The tuberculosis pandemic: implications for health in the tropics

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Abstract

Among infectious diseases, tuberculosis is the leading cause of death, killing around 3 million people each year. Most cases occur in young adults but it is also a major cause of illness and death in children. The problem has been exacerbated in recent years by the HIV pandemic and by the emergence of multidrug resistance. Co-infection with HIV greatly enhances the risk of overt tuberculosis and in 1999 it is expected that tuberculosis will account for 30% of the predicted 2.5 million AIDS-related deaths. By inducing clinically and radiologically atypical forms of tuberculosis, and by increasing pressure on diagnostic facilities by sheer numbers, serious diagnostic difficulties are increasingly occurring in both adults and children in the tropics. At the present time, 2% of all cases of tuberculosis are multidrug resistant but, as the treatment of such cases is often grossly inadequate in many tropical countries, their frequency will doubtless grow. There are no simple solutions to the global emergency of tuberculosis: clearly there is a need for better use of available control measures but there is also a need to reach a much clearer understanding of the underlying immune phenomena in this disease so as to develop more effective vaccines and therapeutic agents. Finally, it cannot be ignored that tuberculosis is a disease of poverty—95% of cases and 98% of deaths due to it occur in the developing nations—and thus a major control measure is a resolution of the gross inequities in health care provision both between and within nations.

Keywords: tuberculosis, HIV, multidrug resistance, immunity, diagnosis, poverty, globalization

Introduction

The 17th century English evangelist John Bunyan termed tuberculosis ‘the Captain of all these Men of Death’ and today, despite the availability of effective therapy, this epithet is still appropriate in many parts of the world. The reason is that this disease is now out of control in most developing countries and 2 serious problems adding to the emergency have arisen in recent years: the human immunodeficiency virus (HIV) pandemic and multidrug-resistant tuberculosis. So threatening is the situation that, in 1993, the World Health Organization took the unprecedented step of declaring tuberculosis a global emergency (WHO, 1994). Since then, the incidence has continued to rise and urgent and concerted action is thus required to avert a tragedy on an unprecedented scale early in the new millennium.

The global burden of tuberculosis

Human tuberculosis is caused by members of the Mycobacterium tuberculosis complex, principally M. tuberculosis (and the closely related M. africanum in some parts of Africa) but disease due to M. bovis (the bovine tubercle bacillus) occurs in some countries where cattle tuberculosis has not been eliminated. Infection usually occurs by inhaling small droplets of cough aerosol, about 5 μm in diameter, containing tubercle bacilli. Infection by M. bovis is also acquired by drinking infected milk, leading to primary lesions in the pharynx or intestine.

A third of the human population, i.e., about 2000 million persons, have been infected by M. tuberculosis (WHO, 1988) and are at risk of developing the disease later in life. The number actually developing disease each year is over 7 million (Figure). Each year, around 3 million people die of tuberculosis, mostly young adults in developing countries, and it is an important cause of morbidity and mortality among children (CHINTU & ZUMLA, 1997). Being a chronic disease, with less than a quarter of patients receiving adequate therapy, there may be as many as 20 million active cases at any given time. About half of these have transmissible forms of the disease and infect at least 100 million people each year. Tuberculosis is a disease of poverty: 95% of cases and 98% of deaths due to it occur in the developing nations.

Factors affecting susceptibility to tuberculosis

The concept of racial or 'innate' immunity is controversial. Tuberculosis was rampant in Europe in the last century and its relative rarity nowadays may, the impact of improved housing and nutrition notwithstanding, reflect a well-adapted co-existence in contrast to Africa where exposure is comparatively more recent. Any cause of immunosuppression predisposes to the development of tuberculosis while, in addition to BCG vaccination, varying levels of protection have been attributed to natural exposure to mycobacteria in the environment (MHE, 1995).

There are differences in susceptibility to tuberculosis, and in the type of disease that develops, in children of different ages (DONALD et al., 1999). Those aged under 5 years are susceptible but they develop consolidation and pneumonia without cavitation or caseous necrosis. Between the ages of 5 and 10 years (i.e., during adrenarche) children appear to be resistant to the disease despite continuing exposure demonstrated by an increasing incidence of tuberculin-test positivity. This age-range was thus known as the 'safe school age' in 19th century Europe, and the phenomenon is now seen in high incidence areas such as Cape Town. Finally, susceptibility returns at puberty, with the disease resembling that seen in adults, with cavitation and necrosis.

These changes suggest an underlying endocrinological cause, and hypotheses as to how endocrine factors may affect immune responses have been developed (ROOK et al., 1997).

