

The Growing Menace of Drug-Resistant Tuberculosis

The problem of treatment failure due to the emergence of drug resistance became apparent soon after the introduction of anti-tuberculosis chemotherapy and led to the universal advocacy of multidrug regimens. Unfortunately, sub-optimal use of the available drugs has led to the widespread emergence of strains resistant to one or more of the first-line anti-tuberculosis drugs and, in some cases, to many of the second-line drugs as well. After the resurgence of tuberculosis caused by the HIV/AIDS pandemic, the world is now faced with the 'third epidemic' of drug- and multidrug-resistant disease (Neville *et al.*, 1994).

There are two forms of drug resistance — acquired and primary (or initial). Acquired resistance occurs as a result of sub-optimal drug regimens which permit the selective growth of drug-resistant mutants. Primary resistance is the result of infection by a tubercle bacillus already resistant to one or more drugs. These two forms of resistance have different epidemiological significances. A high incidence of acquired resistance indicates that drug regimens or supervision of therapy are at fault while the occurrence of primary resistance indicates that control of transmission of disease in the community is inadequate. Sequential selections of mutants results in the development of resistance to several drugs. Multidrug resistance (MDR) is defined by the WHO as resistance to the principal first-line drugs, isoniazid and rifampicin, with or without resistance to other drugs (Kochi *et al.*, 1993).

There are many reasons, almost all avoidable, for the development of drug resistance. These include intermittent drug supplies, unavailability of combination preparations, poorly-formulated combination preparations, use of time-expired drugs, inappropriate prescribing, poor supervision of therapy and unregulated over-the-counter sale of drugs. In respect to the latter, cough mixtures containing isoniazid are readily available without prescription in some countries. A common iatrogenic cause of drug resistance is the addition of a single drug to a failing regimen in the absence of bacteriological control. It is usually assumed that drug resistance does not develop if the patient receives

combination preparations of drugs, but Mitchison (1998) has described cases, and explanations, of multidrug resistance arising in patients who take such preparations irregularly and intermittently.

The determination of drug resistance is not easy as it requires laboratories able to isolate the tubercle bacillus and to perform the somewhat lengthy test procedures with good quality control (Vareldzis *et al.*, 1994; Collins *et al.*, 1997). Even in the best equipped centres, errors are not uncommon and may only become apparent if laboratory reports and clinical data are considered together (Nitta *et al.*, 1996). In addition, there are a variety of methods for drug susceptibility testing and there has been a lack of standardisation. For these reasons, information on the incidence of drug resistance worldwide is poorly documented. While the majority of clinical isolates in industrialised countries such as the USA and the UK are subjected to drug susceptibility testing by reliable procedures, surveys in many countries have been based on the testing of small and probably unrepresentative samples. This is evident from a comprehensive review of the world literature of drug resistance surveys carried out between 1985 and 1994 inclusive (Cohn *et al.*, 1997). In view of these problems, the WHO, in cooperation with the International Union Against Tuberculosis and Lung Disease, has established an extensive project on the global surveillance of drug resistance. This has involved the preparation of guidelines for standardised surveillance techniques and the establishment of a network of supra-national reference laboratories to coordinate surveillance and to provide technical aid (World Health Organization, 1994b, 1997b; Drobniewski *et al.*, 1997).

Estimates of the magnitude of the future problem of drug resistance and the cost of managing it are rendered very difficult by the lack of firm epidemiological data on the present incidence. Thus, an analysis of the available data gives a very broad range of possible scenarios. In sub-Saharan Africa, for example, the incidence of multidrug resistance per 100,000 of the population in the year 2000 could range from 2.3 to 32 (Carpels *et al.*, 1995). The latter figure, which is not improbable, implies that there could be as many as 250,000 cases in this region in the year 2000.

Multidrug resistance is not restricted to the developing nations only. A number of well-documented epidemics have occurred in New York City and other parts of the USA (Morse, 1994). Although the blame was laid on the HIV/AIDS pandemic, as over 40% of tuberculosis patients in New York City were HIV positive, this pandemic merely served to accelerate the spread of drug resistance generated by other factors. Thus, the incidence of drug-resistant tuberculosis had been rising in the USA before the occurrence of the HIV-related epidemics: the incidence of initial isoniazid resistance increased from less than 2% in 1968 to 9% in 1991, and rifampicin resistance increased from less than 1% in the period 1982–1986 to 4% in 1991. Almost a fifth of cases of tuberculosis in New York City were caused by multidrug-resistant bacilli in 1991, and 5% of patients were infected with bacilli resistant to six or seven drugs. Fortunately, the problem is a relatively localised one: more than 60% of all cases of multidrug-resistant tuberculosis occurring in the USA in 1994 were reported from New York City.

