In some quarters, there is a firm belief that tuberculosis (TB), like the weather, can be described but not controlled. Tuberculosis declines if socioeconomic conditions improve.\textsuperscript{1,2} This fact has led some observers to mistakenly conclude that TB can only be controlled if living conditions improve. However, it was predicted on theoretical grounds,\textsuperscript{3} and has now been convincingly demonstrated in practice, that TB can be controlled in almost any socioeconomic circumstances\textsuperscript{4-6}—with the important exception of the context of an epidemic of human immunodeficiency virus (HIV) infection.

Methods

We reviewed data for the amenability of TB to control. We considered separately control of deaths, prevalence, rate of infection and incidence.

Results

Tuberculosis mortality can be reduced by more than 80\% in less than 5 years. The prevalence of TB can be reduced by 30\% or more annually; sustained annual decreases of 17\% have been documented in a developing country. The TB infection rate can be reduced by 15\% annually. In the absence of human immunodeficiency virus (HIV), TB incidence can be decreased by as much as 25\% per year and up to 10\% annually in developing countries. A high prevalence of untreated HIV infection in the adult population of a developing country will inevitably result in a significant increase in TB incidence despite optimal use of currently available technologies.

Conclusions

Tuberculosis can be controlled if appropriate policies are followed, effective clinical and public health management is ensured, and there are committed and co-ordinated efforts from within and outside the health sector. However, in the context of a large epidemic of AIDS, TB incidence will inevitably increase. By 2001, less than 30\% of global TB cases were reported to have received effective diagnosis, treatment and monitoring. Rapid expansion of effective TB control services is urgently required, both to avert the continued high burden of morbidity and mortality from TB and because of the HIV pandemic.

Keywords

Tuberculosis, short-course chemotherapy, disease control, burden of disease

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Results

Mortality

Directly observed treatment of TB rapidly reduces mortality. This was seen even in the first days of anti-TB treatment; treatment with a single drug resulted in dramatic, albeit transient, reductions in mortality. Current regimens, given under appropriate management conditions, are nearly 100% curative for patients with drug-susceptible organisms; the reduction in mortality is dramatic and sustained. Untreated, 50–80% of patients with smear-positive TB will die of their disease. In a poorly implemented TB programme, as many as 30% of patients with smear-positive TB die. In contrast, death rates in DOTS programmes throughout the world are generally less than 5%; of 725 275 new smear-positive patients treated in DOTS programmes in 1998, only 3.8% were documented to have died. Even if one-third of patients who were lost to follow-up died, the total proportion of deaths would still be less than 10%.

In countries where baseline data exist, it is possible to make a reasonable estimate of the reduction in mortality achieved through DOTS implementation. Peru has been able to implement a highly effective DOTS programme, with a striking 80% reduction in mortality within just 3 years. This has been achieved by reducing the case fatality rate among treated patients through prompt diagnosis, effective and directly observed treatment, and increasing the proportion of patients treated. In India, mortality among smear-positive patients in the previous programme was 20–30%, compared with 4% in the DOTS programme—approximately a sevenfold reduction. Considering both smear-positive and smear-negative cases in India, DOTS reduces the case fatality rate by about 80%, even if neither secondary cases and their mortality, nor the increased detection rate, is taken into account. By early 2002, the Indian DOTS programme will have treated more than a million patients (see www.tbcindia.org), thereby saving nearly 200 000 lives. In China, national coverage with DOTS would prevent more than 60 000 deaths per year.

Prevalence of disease

Prevalence of TB can also be reduced rapidly. In a poorly functioning TB control programme, a ratio of incidence to prevalence as high as 1:3.5 has been documented. Achievement of the global targets for TB control, even if only a small proportion of prevalent cases is treated each year, will result in a rapid reduction in prevalence. This point is illustrated in a simple model (Figure 2). In this model, at the outset there are 100 new smear-positive cases per 100 000 population and the ratio of incidence to prevalence is 1:3. This model assumes that 70% of newly arising smear-positive cases are detected each year, that about half as many prevalent smear-positive cases as incident smear-positive cases are treated each year, and that 85% treatment success is achieved, that the proportion of patients who fail treatment is as per the global averages in DOTS programmes, and that there is a 5% decrease in incidence per year (see below). As can be seen, prevalence can decline very rapidly, being reduced to less than half of its previous level within 3 years.

