Clinical basics

Tuberculosis: 12. Global disease and the role of international collaboration

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The burden of tuberculosis (TB) today is greatest in low-income countries: over 90% of all cases arise there, and over 95% of deaths from the disease occur there;[1] moreover, a high and increasing proportion of cases in many industrialized countries occur in people who were born and became infected in low-income countries, before they moved to the country where their TB has been detected.[2] The horrendous impact of the HIV epidemic, including its pathophysiological, clinical and epidemiological interaction with TB,[3] has been most evident in sub-Saharan Africa (particularly eastern and southern Africa) and is rapidly becoming apparent in India and Thailand. Estimates of the global impact of TB indicate that TB is the most frequent cause of death in the world from a single agent in young adults[4] and that at least 20 million people have died unnecessarily of this disease in the past decade. These facts necessitate international collaboration in interventions to deal with TB. In this paper I present an overview of global interventions to eliminate TB, focusing in particular on the roles of scientific and technical experts, government agencies, and voluntary associations in these cooperative efforts.

The objective of intervention

To be effective, global action on TB must have clear objectives. Ultimately, the aim of any interventions should be elimination of the disease. Global elimination of an infectious disease has been achieved only once before, for smallpox, but there are divergent views as to whether this goal can be accomplished for TB.

The following characteristics facilitated the elimination of smallpox: an effective vaccination strategy, no natural reservoir outside humans and no carrier state for the virus. TB does not have these characteristics. Instead, the prevention strategy is based on case management, there are animal reservoirs of the bacteria and most infected people carry viable bacilli without symptoms.

On what grounds, then, can we hope that TB can be eliminated?

Models of intervention

A vaccine containing attenuated *Mycobacterium bovis*, developed by Calmette and Guérin[4] (the bacille Calmette–Guérin [BCG] vaccine) was tested in humans in 1921, and the results were promising.[5] After World War II, rigorous efficacy trials were undertaken,[6] a comprehensive program for administration of the vaccine was developed[7] and an extensive program of epidemiological research into the prevalence of TB disease and infection was launched.

Although the protective efficacy of BCG vaccination was demonstrated in many trials, its role in preventing TB infection was questioned.[8] Styblo and Meijer[8] argued, convincingly, that vaccination at birth was effective primarily in preventing TB in young children, who suffer from forms of disease (disseminated and primary types) that are not highly infectious and have little impact on the transmission of the infectious agent, *Mycobacterium tuberculosis*; in contrast, vaccination at birth has a negligible effect on transmission of TB in adults, who represent the bulk of highly infectious cases (those that are sputum smear positive). Vaccination at school-leaving age,[9] practised in Britain and in Norway, was developed to address this deficiency, but so far there has been no unequivocal demonstration of the effectiveness of this strategy in reducing transmission of *M. tuberculosis*.

The introduction of chemotherapy in the 1950s effectively curtailed the period

Review

Synthèse

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This article has been peer reviewed.

CMAJ 2000;162(1):57-61

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of infectivity of TB patients.[10] Moreover, it was determined that sputum-smear-positive patients were the most potent sources of transmission.[11,12] Consequently, the early detection and treatment of such patients became the objective of efforts aimed at controlling TB.[13]

The immediate positive impact of multidrug chemotherapy on TB in industrialized countries led to efforts to extend this success to low-income countries. The Tuberculosis Program was the first disease-specific program of the World Health Organization (WHO). Under its leadership, interventions and their priorities were defined through a comprehensive program of research arising out of the International Tuberculosis Campaign,[7] the community-based intervention in Kolin, Czech Republic,[14] and social and behavioural investigations undertaken in Bangalore, India.[15] Mathematical modelling[16] indicated that priority should be given to case-finding, rather than to treatment, in the case-management strategy.

Key points

- The aim of any global interventions against tuberculosis (TB) should be elimination of the disease.
- Although vaccination at birth prevents TB in young children, it has little effect on transmission of the disease in adults, who account for the bulk of the most infectious cases.

