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Tuberculosis: World Perspective and the Challenges Ahead

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This brief review begins with an outline of the present global situation regarding tuberculosis, largely using estimates by the World Health Organization (WHO). The WHO figures support the claim that, with the explosion of the HIV epidemic in Africa, and the incipient explosion in Asia and Latin America, there is indeed a major global crisis. This, is made even more alarming by the threat of multi-drug resistance (MDR) which might result in an untreatable epidemic that could spread globally.

The review is followed by a list of some of the main challenges (political, economic, organizational, educational and technical) preventing disease control, which has so long been theoretically feasible (Crofton 1960).

The World Crisis

The global outlook

WHO (1993a, 1996) estimates that a third of the world's population are infected with the tubercle bacillus. In 1995, owing to increasing death rates in the exploding populations of the Third World, there were more tuberculosis deaths than in any previous year in history. Thirty million people will die in the next ten years if present trends continue. There are particularly high rates among the world's vast numbers of refugees. WHO estimates of global cases and deaths in 1990 and in the year 2000 are shown in Fig. 1, which summarizes the grim prospect.

Regional tuberculosis/HIV rates

More HIV-positive patients die from tuberculosis than from any other disease. WHO estimates of the percentage of patients with tuberculosis who were (1990) or will be (2000) HIV-positive are shown in Fig. 2. Recent figures for HIV in India (Lalvani & Shastri 1996) suggest that the WHO estimates for the year 2000 may prove too low, at least for Asia. In India, as in Africa, tuberculosis is already proving the commonest presentation of AIDS. Figures are still very low in the UK (Leitch et al 1996).

The Response to the Crisis

Developed countries

Gradually, in the 1960s, most richer countries, though at very variable rates, began to use effective methods of chemotherapy. In these countries both mortality and incidence of tuberculosis began to fall more steeply and it was assumed that the problem had been solved. But in recent years, in many richer countries, rates have ceased to fall and in a number have even risen. The reasons have varied between countries. Immigration from high prevalence countries may be an important factor, as may increases in poverty (Darbyshire 1995). Neglect and underfunding of tuberculosis services has been important in certain areas of USA where increase in the incidence of HIV has also been a factor.

The Third World

In the Third World the British Medical Research Council (BMRC) had demonstrated through research projects that hospital treatment for TB was unnecessary, and had evolved cheaper methods of treatment using thiacetazone to prevent resistance to the more powerful drugs. Later the BMRC showed that, using rifampicin and pyrazinamide, treatment could be shortened to 6–8 months (Fox 1979). Sadly, there was relatively little resulting fall in prevalence, as in most poor countries these new methods were not used on a mass scale, if at all.

However, building on the BMRC's work, in the early 1980s the International Union against Tuberculosis and Lung Disease (IUATLD) convinced the governments of several African countries of the size and importance of the problem and that the disease could be effectively dealt with through routine general medical services. With good organization, intensive training, persuasive motivation and some bilateral international help to pay for the more expensive drugs, 70–80% cure was achieved in Tanzania, Malawi, Benin and Mozambique (IUATLD 1992, 1996; Enarson 1995).

The World Bank, after surveying the IUATLD programmes, concluded that they ranked globally as the most cost-effective of all health programmes in terms of years of life saved (Murray et al 1991). Consequently, since 1991, with World Bank help, WHO has been seeking to aid governments in establishing national tuberculosis control programmes in developing countries (WHO 1993a). In a large scale pilot programme in China, cure rates of almost 90% have been

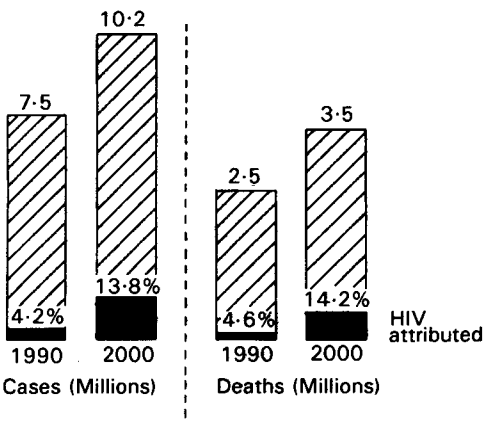

FIG. 1. WHO projections of future global tuberculosis (WHO 1993b)

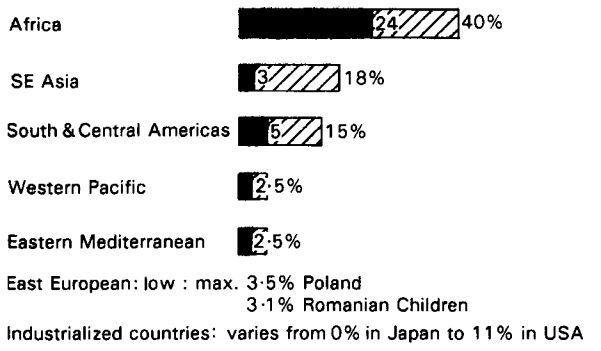

FIG. 2. WHO estimates of regional HIV and TB rates (WHO 1993b). ■ 1990 and ▨ 2000.

achieved among 55 213 new cases and 81% among 57 629 previously treated cases (China Tuberculosis Collaboration 1996).

