Global epidemiology of tuberculosis

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Tuberculosis is the leading cause of death from a curable infectious disease.[1] On the basis of results of surveys of the prevalence of infection and disease, assessments of the effectiveness of surveillance systems, and death registrations, there were an estimated 8·9 million new cases of tuberculosis in 2004, fewer than half of which were reported to public-health authorities and WHO. About 3·9 million cases were sputum-smear positive, the most infectious form of the disease.[2–4] The WHO African region has the highest estimated incidence rate (356 per 100 000 population per year), but the majority of patients with tuberculosis live in the most populous countries of Asia; Bangladesh, China, India, Indonesia, and Pakistan together account for half (48%) the new cases that arise every year (figure 1). About 80% of individuals newly diagnosed with the disease every year live in the 22 most populous countries.

Tuberculosis is primarily a disease of men. Where the transmission of *Mycobacterium tuberculosis* has been stable or increasing for many years, the incidence rate is highest among young adults, and most cases are due to recent infection or reinfection. As transmission falls, the caseload shifts to older adults, and a higher proportion of cases are attributable to the reactivation of latent infection. In the countries of western Europe and north America, which now have low incidence rates, indigenous patients with tuberculosis tend, therefore, to be old, whereas patients who are immigrants from high-incidence countries tend

to be young adults. Allowing for the difficulties of diagnosing childhood tuberculosis, estimates indicate that there are relatively few cases among 0–14 year olds, even in areas of high transmission (10% of all new cases in Africa in 2004, but only 2% in the established market economies). In 2004, countries reported 1·4 million smear-positive cases in men, but only 775 000 in women. In some instances, women have poorer access to diagnostic facilities, but the broader pattern is also a sign of the real epidemiological differences between the sexes, both in exposure to infection and in susceptibility to development of active disease.

Although the incidence rate of tuberculosis per head seems to be growing slowly in the world as a whole, case notification rates have been steady or falling for at least two decades in the South East Asia and Western Pacific regions, in the established market economies and central Europe, and in the Latin America and Eastern Mediterranean regions (figure 2). The global increase is attributable to the striking proliferation of cases in countries of eastern Europe (mainly the former Soviet Union) since 1990 and in sub-Saharan Africa since the mid-1980s. However, trends in case reports suggest that the rate of increase in both regions has slowed considerably since the mid-1990s, and the incidence in eastern Europe might now be in decline.[4,5] The downturn in case notifications in eastern Europe is clear in data from Russia and the Baltic States of Estonia, Latvia, and
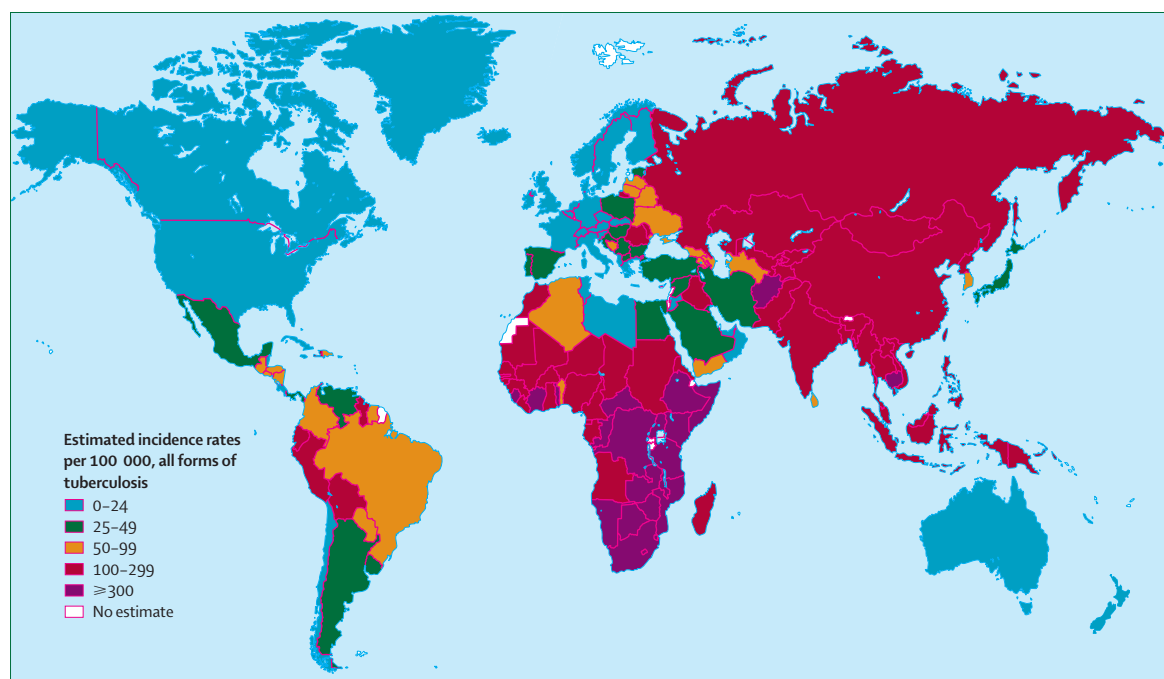

