TB is 20- to 100-fold more expensive to diagnose and treat than drug-susceptible TB. In an era in which a highly cost-effective cure exists, it is unacceptable not to act quickly, decisively, and together. Recognizing clearly these considerations, the many partners of the Stop TB initiative have coalesced into a global movement that may be able to foster the development of political will and marshal the resources to effectively control TB worldwide.

SUMMARY

*Mycobacterium tuberculosis* has been identified in prehistoric remains of humans. Despite references to TB by Hippocrates and Galen, humankind had limited understanding of and few tools to defend itself against TB until the later 19th century. Subsequently, landmark advances in the 20th century provided the means to control and prevent this disease. At the same time, epidemiological developments and fundamental problems related to human behavior, socioeconomic conditions, and political circumstances continue to thwart efforts to diminish the burden of suffering and death caused by TB. This article reviewed some of these issues including the global failure of TB control in the late 20th century, the worldwide emergence of drug-resistant TB, the extensive spread of HIV infection and its impact on TB incidence; and changing health care and political environments. The obstacles to TB control remain and will remain challenges in the coming years. Still, recent developments in immunology, biochemistry, and molecular biology suggest that new knowledge and tools are just around the corner. These will enhance the ability to conquer this microbe by the end of the current century.

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