The cost of treating patients with multidrug-resistant tuberculosis in the USA is very high, sometimes exceeding \$250,000, compared to \$2,000 for treating a patient with the drug-susceptible disease. Even with very well-supervised therapy and good supportive care, the mortality is high. In some reports up to 45% of HIV-negative, and 85% of HIV-positive, patients die within two years of diagnosis. The prognosis for the patients, most of whom are HIV positive, with disease due to bacilli resistant to six or seven drugs is much worse: about half die within one month of diagnosis. On the other hand, early diagnosis of multidrug-resistant tuberculosis and treatment with at least two drugs to which the organism is susceptible has been reported to prolong life and improve the cure rate, even in severely immunosuppressed HIV-positive persons (Turett *et al.*, 1995).

As mentioned above, HIV infection is not *per se* a predisposing factor for the generation of multidrug resistance. The association between such resistance and HIV positivity, as has occurred in New York (Gordin *et al.*, 1996) and Ethiopia (Mitike, 1997), is probably coincidental. If multidrug-resistant tuberculosis enters a community in which many

HIV-positive persons are crowded together, e.g. in hospitals, prisons or common lodging facilities, then an epidemic of overt multidrug-resistant disease can rapidly develop. No such association is found in other countries such as South Africa (Anastasis *et al.*, 1997) and Burkina Faso (Ledru *et al.*, 1996).

The prevalence of drug resistance often varies considerably in different communities within a country. The example of the USA has been discussed above. Ethnic minority communities, originating in countries where drug resistance is common, often have higher levels of drug resistance than the indigenous populations. An example from South-East England is shown in Table 7 (Grange and Yates, 1993).

Table 7. Prevalence of tuberculosis due to drug-resistant strains of *M. tuberculosis* in South-East England, 1984–1991. Data from Grange and Yates (1993).

Type of resistance	Ethnic origin of patients		
	European (<i>n</i> = 4594)	Indian subcontinent (<i>n</i> = 4099)	Others (<i>n</i> = 625)
1. Drug			
Isoniazid	60	119	16
Streptomycin	30	72	21
Pyrazinamide	15	12	2
Rifampicin	3	5	1
Ethambutol	1	–	–
2. Drugs			
Isoniazid + Streptomycin	16	83	22
Isoniazid + Rifampicin	4	4	4
Others	1	7	–
3. Drugs	1	28	1
4. Drugs	1	14	5
5. Drugs	1	3	1
6. Drugs	–	1	–
Total (percent) resistant	133 (2.9)	348 (8.5)	73* (11.7)

*35 African, 31 from the Far East and 7 others.

There is evidence that the incidence of drug-resistant tuberculosis in a community can be reduced by rigorous application of disease control

measures. Thus, the incidence of initial single drug resistance declined from over 30% in 1980 to 15% in 1990 in South Korea and from 15% in 1981 to 6.3% in 1985 in Algeria (Vareldzis *et al.*, 1994). The impact of control measures on the incidence of multidrug resistance remains to be determined.

Bovine Tuberculosis and Implications for Human Health

It is generally forgotten nowadays that one of the most effective control measures ever undertaken for any bacterial disease was the virtual eradication of cattle tuberculosis in most developed countries (Moda *et al.*, 1996). Indeed, human tuberculosis caused by *M. bovis* (the bovine tubercle bacillus) in countries where such control measures have been applied successfully is extremely rare. In South-East England, *M. bovis* is responsible for less than 1% of all bacteriologically-confirmed cases of tuberculosis. Almost all patients were born before 1960, the year in which the bovine tuberculosis eradication programme was completed, and developed the disease as a result of late endogenous reactivation (Grange and Yates, 1994). The situation in the USA and most other European countries is very similar. There have been a few reports of human-to-cattle transmission of tuberculosis caused by *M. bovis* in Europe and there is limited and anecdotal evidence for human-to-human transmission but, as a general rule, this disease poses a minor and diminishing health problem in the developed world. Of more concern is the infection of cattle from wildlife reservoirs such as the badger in the UK and Ireland and the opossum in New Zealand (O'Reilly and Daborn, 1995). There have, however, been a few reports of the occurrence of tuberculosis due to *M. bovis* in younger HIV-infected persons, including a small but explosive epidemic of cases due to exposure to a source case in a hospital (Bouvet *et al.*, 1993).

Data on the incidence of cattle tuberculosis in countries in which little or no attempt to control the disease has been made are limited, although the disease is known to exist in 94 of 136 tropical countries