Tuberculosis: an international perspective

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This article summarises a comprehensive review of the global tuberculosis (TB) epidemic and the impact of the human immunodeficiency virus (HIV)1. There is also a brief description of the World Health Organization (WHO) recommended TB control strategy, an update on the current status of TB control worldwide, and a look at future prospects for global TB control. An accompanying article by Drobniewski covers the increasingly important issue of drug resistance.

The global tuberculosis burden: notifications and estimates

Case notifications often represent only a fraction of the true incident cases, particularly in those developing countries where access to effective TB care is limited. WHO estimates of incidence2 are derived:

• for developing countries, from the annual risk of TB infection
• for low prevalence, industrialised countries, from notification data.

Figure 1 shows estimated TB incidence rates by country in 19962.

The impact of HIV on tuberculosis

HIV is the most important risk factor for progression of Mycobacterium tuberculosis infection to clinical disease3. WHO estimated that 30.6 million people were living with HIV infection worldwide at the end of 1997, 20.8 million (68%) of them in sub-Saharan Africa4. The HIV pandemic has magnified the TB epidemic where there is overlap between M. tuberculosis- and HIV-infected populations.

Using estimates of the prevalence of M. tuberculosis5 and HIV infections6 in various regions, WHO has estimated that at the end of 1997 there were about 15 million persons with M. tuberculosis and HIV co-infection worldwide, of whom the great majority were in sub-Saharan Africa (12 million) and most of the rest in South-East Asia (3 million). These estimates are likely to be conservative because the risks of infection with M. tuberculosis and HIV were assumed to be independent, but it is likely that they share common risk factors. The annual risk of progression to TB among persons infected with both HIV and M. tuberculosis is 5–15%, depending on the degree of immunocompromise7–10, compared with an estimated 10% lifetime risk in persons infected with M. tuberculosis alone.

Many countries in Eastern and Southern Africa (eg Uganda, Malawi, Zambia and Tanzania) have reported nationwide HIV seroprevalence rates among new TB patients of at least 30%11. In Asia, Northern Thailand12,13 and certain urban areas of India14 have reported rapidly-increasing HIV seroprevalence rates among TB patients. The number of reported cases of TB has increased dramatically since the 1980s in areas where HIV seroprevalence has increased among TB patients. The increased number of cases poses a challenge to health services, TB control programmes and clinicians15. Tables 1 and 2 show estimated TB incidence and deaths respectively, including those attributable to HIV16.

Studies in various regions have shown that about 25% of patients had TB during the course of HIV infection in Latin America17, Mexico18 and Haiti19,
and about 50% in Africa20-22 and Asia (India23, Thailand24). Worldwide, TB is probably the most important single cause of morbidity and mortality among HIV-infected people.

Tuberculosis in industrialised countries

TB case notifications in developed countries steadily declined long before the introduction of anti-TB chemotherapy, largely because of socioeconomic improvements. Widespread effective chemotherapy further accelerated the decline. Recently, however, several countries have seen an interruption in the expected continued decline, and others have seen the trend reversed, with case notifications increasing for the first time in many years. For example, in the USA, after 30 years of decline, case notifications increased regularly between 1985 and 199225.

Factors responsible include:

- increased poverty among marginalised groups in inner cities
- immigration from high TB prevalence countries
- the impact of HIV
- the failure to maintain the necessary public health infrastructure.

Many countries in Europe, including Denmark, the Netherlands, Sweden and the UK, also reported a failure of the expected continued decline – or even a steady rise – in case notifications26. The high percentage of cases in the foreign-born (eg France 24%, the Netherlands 51%, Sweden 54%, Switzerland 68%) suggests that immigration is the main cause of this change27. Annual case rates in foreign-born populations often exceed 50 per 100,000 (in the Netherlands, even 100 per 100,000), in contrast to rates usually below 15 per 100,000 in indigenous populations27. TB control in industrialised countries requires global TB control.

The impact of HIV on TB in Western Europe is limited to certain countries (eg Spain, Portugal) and cities (eg Paris, Amsterdam)26. In most Western European countries, the percentage of AIDS cases diagnosed with TB is low (<17%). The two notable exceptions are Spain and Portugal, where the overlap between the populations infected with both HIV and M. tuberculosis is greater than in the other countries of Western Europe. The percentage of AIDS cases diagnosed with TB in Spain and Portugal is 42% and 51%, respectively28.