Estimated incidence rates per 100 000, all forms of tuberculosis
- 0–24
- 25–49
- 50–99
- 100–299
- ≥300
- No estimate

*Figure 1:* Distribution of tuberculosis in the world in 2003[4]

Lithuania, although incidence rates might still be increasing in the central Asian republics of Tajikistan and Uzbekistan.[4]

Adding data together from the nine regions in figure 2 gives the global trend in incidence; the case rate per head was increasing most quickly at 1·5% per year in 1995, but, because of the dynamics in Africa and eastern Europe, has since been decelerating. The continued increase in tuberculosis incidence globally from 2004 onwards is, in our estimation, entirely attributable to the continued rise in the two regions of Africa.

The resurgence of tuberculosis in eastern Europe can be explained by economic decline, poor tuberculosis control, and substandard health services since 1991. Based on the results of periodic surveys, more than 10% of new tuberculosis cases in Estonia, Latvia, and some parts of Russia are multidrug-resistant (MDR-TB)—that is, resistant to at least isoniazid and rifampicin, the two most effective drugs against the disease.[6,7] Drug resistance is probably a byproduct of the events that led to tuberculosis resurgence in these countries, not the primary cause of it. Although parts of eastern Europe are clearly hotspots for MDR-TB, only 3% of all the new tuberculosis cases that arise worldwide every year are estimated to be multidrug resistant,[8] although the frequency among previously treated cases is higher.

Much of the increase in global tuberculosis incidence seen since 1980 is attributable to the spread of HIV in Africa.[3–5] Globally, an estimated 13% of adults with newly diagnosed tuberculosis were infected with HIV in 2004, but there was great variation among regions—from 34% in the African region to 1·4% in the Western Pacific region. Rates of HIV infection in patients with tuberculosis have so far remained below 1% in Bangladesh, China, Indonesia, and Pakistan. In African populations with high rates of HIV infection, a relatively high proportion of patients with tuberculosis are women aged 15–24 years.[3,4] The rise in the number of tuberculosis cases is slowing in Africa, almost certainly because HIV infection rates are beginning to stabilise or fall.[9] HIV has probably had a smaller effect on tuberculosis prevalence than on incidence because the virus significantly reduces the life expectancy of patients with tuberculosis.[10] Where HIV infection rates are high in the general population they are also high among patients with tuberculosis; estimates for 2004 exceeded 50% in Botswana, South Africa, Zambia, and Zimbabwe, among other countries.

Although HIV infection has clearly had a profound effect on tuberculosis epidemiology, other potentially important risk factors have been somewhat neglected. In the coming years, more attention needs to be given to the interaction between chronic diseases and tuberculosis, including diabetes, undernutrition, and respiratory illnesses caused by tobacco and air pollution.
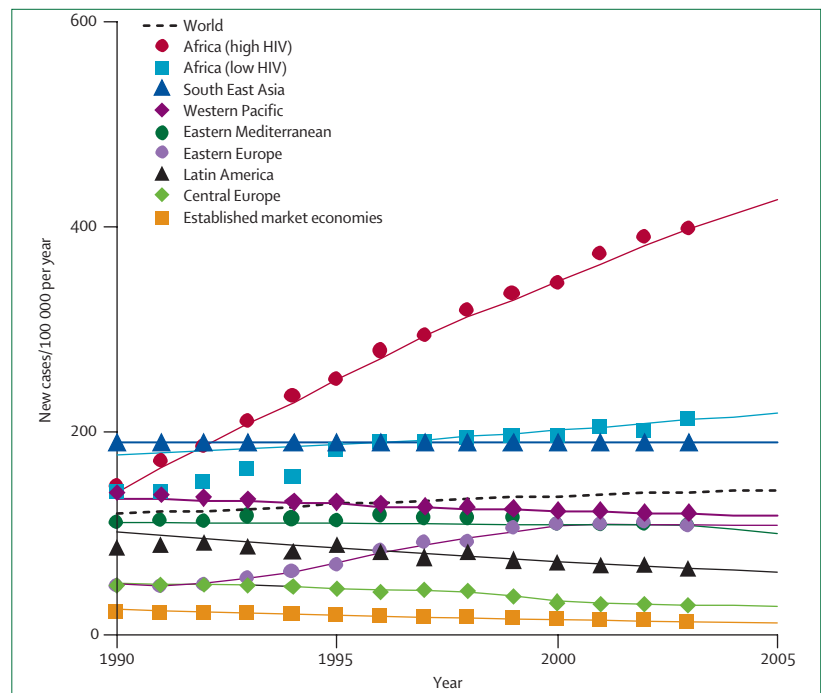
Figure 2: Trajectories of tuberculosis epidemic for nine epidemiologically different regions of the world

Points mark trends in estimated incidence rates, derived from case notifications for 1990–2003. Groupings of countries based on WHO regions. High HIV=incidence ≥4% in adults aged 15–49 years in 2003; low HIV=<4%. Established market economies=all 30 OECD (Organisation for Economic Co-operation and Development) countries, except Mexico, Slovakia, and Turkey, plus Singapore. Countries in each region listed in full elsewhere.[4] Adapted from reference 5 with permission of the American Medical Association.