The logic of focusing on case-finding was as follows. It is possible to achieve at least modest success in the treatment of TB, even under difficult circumstances. If good success could be achieved in treatment (for example, 75%) but only a minority of cases could be identified (say, 15%), the reduction in the burden of infectious cases in the community would be 11.3%. On the other hand, if even limited success could be achieved in treatment (for example, 50%) but a high proportion of cases could be identified (say, 70%), the reduction in the burden of infectious cases would be much greater (35%). Such thinking led major figures in medicine and public health to advocate, for low-income countries, what was known even then to be suboptimal chemotherapy, since, with the emphasis on case-finding, the net effect was expected to be positive.[17]

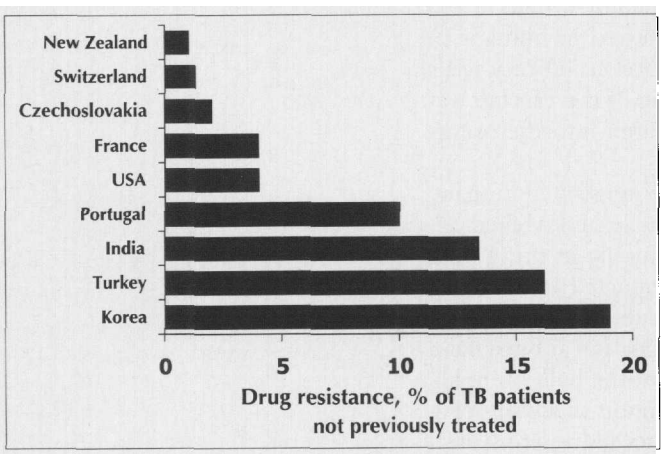

Fig. 1: Prevalence of initial resistance to isoniazid among patients with tuberculosis (TB) for various countries in 1975–1983.[18]

However, the negative impact of this policy became evident through the extent of drug resistance that it caused (Fig. 1).[18] There was also the problem of increasing levels of infection. In the early 1970s Grzybowski and Enarson[19] presented to the Tuberculosis Surveillance Research Unit (an independent research body in which the WHO and a number of member organizations participate) a damning critique of the Tuberculosis Program's approach. Our analysis showed the epidemiological harm of chemotherapy that prevented death while failing to cure infectious cases, a situation that led to an *increase* in the number of infectious people in the community. These observations had been made many years before, when chemotherapy was first introduced,[20,21] but had not been taken into account in previous exercises in setting the priorities of case management. Ultimately, the poor results led to the progressive reduction of the WHO Tuberculosis Program in the 1980s.

In 1978 a revision in the priorities of case management to emphasize success in treating sputum-smear-positive cases was implemented by Zhang and Kan in Beijing[22] and by Styblo in Tanzania;[23] after about 15 years of application, this approach was assessed by the World Bank and determined to have been highly successful.[24] This success led to the revitalization of the WHO Tuberculosis Program and to the declaration in 1993 of TB as a global emergency. The essential components of the new model of intervention for TB are encompassed by the term DOTS — directly observed therapy, short course — whereby the emphasis is on ensuring compliance with effective chemotherapy.[25] The components of the strategy, as developed by Styblo when he was Director of Scientific Activities of the International Union Against Tuberculosis and Lung Disease (IUATLD), included political commitment on the part of government, a secure supply of drugs and materials, a network of microscopy centres with quality control, and proper recording and reporting of cases. Additional requirements for the introduction of short-course chemotherapy included adequate supervision of drug taking during the initial intensive phase, proper training and supervision of NTP staff and step-wise introduction of short-course chemotherapy.[23] The DOTS approach was adopted as the main strategy of the WHO and has now been disseminated throughout the world.

Prospects of achieving the objective

The question remains, however, whether this approach to case management can eliminate TB.

Whether or not there is scientific evidence that the objective can be achieved, it could be argued that elimination should remain the goal, at least with regard to setting the scientific agenda.[26,27] Why? Only if the objective is set at elimination can the obstacles to achieving that objective be clearly identified, and it is the obstacles that establish the research agenda.

Prevention based on DOTS implies the efficient identification of the majority (the target is set at 70%) of the most potent sources of infection (sputum-smear-positive cases) and a high success rate (the target is set at 85%) in their treatment, which together should drastically reduce the probability of infection of new generations of the population. Elimination would be achieved if the targets could be met over a whole generation after transmission of *M. tuberculosis* had been virtually stopped (say, for over 5 decades).

Consider, then, the possible obstacles to meeting the objective of elimination:

- Can the number of smear-positive cases in a community be accurately determined (to evaluate whether the target has been achieved)?
- Can infection with *M. tuberculosis* be reliably measured?
- Can the strategy be efficiently maintained when cases become rare?
- Can infection be prevented even when the number of cases increases because of a decline in economic conditions, a reduction in the availability of health care services or the effects of the HIV epidemic?
- Can the final stage of elimination be hastened by reducing the reservoir of latent infection or by preventing reactivation?