HIV/AIDS pandemic and its effects on tuberculosis control

Over the past decade, infection by HIV has emerged as by far the most important of the factors known to increase the risk of an infected person developing tuberculosis (WHO, 1996). While non-immunocompromised people who overcome the primary infection have about a 5% chance of developing post-primary tuberculosis later in
life, the chance rises to 50% in the HIV-positive person. As those infected with HIV have a shortened life expectancy, the annual risk of developing tuberculosis is around 8%—over 20 times higher than in HIV-negative persons infected by the tubercle bacillus (DOLIN et al., 1994).

An HIV-infected person may also be infected or reinfected by exposure to a tuberculosis source case. The risk of developing tuberculosis is then very high and progression to clinically active disease is 'telescoped' down to a few months rather than years. As a result, there have been a number of explosive mini-epidemics—a phenomenon that originally indicated the seriousness of the impact of HIV infection on the epidemiology of tuberculosis. In 1998, there were an estimated 33 million HIV-positive persons worldwide (UNAIDS, 1998). Assuming that one-third are co-infected with tuberculosis bacilli and thus have an 8% annual chance of developing tuberculosis, an additional million cases of this disease are expected in 1999, with 70% occurring in sub-Saharan Africa. Tuberculosis is expected to account for 30% of the predicted 2.5 million AIDS-related deaths in 1999 (UNAIDS, 1998), with the major impact being felt in sub-Saharan Africa. In 1994, autopsy studies showed that, in Africa, 38% of all HIV-positive cadavers and 43–54% of those dying with AIDS-defining conditions had active tuberculosis (LUCAS & NELSON, 1994). The frequency is now certainly higher and HIV-related tuberculosis is therefore having a devastating effect on health services and societal structure in this continent. In Zambia, 1 in 4 pregnant women are infected with HIV (FYLKESENES et al., 1997) and tuberculosis is now one of the top non-obstetric causes of maternal death.

Understanding immune responses in tuberculosis
An understanding of the immune responses and mechanisms of protection in tuberculosis is essential for the development of novel vaccines and immunotherapeutic strategies but, despite extensive and elaborate research programmes, progress has been slow.

The immune response to initial infection with M. tuberculosis restricts its replication and spread in most cases but dissemination of bacilli via lymphatics and the bloodstream may lead to foci of disease elsewhere in the body. Many factors, including disturbances of non-specific and specific host immune responses, determine whether the initial lesions resolve or progress to overt primary tuberculosis. Both non-specific and specific effector mechanisms appear to play a role in immunity to tuberculosis.

There is evidence that the outcome of tuberculosis is closely related to the balance between Th1 and Th2 lymphocyte responses, with protective immunity being Th1-mediated and a superimposed Th2 response being harmful (NEWPORT et al., 1996; ROOK & HERNANDEZ-PANDO, 1996; COOPER et al., 1997).

Most mycobacteria are probably killed by macrophages activated by cytokines such as interferon gamma (IFNy) produced by Th1 lymphocytes, although the actual killing mechanism in humans is not known. Whatever the mechanism, a key feature of the immune response against M. tuberculosis is the formation of granulomas which are dynamic structures characterized by the accumulation of activated macrophages and infiltration by T lymphocytes. Though primarily restricting the spread of the infection, granuloma formation can also contribute to destruction of surrounding normal tissues. The morphological features of granulomas and the extent of their formation vary considerably and a wide spectrum of reactions is seen in tuberculosis (RIDLEY & RIDLEY, 1986). At one end of this spectrum, immunocompromised individuals show poor granulomatous responses but instead show extensive necrotic lesions containing large numbers of mycobacteria. At the other extreme, immunocompetent patients with indolent paucibacillary forms of tuberculosis, such as lupus vulgaris, display florid non-caseating granulomas containing few mycobacteria.

The characteristic feature of active tuberculosis is tissue necrosis but the underlying mechanism, and its relation to protective immunity, has been the topic of much debate since it was first documented by Robert Koch in the 1890s (Koch, 1891). There is evidence that such necrosis is associated with tumour necrosis factor (TNFa), a cytokine produced during the immune response to tuberculosis. According to one hypothesis, too much TNFa causes tissue damage as well as symptoms of tuberculosis, such as fever and weight loss (KAPLAN, 1994). Alternatively, TNFa may become damaging, not because it is in excess but because a Type 2 component to

Figure. The estimated incidence of new cases of tuberculosis in the World Health Organization regions in 1998. Data from WHO (1998).
the immune reaction renders tissues highly susceptible to killing by TNF-α, thereby leading to extensive necrosis instead of protective granuloma formation (ROOK & HERNANDEZ-PANDO, 1996). This might explain why, as mentioned above, protective immunity to tuberculosis requires a Type 1 response but the addition of a Type 2 response opposes protection.