In the former socialist block, annual case notification rates are higher in central and eastern Europe and in countries of the former Soviet Union than in western Europe, with rates ranging from 18 per 100,000 (Czech Republic) to 102 per 100,000 (Romania).
Table 1. Estimated tuberculosis (TB) incidence and HIV-attributable TB cases in 1990, 1995 and 2000.

| Region             | 1990 Total TB cases | 1990 Rate* | 1995 Total TB cases | 1995 Rate | 2000 Total TB cases | 2000 Rate | 1990 - 2000 Increase |
|--------------------|---------------------|------------|---------------------|-----------|---------------------|-----------|----------------------|
| South-East Asia    | 3,106,000           | 237        | 3,499,000           | 241       | 3,952,000           | 247       | 571,000              |
| Western Pacific**  | 1,839,000           | 136        | 2,045,000           | 140       | 2,255,000           | 144       | 416,000              |
| Africa             | 992,000             | 191        | 1,467,000           | 242       | 2,079,000           | 293       | 604,000              |
| Eastern Mediterranean | 641,000         | 165        | 745,000             | 168       | 870,000             | 168       | 38,000               |
| Americas+          | 569,000             | 127        | 606,000             | 123       | 645,000             | 120       | 7,000                |
| Eastern Europe++   | 194,000             | 47         | 202,000             | 47        | 210,000             | 48        | 6,000                |
| Industrialised countries†  | 196,000       | 23         | 204,000             | 23        | 211,000             | 24        | 6,000                |
| **Total**          | **7,537,000**       | **143**    | **8,768,000**       | **152**   | **10,222,000**      | **163**   | **1,410,000**        |

Increase since 1990 16.3% 35.6%

* Crude incidence rate per 100,000 population.
** Includes all countries of the Western Pacific Region of the World Health Organization (WHO), except Japan, Australia and New Zealand.
† Includes all countries of the American Region of WHO, except USA and Canada.
+++ Eastern European and independent states of the former USSR.
†† Western Europe, USA, Canada, Japan, Australia and New Zealand.

Table 2. Estimated total tuberculosis (TB) deaths and HIV-attributable TB deaths in 1990, 1995 and 2000. (Estimates assume regional treatment coverage rates remain at their 1990 level).

| Region             | 1990 Total | 1990 Attributed to HIV | 1995 Total | 1995 Attributed to HIV | 2000 Total | 2000 Attributed to HIV |
|--------------------|------------|------------------------|------------|------------------------|------------|------------------------|
| South-East Asia    | 1,087,000  | 23000                  | 1,225,000  | 88,000                 | 1,383,000  | 200,000                |
| Western Pacific*   | 644,000    | 7,000                  | 716,000    | 11,000                 | 789,000    | 24,000                 |
| Africa             | 393,000    | 77,000                 | 581,000    | 150,000                | 823,000    | 239,000                |
| Eastern Mediterranean | 249,000  | 4,000                  | 290,000    | 6,000                  | 338,000    | 15,000                 |
| Americas**         | 114,000    | 4,000                  | 121,000    | 9,000                  | 129,000    | 19,000                 |
| Eastern Europe+    | 29,000     | <200                   | 30,000     | <600                   | 32,000     | <900                   |
| Industrialised countries†  | 14,000       | <500                   | 14,000     | 1,000                  | 15,000     | 2,000                  |
| **All regions**    | **2,530,000**| **116,000**          | **2,977,000**| **266,000**            | **3,509,000**| **500,000**            |

Increase since 1990 17.7% 38.7%

* Includes all countries of the Western Pacific Region of the World Health Organization (WHO), except Japan, Australia and New Zealand.
** Includes all countries of the American Region of WHO except USA and Canada.
† Eastern Europe and independent states of former USSR.
†† Western Europe, USA, Canada, Japan, Australia and New Zealand.

In 1995, and exceeding 30 per 100,000 in 19 of 27 countries in many countries, the previous decline in case notifications has stopped or reversed. For example, annual case notification rates increased in Russia by 70% from 1991 to 1995, and in Romania by 81% from 1985 to 1995, with an increased percentage of cases in young adults. With the recent dramatic social changes, reversal of the previous trend is due to increased poverty and poor living conditions (resulting in malnutrition, crowding and stress), deteriorating health services and lack of drugs and, in some cases, civil conflicts and wars. In most of these countries TB mortality rates have also stopped declining, and in some are increasing. For example, TB mortality rates increased in Russia from 7.7 per
100,000 to 14.4 per 100,000 between 1989 and 1994, probably because of the collapse of public health infrastructure and shortages in first-line drugs.

World Health Organization strategy for tuberculosis control

The global TB burden is increasing for several reasons:

- poverty, including that in inner-city populations in developed countries
- poor TB control
- changing demography
- the impact of the HIV pandemic

Developing countries suffer the brunt of the TB epidemic, with 95% of estimated TB cases and 98% of estimated TB deaths. These deaths comprise 25% of all avoidable deaths in developing countries.

TB is the only disease which WHO has declared a global emergency and, as a response, has adopted an available, effective and affordable strategy: the 'directly observed treatment, short course' (DOTS) strategy. DOTS consists of a five-point policy package which provides the organisational and management framework for case-detection and cure:

1. Government commitment to the national TB control programme.
2. Case-finding by sputum smear examination of TB suspects in general health services.
3. Standardised short-course chemotherapy, at least for all smear-positive cases, under proper case management conditions.
4. Regular, uninterrupted supply of all essential drugs.
5. Standardised recording and reporting system.