Key points

- Initial efforts to control the disease in low-income countries focused on case-finding, but this strategy led to increases in drug resistance and in numbers of infectious cases.
- The focus of case management is now on successful treatment of sputum-smear positive cases, through DOTS — directly observed therapy, short course.
- The obstacles to eliminating the disease set the research agenda.

Because there is as yet no unequivocal answer to any of these questions, a comprehensive research program is needed. The results of the research will in turn bolster the advocacy campaign required to ensure political commitment to the strategy of elimination. These questions must be addressed if TB services are to be maintained in the increasingly competitive environment associated with dwindling economic resources in the health care sector.

It must be remembered that the elimination strategy cannot be carried out in isolation, in one country or one region of the world; to be successful, it must be implemented globally, and therefore international collaboration is a *sine qua non*.

The record of international collaboration

The spirit of international cooperation is wonderfully illustrated by a remarkable Canadian, the late Eddie O'Brien, who was founding Executive Secretary of the Ontario Tuberculosis Association (the forerunner of the Ontario Lung Association). In 1957 he began, at the request of the IUATLD a collaboration with Nepal and other Asian countries to promote health services for TB patients. From this initiative the Eastern Region of the IUATLD was established. In 1961 the Mutual Assistance Programme of the IUATLD was established, which ultimately led to the development of the DOTS strategy. The story of this remarkable man was recounted in an article in *The Mirror* of Jan. 17, 1973.

Role of scientific and technical experts

Understanding the pathogenesis and transmission of TB is essential to the development of effective interventions, and the rigorous evaluation of those interventions in turn establishes the basis for effective control. Scientific and technical experts are key to ensuring that the pathogenesis and transmission of the disease are elucidated and that the interventions are properly evaluated. However, when experts in the developed world have presumed to speak on behalf of researchers and clinicians in less developed countries in making recommendations for ways to eliminate TB, harmful effects have resulted. Clear examples are the use of isoniazid alone[28] and the emphasis on case-finding as a priority in control efforts.[13]

Nonetheless, in the model programs developed by the IUATLD (the international federation of national voluntary associations dealing with TB and lung diseases), marketed by the WHO as the DOTS strategy, a key element has been the support of technical experts in developing the strategy both locally and nationally. Rigorous implementation — in particular, the direct observation of the swallowing of medications when rifampin is given — has been a struggle in every location where it has been introduced. Technical advisors have been essential in this struggle.

In providing technical assistance to a large number of countries (22 of the poorest countries in the world in 1996/97) over a long period (since 1978), the IUATLD has gained extensive experience. From this experience it is clear that technical consulting is a professional activity, which implies formal training and qualifications, and that it is an occupation, rather than a hobby. The technical assistance consists of giving advice and direction to national governments, training those implementing and managing the DOTS strategy, and carrying out collaborative re-

search within the context of service provision, research that continuously evaluates and further develops the strategy. The entry criteria for training of such an expert include full qualification in a specialty of pulmonary medicine, infectious diseases or public health; clinical experience in the care of TB patients; and time spent in the provision of health care services in a low-income country. The training is thus similar in nature to postdoctoral work.

Role of government agencies

The development of a successful model of TB programs by the IUATLD was possible only through the support of various government agencies. Primary support came through regular, unlinked grants made directly by the Parliament of Norway through that country's Ministry of Foreign Affairs. These grants financed the scientific research necessary for developing the model. In addition, a contract with the Swiss Development Cooperation permitted the field activities that were undertaken in collaboration with the Tanzanian government and that led to the model program, which was later extended to other low-income countries.

Key points

- Development and dissemination of the DOTS strategy requires the support of various national government agencies.
- Voluntary associations constitute the basis for advocacy for TB programs.
- The Mutual Assistance Program allowed for the establishment of national voluntary associations in low-income countries.

Extension of the model to other countries has depended heavily on support from government development agencies and on loans from the World Bank. This engagement of the wider development community (bilateral and multilateral) has been particularly important for convincing governments of the priority that must be given to TB and has also been necessary to meet hard-currency requirements for supplies of medications and diagnostic materials.

Role of voluntary associations

The IUATLD is the oldest international nongovernmental organization dealing with health in the world, with origins that go back to 1867. Yet the idea of collaborating with low-income countries came from one individual, Eddy O'Brien. He was personally convinced of the importance of solidarity and collaboration and persuaded the IUATLD to embark on what became known as the Mutual Assistance Program. This program culminated in the model for TB control in low-income countries and the program of technical assistance, which, by the end of 1996, had provided quality care to more than a million TB patients in low-income countries. The initial phase of this program, which was financed in part by grants from Canada, consisted of supporting the development of national voluntary associations, particularly in Asia. Many of the original partners in the Mutual Assistance Program, such as the national voluntary associations in Nepal, Indonesia and Malaysia, are now leaders in the revised national TB programs.