The validity of this model has been confirmed under programme conditions in both developed and developing countries. In Kolín, former Czechoslovakia, an intensive surveillance and control programme in a population of 100 000 reduced the prevalence of chronic TB by more than 33% per year—to less than one-quarter of its earlier rate in 3 years. In New York City, the number of patients with persistently positive cultures fell by two-thirds in 3 years—more than 30% annually. This could be documented because the monitoring system identifies virtually every patient with bacteriologically proven TB. In Beijing, the prevalence of smear-positive cases, as documented by community surveys, decreased by 87% between 1979 and 1990, from 127 to 16/100 000—a 17% annual decrease sustained over 11 years. In contrast, a programme which achieves low cure rates may actually increase the burden of disease by increasing the number of prevalent, chronically ill, infectious patients.

Rate of infection

For the long-term control of TB, the rate of decline of the risk of infection with the TB bacteria is the most important indicator. If infection rates consistently decline, TB will eventually disappear. In industrialized countries, the risk of infection with TB bacteria decreased by approximately 5% or more per year even before the introduction of chemotherapy. With the introduction of effective treatment, the rate of infection decreased by 15% or more per year. In contrast, in developing countries, unless effective TB treatment services are in place, there is little or no decline in the annual risk of TB infection.

Effective diagnosis and treatment of TB can rapidly reduce the risk of infection. With effective treatment, the risk of infection in developed countries can be reduced by 10–15% per year. In Alaska, under rudimentary conditions not dissimilar to those in developing countries today, an intensive treatment programme resulted in a dramatic decline in the annual risk of infection by 10–15% per year. However, few studies have attempted to document this in developing countries. Such studies are difficult logistically, and are further complicated by difficulties in the interpretation of tuberculin tests in the presence of other infections.
Dynamics of smear-positive tuberculosis if global targets are met
(1 million population; rate of smear-positive tuberculosis = 100/100 000)

Figure 2 Dynamics of smear-positive tuberculosis if global targets are met. SS+: sputum-smear positive (see text for detailed explanation)
same population over time. One such survey in the Republic of Korea found an annual decrease in the risk of TB infection of 8–14% between the years 1965 and 1995, even though the treatment success rate (the proportion of patients cured plus those completing treatment) did not quite reach 85%. At a constant rate of BCG vaccination, the incidence of tuberculous meningitis in infants reflects the annual risk of infection. In Beijing, tuberculous meningitis decreased from 2.1 to 0.1 per 100 000 between 1986 and 1996, a decrease of 26% per year. However, some of this decrease may have been due to improved vaccination practices.

**Incidence of disease**

The incidence of TB is the combination of (i) recurrent TB in patients who have had previous episodes of disease, (ii) rapid progression to TB disease among individuals infected or re-infected within a relatively short period (e.g. 2 years) of infection, and (iii) reactivation of TB infection contracted many years previously. Recent developments in molecular epidemiology, along with conventional epidemiological investigations, have helped to determine the relative proportion of cases arising from each of these groups. A comprehensive study of TB epidemiology in South India found that, in 1972, only 37% of all smear-positive cases of TB arose from individuals who had a normal chest radiograph at the outset of the survey. Within 12 years, this fraction had increased to two-thirds, suggesting that a much higher proportion of cases arose from recent infection.