Current status of tuberculosis control achievements worldwide

TB control falls in many programmes because only about half the infectious cases are detected, and only about half those detected are cured. A TB epidemic, which is out of control in many parts of the world, demands increased global attention and funding. There has been some — so far inadequate — progress. Figure 2 shows the status of implementation of WHO-recommended TB control strategy by reporting countries. This strategy had been adopted by 96 of the 181 countries reporting to WHO in 1996. The number of countries adopting it is steadily increasing, but at present only a fraction (32%) of the world’s population lives in areas where this strategy is available.

Future prospects for global tuberculosis control

In the absence of wide implementation of the recommended TB control strategy in high TB prevalence countries, the global epidemic is likely to worsen. Unless there is considerable improvement in global control, WHO has estimated that a cumulative total of nearly 90 million new cases and over 30 million deaths can be expected to occur in the last decade of this century.

The future of the TB epidemic hinges on the balance between the implementation of effective control and those factors promoting the epidemic, including HIV, war and natural disasters, demographic changes, and increasing anti-TB drug resistance. Research efforts are crucial to facilitate the widespread implementation of the recommended TB control strategy and to develop new tools to combat the epidemic, for example new drugs and a better vaccine.

Government expenditure on health, including TB control, is falling in many developing countries. TB control globally is still underfunded, despite an increase in external aid flows to developing countries from $16 million in 1990 to $40–50 million in 1995 (A Kochi; personal communication). The expression of the necessary political will for global TB control is the commitment of governments to provide adequate funds both to implement effective TB control programmes and to invest in research. All concerned with TB control have a part to play in mobilising this political will.

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Key Points

- Previous efforts to control the global TB epidemic have failed — the means exist for diagnosis and cure but the organisational capacity to deliver TB control has been lacking
- The HIV epidemic and increasing drug-resistance pose additional challenges for global TB control
- The internationally recommended TB control strategy relies on an organisational framework to ensure the diagnosis and cure of the infectious cases
- TB does not respect national boundaries — controlling TB in the Western world is impossible without controlling TB in developing countries
- Political will is necessary to ensure the mobilisation of resources for implementing effective national TB programmes worldwide
Figure 2. Implementation status of World Health Organization (WHO) tuberculosis (TB) 'directly observed treatment, short course' (DOTS) control strategy by reporting countries, 1996.

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Drug resistant tuberculosis in adults and its treatment

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Mycobacterium tuberculosis (MTB), the bacterium that causes tuberculosis (TB), is estimated to have infected almost one-third of the world's population, producing eight million new clinical cases each year and leading to almost three million deaths. Over 95% of the cases occur in the developing world.

Drug resistance

Drug resistance develops spontaneously in bacteria. Combinations of drugs are used to make clinically significant resistance, and thus treatment failure, unlikely. Non-adherence to therapy, inappropriate prescribing, malabsorption of drugs, and deterioration of the clinical and public health infrastructure necessary for adequate supervision of treatment are all associated with the selection of drug resistant strains and treatment failure. Overall trends in drug resistance are also a crude indicator of the effectiveness of a national TB programme. NTP. High rates of multiple drug resistant TB (MDRTB) — that is, resistant at least to isoniazid and rifampicin, two of the major first line drugs — are indicative of poorly functioning programmes. Recent outbreaks of MDRTB in the USA and Europe, particularly in HIV-infected patients, have focused attention on the emergence of drug resistance.

The worldwide level of drug resistance in TB is not known, and methodological problems in many studies have prevented the development of a clear global picture. These include:

- the selection bias of many surveys
- the absence of high quality culture facilities.

In 1994, the World Health Organisation (WHO) and the International Union Against Tuberculosis and Lung Disease began the Global Project on Anti-tuberculosis Drug Resistance Surveillance. The recently published results of surveys and surveillance programmes from 35 countries report drug resistance in all countries. MDRTB was found to be widespread, with one-third of the countries surveyed having levels above 2% in new patients (median prevalence 1–4%; range 0–14%). High rates were found in former countries of the USSR, the Baltic Republics, Argentina, India and China. In general, countries with poor NTPs had a higher prevalence of drug resistance, especially MDRTB.

A laboratory-based surveillance programme, MYCOBNET, was created in the UK in 1994 to monitor drug resistance in TB. Preliminary trend analysis published for the period 1993–1996 showed that in initial isolates, resistance to isoniazid over this period rose from 4.6% to 6.1%, mono-resistance to rifampicin from 0.6% to 1.8%, and multidrug resistance from 0.6% to 1.6%. During the same period, the combined clinical prevalence of MDRTB (the total level of resistance occurring in a year) rose from 0.6% to 1.7%.

Treatment of tuberculosis

The principles underlying the treatment of TB have not changed since chemotherapy became possible in the 1940s: that is, combination chemotherapy in standardised regimens for the appropriate period of time.