Tuberculosis remains prominent in international statistics of ill health mainly because it kills young adults. More than 80% of the burden of tuberculosis, as measured in terms of disability-adjusted life years (DALYs) lost, is due to premature death rather than illness. About 1·7 million people died of tuberculosis in 2004, including 264 000 patients who were coinfected with HIV.[3,5] Because few countries with high burdens of tuberculosis compile reliable statistics on the cause of death, the global and regional trends in tuberculosis deaths are uncertain. However, the findings of one assessment based on modelling indicate that death rates from tuberculosis could have been falling since around year 2000, after rising during the 1990s.[4,5]

Based on our assessment of trends, UN Millennium Development Goal (MDG) 6, Target 8, to "have halted by 2015 and begun to reverse incidence of malaria and other diseases" (including tuberculosis), should not be hard to achieve. However, within the MDG framework, the Stop TB Partnership aims to halve prevalence and death rates globally between 1990 and 2015. These additional targets are much more of a challenge, especially in Africa and eastern Europe.

Conflict of interest statement
I declare that I have no conflict of interest.

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Priorities in tuberculosis research

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In 1991, the World Health Assembly set a target to detect 70% of all infectious cases of tuberculosis, and to cure at least 85% of them, by 2005.[1] These targets, despite intensified efforts, were not met;[2] more than 80% of known cases are successfully treated, but only 45% of cases are detected.[3]

To meet the new targets set by the Stop TB Partnership[2] and the Millennium Development Goals the generation and implementation of new information is needed. The table details the recommendations of the scientific working group of the UNICEF/UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases (TDR) for priority research into tuberculosis, and described below are the two general research areas identified within the sixth element of the WHO recommended Stop TB Strategy[2] as those most important for control of tuberculosis.

First, research into programme effectiveness is essential, and has been called for in the past.[4] Up to 60% of tuberculosis cases can be detected by existing diagnostic methods and nearly all can be cured with existing regimens, suggesting inadequate knowledge about how to implement these proven approaches. As such, the Stop TB Partnership's Global Plan for 2006–15 calls for a "strengthening of laboratory networks to facilitate detection of all forms of TB including smear negative TB". Research into the social and behavioural factors that limit case detection is also necessary, as is the assessment of new strategies of case detection and of barriers to care—eg, lack of transport, malnutrition, unemployment, the cost of care, and sex discrimination. Improved clinical diagnostic algorithms and case definitions are needed to aid diagnosis of tuberculosis in children and adults coinfected with HIV. Furthermore, the effect on rate of case detection of different diagnostic strategies—sputum concentration methods, fluorescence microscopy, improved mycobacterial culture system—to those generally used should be assessed. Diagnostic algorithms, including the use of empiric antibiotic trials to exclude tuberculosis, need to be carefully reassessed and improved. Research into programme performance should involve assessment of the potential to integrate tuberculosis care within district health centres to overcome problems associated with lack of manpower and infrastructure.

With respect to the treatment outcomes, the growing proportion of individuals coinfected with HIV and *Mycobacterium tuberculosis* warrants investigation. WHO has provided a guidance document[5] on how best to increase collaboration between tuberculosis and HIV/AIDS programmes and decrease the burden of one disease in those affected by the other. The different models of collaboration between programmes within health systems in disease endemic settings need urgent assessment.

Second, new methods for the diagnosis, treatment, and prevention of tuberculosis are called for. A persistent difficulty in tuberculosis management in developing countries is that there is no specific, sensitive, inexpensive, and rapid method of diagnosis of the disease. As many as 3 million individuals who present every year with suspected tuberculosis actually have sputum smear-negative pulmonary disease or extrapulmonary disease, which cannot be confirmed by sputum-smear microscopy; paediatric and multidrug-resistant tuberculosis (MDR-TB) pose additional diagnostic challenges not addressed by sputum-smear microscopy. In terms of treatment, short-course chemotherapy requires 6 months of adherence to drugs with suboptimum toxicity profiles; drug interactions between those given for tuberculosis and those given for HIV represent a major new challenge, and there is no proven, simple regimen for simultaneous treatment. Thus, the development of new drugs with novel means of action is particularly important. Thankfully, the 30-year lull in investment in drug development for tuberculosis is over.[6] In the long term, the sequencing of the genome of *M tuberculosis* and refined techniques for elucidating metabolic pathways will open up new avenues of research. In the short term, there are six new drug candidates for