The amenability of TB incidence to control, even in the absence of an epidemic of HIV, depends to a great extent on local epidemiology. At one extreme are situations in which the vast majority of TB cases arise from remote infection. A recent survey in Norway has shown that fewer than one in five patients developed TB as the result of recent infection; the overwhelming majority of cases arose from remote infection or recurrent TB. Most such cases will not be prevented with current technologies. Many individuals with remotely acquired infections will not be candidates for preventive treatment, and, even if preventive treatment is attempted on a mass scale, its success is far from assured because adherence may be low. At the other extreme are populations in which as many as half of all TB cases arise from infection or re-infection within the preceding 2 years. In such a context, the application of effective TB control measures can result in a very rapid decline in TB cases. For example, in New York City the incidence of TB among people born in the US declined by 25% annually over the 5-year period of 1992–1996; incident cases of multidrug-resistant TB, many of which were linked to ongoing transmission in health facilities, declined by 34% annually in the same time period. Similarly, an elegant study in San Francisco documented that more than one-third of cases resulted from recent transmission, as indicated by clustering of DNA fingerprints. With improved control measures, the overall case rate declined by 7% per year; the rate of clustered cases declined by 15% per year while non-clustered cases declined by only 5% per year. In New York City, molecular epidemiological studies documented a 26% decline in the estimated incidence of clustered smear-positive TB between 1991 and 1997 (ref. 31 and New York City Department of Health, unpublished data, 1997).

A limited number of surveys in developing countries suggest that the proportion of new cases caused by recent infection may range from 29% to 48%. Such cases can be rapidly decreased by effective treatment. In addition, cases arising from reactivation of TB may decline steadily over a longer period of time. Thus, on theoretical grounds, it should be possible to control incidence even in developing countries. This prediction has been borne out by experience.

In developing countries where effective treatment practices have not been implemented, the incidence of TB remains essentially static. In contrast, rapid declines in TB incidence have been documented in the developing world when effective TB control measures are applied. In underdeveloped parts of Alaska and Canada, incidence decreased by 15% annually when the government devoted sufficient resources to ensure effective treatment. In Beijing, during a period when the proportion of incident cases that was notified was believed to be high and constant, a 9% annual decrease in new smear-positive cases was documented between 1986 and 1996. In Cuba, with application of directly observed treatment and efficient treatment organization achieving high rates of treatment success, the reported rate of new smear-positive cases decreased by 10% per year over a 26-year period. In Peru, cases of TB declined by approximately 8% per year from 1994 to 2000. An 8–10% annual reduction will cut the number of cases by half in 7 years. Thus, in the absence of an HIV epidemic, the incidence of TB can be significantly reduced even in developing countries.

**Tuberculosis control in the context of HIV**

The HIV epidemic undermines TB control. In the context of HIV, mortality, prevalence, and possibly rate of infection can still be controlled by an effective TB control programme. However, this can only be done with significantly increased effort, and with a very small margin for error.

An HIV epidemic increases the incidence of TB by increasing the risk of reactivation in patients already infected with the TB bacteria, as well as by rapid and widespread dissemination of TB in HIV-infected populations. As a result, the incidence of TB will inevitably increase in most areas of the world if the rate of HIV infection in the adult population is high (e.g. >5%) (Table 1). Hence, in the presence of a significant proportion of untreated HIV infection among adults, TB incidence cannot be reduced with current technologies.

The calculations in the Table relate to untreated HIV infection. Widespread and effective use of highly active anti-retroviral treatment could potentially reduce the prevalence of TB by decreasing the prevalence of severe immunocompromise among HIV/TB co-infected individuals. However, this would require ensuring lifetime adherence to the relatively toxic and complex medications required for this regimen of HIV treatment.

An effective TB control programme can blunt the impact of HIV-associated TB, and can also prevent the related emergence of multidrug-resistant TB. Tuberculosis has increased explosively in areas of the world where HIV is endemic; these increases have been significantly less in areas with effective TB control services.

Experience in the United Republic of Tanzania may be somewhat encouraging in this regard. Although the country is in the midst of a substantial epidemic of HIV, systematic surveys for annual risk of infection over the past 15 years have documented continued stable or even slightly declining (~2% annually)
rates of TB infection. This suggests that an effective TB control programme can, by means of prompt diagnosis and effective treatment, limit the number of secondary infections and cases.