Because treatment failure and relapse is largely due to the patient discontinuing the drugs on feeling better, the patient must be observed taking each dose of drug, especially in the first two months of intensive treatment. This is known as "DOTS" (Directly Observed Treatment, Shortcourse). WHO (1996) reported that in a survey of 214 countries, only 45 had even begun to institute a national tuberculosis control programme on modern lines. In only 13 of these countries were most patients already receiving DOTS; accounting for only 0·5 million out of 8 million new cases worldwide. An estimated 3 million were receiving no treatment at all.

Challenges for 1996

Underfunding

WHO (1996) has given data (admittedly from 1990) of external (global) funding in support of campaigns against infectious and parasitic diseases. Tuberculosis, with 2 million deaths, received $16 million; compared to $185 million for AIDS and sexually transmitted disease with 0·5 million deaths, $74 million for tropical diseases with 0·2 million deaths, and $47 million for malaria with 0·9 million deaths. Since 1990 there has been some improvement (Donosos-Clark 1996) though international resources are still grossly insufficient. England and Wales are not even paying their national subscription to IUATLD, though Scotland pays more than its due!

Persuading governments

Governments must be persuaded that they have a grim and urgent problem which is, nevertheless, soluble if quite modest national efforts and resources are devoted to it. The data on the use of DOTS, given above, show how far we still have to go. But many more Third World governments are now alerted and are asking for help. Given the lack of manpower and resources in IUATLD and WHO, this help is bound to be delayed.

Ensuring well organized national tuberculosis control programmes

The principles evolved by IUATLD are now adopted by WHO and are generally accepted (Enarson 1995; IUATLD 1996). The problem is to ensure that they are implemented in practice. Constraints to effective implementation, and potential ways of overcoming these constraints, are summarized in Table 1. For more detail see Crofton et al 1992, Enarson 1995 and IUATLD 1996.

Ensuring good treatment for tuberculosis/HIV (Harries & Maher 1996)

The tuberculosis element responds to modern shortcourse therapy. This prolongs life though the patient later dies from some other complications of AIDS. Moreover, there is evidence that tuberculosis accelerates progression of AIDS. From the public health point of view, treatment interrupts the spread of infection. Chemoprophylaxis in HIV-infected patients does seem to reduce the incidence of tuberculosis, but there are major administrative constraints to mass prophylaxis, including both cost and the misuse of drugs risking the spread of drug resistance.

In countries with a high prevalence of both diseases there is an enormous challenge to co-ordinate preventive and care programmes. A recent WHO workshop has outlined the problems and proposed lines of research, both operational and otherwise (Hausler 1995). The problems include health economics and healthcare financing, sociobehavioural concerns such as care-seeking and adherence, health system matters such as care access and care delivery and epidemiological and clinical factors. The latter includes the problem of diagnosis of what is often atypical sputum-negative tuberculosis (Shaw 1997). It also includes the problem of integrating the treatment of common HIV-related opportunistic infections into national tuberculosis programmes.

Table 1. Constraints to national tuberculosis programmes.

Constraint	Potential answer
Government commitment	International leadership Technical and financial help
Local leadership	Government commitment International support
Money for drugs	Bilateral finance: Government or Non Governmental Organization (NGO) Bulk buying: cheaper, reliable Buffer stocks
Drug delivery	Reserve transport
Integration with routine services	National and international motivation Intensive consultation Good supervision: vital Training, internal emulation: vital
Drug resistance due to bad treatment	Reliable regimens Extensive education: under- and post-graduate Good, convenient government service Reliable control of drug use Litigation against bad doctors

Multidrug resistance, its prevention and treatment (Prignot 1993; Crofton 1994)

The commonest cause of multidrug resistance in tuberculosis treatment is the "Addition Syndrome" (Crofton 1987). The patient is first given an unreliable combination of drugs, or even a single drug. This results in initial improvement followed by deterioration as resistance develops. A new drug is then added. As the bacilli are already resistant to all the drugs being used, this amounts to monotherapy. The pattern of initial improvement and subsequent deterioration is repeated. Another drug is added and so, tragically, on.