The complex series of interactions between mycobacteria, immunocompetent cells and their secreted cytokines and, possibly, endocrine effects underlies the variety of presentations of tuberculosis seen in clinical practice. The pathogenesis of tuberculosis should be viewed as an interplay between the activation of T cells, immunocompetent cells and their secreted cytokines and, possibly, endocrine effects. The pathogenesis of tuberculosis should be viewed as an interplay between the macrophage-activating Th1 protective immune response and the mechanisms that lead to tissue damage. Despite an enormous literature on the subject, neither the processes nor the relationship between them are yet fully understood.

**Interactions between tuberculosis and HIV infection**

It is recognized that HIV infection increases the chance of developing tuberculosis and modifies its clinical course. Conversely, development of tuberculosis in co-infected persons accelerates progression to full-blown AIDS and enhances HIV replication leading to marked increases in plasma viral loads. A likely mechanism is the activation of latently HIV-infected cells, with virus expression and replication, by cytokines produced in response to infection with *M. tuberculosis* (GOLETTI et al., 1998).

In general, HIV-positive patients with relatively intact immunity develop typical cavitating granulomas and tissue necrosis leading to cavity formation. In the more profoundly immunosuppressed, both these tissue reactions are suppressed so that diffuse infiltrations teeming with acid-fast bacilli are seen and dissemination to other organs is common.

**Clinical features of tuberculosis in the era of HIV**

The diagnosis of tuberculosis still depends on a high index of suspicion and broad knowledge of its clinical features, but co-infection with HIV can have a profound effect on the clinical presentation, as well as the course, of the disease (CHINTU & ZUMLA, 1997). Atypical presentations are more likely in the more profoundly immunosuppressed and include a higher proportion of extrapulmonary disease such as miliary tuberculosis, lesions affecting the lymph nodes, bone and skin and disseminated disease. Chest radiographs are frequently atypical (SANS & POSNER, 1992), the tuberculin skin test is often negative and there is a lower frequency of sputum-smear positivity. The incidences of adverse reactions to anti-tuberculosis drugs, mortality and relapse are also increased. The clinical differences in children between HIV-positive and HIV-negative cases are, however, not as striking as in adults.

**Changing pattern of tuberculosis in HIV-infected children**

There is a lack of reliable clinical criteria for the specific diagnosis of respiratory infections in children, and the changing clinical patterns of respiratory illnesses in children consequent to the HIV pandemic have made the accurate diagnosis of tuberculosis and assessing the prevalence of the disease even more difficult (CHINTU & ZUMLA, 1997; DONALD et al., 1999).

In Zambia and West Africa a high proportion of children presenting at clinics and hospitals have respiratory illnesses which are not easily diagnosed as their signs and symptoms are similar (LUO et al., 1994; SASSAN-MOROKRO et al., 1994; LUCAS et al., 1996; VETTER et al., 1996). The problem is exacerbated in HIV-infected children as several opportunistic infections, such as *Pneumocystis carinii* pneumonia, have clinical and radiological features in common with tuberculosis (TUMBA et al., 1997). Diagnostic difficulties notwithstanding, there is substantial evidence for an increasing prevalence of HIV-related tuberculosis in children in several developing countries (MUGANGA et al., 1991; LUO et al., 1994; SASSAN-MOROKRO et al., 1994; VETTER et al., 1996). In Zambia, the incidence of HIV positivity among children admitted to hospital with tuberculosis rose from 18% to 67% over an 8-year period, compared to a steady rate of about 10% in children admitted for various surgical conditions (CHINTU & ZUMLA, 1997).
Drug-resistant tuberculosis

Resistance to antituberculosis drugs may either be the consequence of the selective growth of drug-resistant mutants (secondary or acquired resistance) or due to infection by a bacillus that is already resistant to one or more drugs (initial or primary resistance). Acquired resistance develops when therapy is suboptimal due to avoidable factors such as intermittent drug supplies, poor quality drugs or combination preparations, poor prescribing practices, unsupervised therapy and unregulated sale of drugs. Primary resistance occurs when transmission of disease from resistant source cases is poorly controlled.

By generally accepted definition, multidrug resistance is resistance to the principal first-line drugs, isoniazid and rifampicin, with or without resistance to other drugs (Kochi et al., 1993). The detection of drug resistance requires good laboratory facilities, a high standard of training and regular quality control (Collins et al., 1997). Thus, documentation on resistance in many developing countries is limited and sporadic. Nevertheless, a global survey has been completed and shows that, with very marked regional variation, around 10% of all isolates show some resistance and 2% are multidrug resistant. For full details see the report by WHO (1997).