Theoretically, preventive treatment for HIV-infected patients who also have TB infection could dramatically reduce the impact of HIV on TB epidemiology. However, since most individuals with HIV infection in developing countries do not know their infection status, and because of the logistic difficulties of giving preventive treatment for latent TB infection to a large number of patients who have no clinical symptoms, the practical applicability of treatment of latent TB infection may be limited to individual rather than public health interventions.

New York City demonstrated that it is possible to control an outbreak of TB even in the context of HIV, and even in an area where multidrug resistance has become common. This was achieved by ensuring prompt diagnosis, high-quality laboratory work, standardized treatment, direct observation as the standard of care, and rigorous cohort analysis with accountability for every patient diagnosed. In addition, the spread of TB in hospitals was curtailed. However, the prevalence of HIV infection among adults in New York City probably did not exceed 3%, in contrast with more than 30% HIV prevalence among adults in some countries of Africa.

Conclusions

Control is a more modest goal than elimination. Tuberculosis elimination has been defined arbitrarily as no more than one new case per million population per year or a prevalence of TB infection of below 1% in the general population. This may be achieved in some developed countries even without additional technological advances within the next 20–50 years. However, migration and continued high rates of TB in many countries of the world may prevent this from occurring unless a concerted effort is made to control TB in all countries. As case rates decrease, there is a significant risk that TB control programmes will be dismantled, resulting in a resurgence of TB. Tuberculosis is not currently a candidate for eradication efforts; eradication is defined as the achievement of a status whereby no further cases of a disease occur anywhere and control measures are unnecessary.

Thus, the answer to the question, ‘Can tuberculosis be controlled?’ is ‘Yes’—if appropriate policies are followed, effective clinical and public health management is ensured, and there are committed and co-ordinated efforts for its control from within and outside of the health sector. Rapid expansion of effective TB control services is urgently required, both to avert the continued high burden of morbidity and mortality from TB and because of the HIV pandemic.

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### Table 1 Impact of human immunodeficiency virus (HIV) infection on tuberculosis (TB) incidence—example with 5% of adults HIV-infected

<table>
<thead>
<tr>
<th>a.</th>
<th>b.</th>
<th>c.</th>
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<th>f.</th>
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<th>h.</th>
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<tr>
<td>Proportion of adults with untreated HIV infection</td>
<td>Proportion of population which is adult</td>
<td>Proportion of HIV-infected persons who are also infected with the tuberculosis bacteria</td>
<td>Annual risk progression to active TB in HIV/TB co-infected people</td>
<td>Number of new cases of tuberculosis among HIV/TB co-infected people alone</td>
<td>Number of cases arising from recent transmission in previously uninfected population</td>
<td>Total additional HIV-related cases (e + f)</td>
<td>Baseline rate of TB in developing countries</td>
<td>Increase in TB rate as per assumptions a through h (a/h)</td>
</tr>
<tr>
<td>5%</td>
<td>50%</td>
<td>30%</td>
<td>7%</td>
<td>(100 000 × a × b × c × d) 50 per 100 000 population</td>
<td>(50–100% of e [refs 29–32]) 25–50 per 100 000 population</td>
<td>75–100 per 100 000 population</td>
<td>150 per 100 000 population</td>
<td>50–67%</td>
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### KEY MESSAGES

- Tuberculosis (TB) is nearly 100% curable with simple technology, even in developing countries.
- Tuberculosis deaths have been reduced by 80% in 3 years in developing countries that have implemented effective control measures.
- Prevalence of TB has been reduced by 30% or more annually in developed countries and more than 15% annually in developing countries.
- Incidence can be reduced by 10–25% annually in the absence of human immunodeficiency virus (HIV).
- However, in the presence of a large epidemic of untreated HIV infection, TB will inevitably increase despite optimal application of currently available TB control technologies.
References