Continued priority for TB and the broader issues of lung health will require vision and input from the nongovernmental sector, that is, the voluntary associations. If the volunteers are not well informed and committed to this struggle, politicians will not support the effort over the long term. Indeed, the voluntary associations must continue to play a ground-breaking role by supporting innovative responses to the problems, such as the activities of the British Columbia Lung Association in the initial application of DOTS for patients in urban slums. In fact, I started my career as the first postgraduate fellow of the BC Lung Association. My fellowship consisted of 18 months of research training at the University of British Columbia, in which I participated in a review of the TB situation and control activities in Canada in 1970–1974. This work was funded by the Muskoka Memorial Foundation, National Sanatorium Association, and formed the basis of most of my early publications. The final stages of the fight to gain an infection-free generation must be led by the voluntary sector, as no government is likely to commit itself to such a task without pressure and vision from the private sector.[27]

Personal collaborators of mine involved in patient organizations in Norway have clearly pointed out that efficient and effective care for TB patients is more than simply a technical exercise, it is also a basic human right. It is the right of a patient to have access to the best care available when that care is so clearly within the economic grasp of even the poorest government. Conversely, many people who claim to speak on behalf of those who suffer from TB point out, for example, that services such as DOTS may infringe patients' rights. It is interesting, therefore, that where resources are most limited and DOTS is offered, a patient will invariably choose DOTS rather than another method of treatment. When I asked a TB patient why he came daily for treatment to the local clinic on the Red Sea in Sudan, he replied, "Because it is the best treatment."

TB is one of the most stigmatized of diseases, and patients often come from the most disenfranchized sectors of the community. Thus, others, such as technical and professional experts or international bodies such as WHO and IUATLD, often propose to speak on behalf of this patient group. Yet patients must be encouraged to speak for themselves and to stand together in solidarity to obtain the care that is their right. In some coutnries, most notably the Nordic countries, organizations of patients themselves address the issues relevant to them. The Norwegian Health

and Lung Association (an organization with over 50 000 members who are heart or lung patients) has engaged itself in encouraging and cooperating in the establishment of such an organization in Namibia.

Toward self-sufficiency in the fight against TB

TB services have been evaluated as among the most cost-effective of any health care intervention in low-income countries, and the World Bank has concluded, on the basis of economic evaluations, that governments that spend money on TB services can expect a positive return on this investment.[24] The World Bank has therefore encouraged some governments to borrow money to provide TB services.[28] Many other countries have obtained donor assistance for provision of TB services.

However, it is unlikely that such assistance will be available over a period of decades, especially when TB is no longer "fashionable."[29] Therefore, the dignity of self-sufficiency for TB services must be a primary objective. Arguments for self-sufficiency already exist (such as those of the World Bank, mentioned above). Nevertheless, the continuing need for hard currency to pay primarily for medications and diagnostic supplies is a key obstacle to maintaining TB services over the long term.

In the collaborative programs of the IUATLD, 60% of the cost of services is borne by local governments; of the funds obtained from external sources (donors), 60% goes toward medications. Since the evaluation of the World Bank,[24] the cost of these medications has been substantially reduced through open tendering and competitive bidding procedures. In 1990 the cost of the cheapest 8-month rifampin-containing regimen was US$45. By 1996 the cost had been reduced to US$13 for the same medications. The determination of the efficacy of an intermittent initial intensive phase of this regimen will further reduce these costs to approximately US$8 (estimated in 1995). This cost is within the reach of any government and even any patient. In addition, the argument for the economic priority of TB programs is further enhanced by the reduction in the costs of medication and should make support for TB programs the highest priority for any ministry of finance; because of this reduction in costs, the previously cost-effective programs will become 25% more efficient. The use of the infrastructure of TB services to deliver other lung health services (or other health care services in general) would also make these services more efficient and should lead to self-sufficiency. Only with self-sufficiency and the political advocacy applied by the nongovernmental sector will the fight against TB be sustainable over the decades it will take to achieve elimination of the disease.

In the face of this record, it is fascinating to note that, although the volume of work at the IUATLD has dramatically increased, the support from the voluntary sector in constant dollars has actually diminished. I wonder what Eddy O'Brien would have said to that.

Competing interests: None declared.

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