The extent of drug resistance in a country relates to the standard of treatment. In the 1950s we showed how rapidly prevalence decreased once all known patients received good treatment (Crofton 1960). In the UK today the problem is small except for immigrants (Ormerod 1993). Although we do not yet have accurate global figures, available evidence suggests that it may be a major problem in many developing countries. Ominous outbreaks have occurred even in some of the richest countries (Prignot 1993).

In some countries, especially the Indian subcontinent, even the poorest people first resort to private practitioners. These may not be Western-trained though they use Western drugs and treatment is often chaotic (Upelkar & Shepard 1991). The implications for MDR are appalling. There is an urgent need for operational research to determine the most effective remedies. These would clearly include intensive and ongoing undergraduate and postgraduate education. They might also include confining the prescription of anti-tuberculosis drugs to specialists, as in Norway and Libya (Khalil & Sathianathan 1978), or even litigation against misbehaving doctors. As virtually all patients with pulmonary tuberculosis should be cured if effective treatment is prescribed and adhered to, prescribing ineffective treatment amounts to malpractice.

Unreliability of drugs. A potentially important cause of resistance is the unreliability of drugs. They may be out-of-date when sold, or even be diluted. A particular problem is the absorption of rifampicin when given in the same capsule with isoniazid, pyrazinamide, or both. Very careful pharmaceutical preparation is required and each batch should be tested for bioavailability (Acocella 1990). In at least one Asian country many of the preparations on the market are unreliable. WHO is aiming to organize regional laboratories to check for reliability.

Standardization of resistance testing. WHO is now attempting to achieve international standardization of resistance testing (Vareldzis et al 1994). Many years ago our group showed that any degree of resistance above the intrinsic variability of the method could be clinically significant (Stewart & Crofton 1964). Methods must therefore be sufficiently sensitive to identify such strains. The development of more rapid, reliable and cheap methods, including the use of molecular techniques, could be a major advance.

Treatment of patients with MDR. Treatment of patients infected with organisms exhibiting MDR, especially those resistant to all or most of the drugs used in shortcourse regimens recommended by WHO and IUATLD (WHO 1993b), is still very unsatisfactory. Overall the available reserve drugs are very expensive, relatively weak and have many side effects. The management of such patients needs much skill and care (Crofton 1987; Iseman 1993; Harkin & Harris 1996). Most poor countries should concentrate resources on effective treatment of new cases. This will prevent MDR. For wealthier countries, WHO will be recommending that the reserve drugs necessary for genuine MDR cases should only be made available to highly skilled special centres where they can be used to their optimum. WHO is preparing guidelines, but only for the use of such centres. Without new, effective and less toxic drugs the results are still likely to be far from satisfactory.

Longterm Possibilities

Development of new antituberculosis drugs

The advances in molecular biology proffer rational leads into the possibilities of new drugs. The aim should be for more effective, more long-acting (allowing intermittent treatment), less toxic, preferably oral and preferably cheaper drugs. For pharmaceutical companies, could not cheap drugs serving an enormous world market have some commercial attractions?

Molecular methods for diagnosis and resistance testing

We need simpler, cheaper and more reliable methods for use in the field.

Molecular methods for epidemiology

These are already in use for identifying strains in local epidemics, such as hospital infections, or for the identification of superinfection in HIV patients.

New vaccines for prevention and even for treatment

The *Mycobacterium vaccae* vaccine proposed for treatment is now, hopefully, being submitted to well-designed control trials in South Africa and London. We look forward to the results. Trials of any new prophylactic vaccine have to be more large-scale and long-term, with resultant delays in determining their value.

Conclusions

For many years we have known that good chemotherapy can cure almost all new cases of tuberculosis. We also know that mass treatment with good chemotherapy is the most effective preventive measure and this has proved highly successful in many richer countries. First IUATLD in the 1980s and then WHO in the 1990s have shown that these methods can be cost-effectively applied in the Third World.

From the mid-1980s the HIV epidemic has exploded in Africa and is now progressing rapidly in Asia and Latin America, resulting in a world crisis of combined HIV and TB. In some developing countries misuse of drugs, particularly by private or unqualified-doctors, has probably resulted in extensive MDR, though the scale has not yet been adequately measured. Misuse has also resulted in patches of MDR even in some prosperous countries. It is essential that well organized tuberculosis control programmes, including control of drug misuse, are established in all poor countries before MDR and HIV give rise to an untreatable epidemic which could spread worldwide.

There is need for extensive operational and basic research to devise, for mass use, the most effective joint antituberculosis and HIV programmes, better reserve drugs and new cheap diagnostic and epidemiological methods based on advances in molecular biology.

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