Operational aspects of tuberculosis control

The aims of tuberculosis control programmes are 3-fold: to cure the patient, to reduce transmission and to prevent the emergence of drug resistance. The usual strategy is to treat those found to be smear-positive on sputum microscopy, and therefore the most infectious. Based on model control programmes, designed by the International Union Against Tuberculosis and Lung Disease on principles established by the British Medical Research Council, the WHO has promulgated a 5-point DOTS (directly observed therapy, short course) strategy (Kochi, 1997):

- **Government commitment to a national tuberculosis programme**.
- **Case detection by sputum-smear microscopy for pulmonary tuberculosis suspects**.
- **A regular, uninterrupted supply of anti-tuberculosis drugs**.
- **A monitoring system for programme evaluation**.
- **Short-course chemotherapy for all smear-positive pulmonary tuberculosis cases, under direct observation for, at least, the initial phase of treatment**.

Evaluations of this strategy in Vietnam and China indicate that it reduces the incidence of tuberculosis in a community (Jochem & Walley, 1999). In contrast, a recent study in Botswana, a country where HIV infection is common, showed a climbing incidence of tuberculosis despite extensive implementation of the DOTS strategy and a low incidence of drug resistance (Kenyony et al., 1999). We should therefore be cautious about the claim that it is the 'medical breakthrough of the 1990s' (Kochi, 1997).

The principles of the WHO DOTS strategy are not contentious. Difficulties are, however, as outlined above, encountered in maintaining the quality of sputum microscopy as a case-detection strategy and also in ensuring access to care, especially for those most disadvantaged: women, the young, the poor and those who are geographically, culturally, economically and racially isolated. In addition, the DOTS strategy directs chemotherapy at patients with smear-positive pulmonary disease, leaving little guidance on how to identify and manage smear-negative and extrapulmonary cases. Although less important than smear positives as sources of infection, transmission from smear-negatives cannot be ignored (Behr et al., 1999). Unless we increase access to chemotherapy we are unlikely to control transmission. The question is how to do this without compromising programme outcomes.

The fifth element, from which the name of the strategy is derived, has come under criticism for not addressing local societal issues such as perception of disease and its treatment, stigma and the disruptive impact of regular supervision on everyday life and work. Thus there is a strong case for modifying this element of the strategy in the light of local studies by social scientists and anthropologists (Ogden, 1999).

An additional controversial issue is whether government support for tuberculosis control should be based on decentralized 'vertical' national programmes or should be part of decentralized, 'horizontal', public health services. This has led to considerable tension as donor agencies favour the centralized approach with direct accountability to a nominated director while the 'neo-liberal' philosophies espoused by the World Bank favour decentralization and privatization of health facilities. While this argument continues, the poor and powerless-amongst whom tuberculosis flourishes—are increasingly denied access to even the most rudimentary health care in many regions (Chaullet, 1998).

Finally, under short-course therapy fails to address the issue of multidrug-resistant tuberculosis and may even magnify the problem by inducing resistance to the other drugs in the regimen. Accordingly, a 'DOTS-plus' strategy, involving the prescription of empirical or laboratory-guided regimens suitable for treating such resistance, has been advocated (Farmer & Kim, 1998). Unfortunately, multidrug-resistant tuberculosis requires prolonged and directly observed treatment with a range of second-line drugs and the cost of such treatment in terms of drugs and supportive services is much higher than standard therapy, which already places a high financial burden on the overstretched health services of many countries.

The future

The incidence of tuberculosis is rising in the developing and the developed world and will continue to do so until there is a radical change in the global approach to this disease. Such a change could be brought about by advances in immunology and molecular biology, particularly the recent sequencing of the entire genome of M. tuberculosis (Cole & Barrell, 1998), which raise hopes for the development of novel vaccines, diagnostic tests and 'designer drugs'.

But we do not know when, or even if, these hopes will be translated into reality. In the meantime, fuelled by the HIV pandemic and the continuing suboptimal control efforts, the entire world could be faced with a massive epidemic of tuberculosis, including many multidrug-resistant cases, and the cost of combating it could run into billions of pounds.

While every effort must be made to strengthen and support national and international tuberculosis control efforts, slavish adherence to all elements of the WHO control strategy is not the answer in the short-to-medium term. We need, urgently, to make room for creative innovation in service delivery for patients with tuberculosis.

Finally, it must never be forgotten that this disease has always been, and still is, associated with poverty and deprivation. Thus, the eventual eradication of this ancient scourge will only come hand in hand with the creation of a caring global society and the ending of the present gross inequity that scandalizes the human race (Zumla & Grange, 1998).

References
