Antituberculosis drug resistance: new global data on an emerging global emergency

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Rates of tuberculosis (TB) infection in the UK have been increasing since the mid-1990s after a century of decline. Previously, the majority of cases were in older UK-born individuals, and mainly resulted from reactivation of latent disease. More recently, however, we are seeing an increasing proportion of cases in individuals born outside the UK, and particularly in recent entrants from countries with high TB incidence, for example sub-Saharan Africa. Over two thirds of notified cases in the UK now occur in foreign-born individuals.[1] This change has led to the publication of a number of Department of Health documents, such as the TB action plan,[2] National Institute for Health and Clinical Excellence (NICE) guidelines on the management of TB,[3] and a TB toolkit for commissioning TB services.[4]

Historically, most TB in the UK has been fully sensitive to standard therapy, with low and stable rates of resistance to single drugs (7.9% prevalence of resistance to any antituberculous drug in 2006), the main drugs affected being isoniazid and streptomycin. Multidrug resistance (MDR), that is resistance to both isoniazid and rifampicin, is much rarer (1.2% of cases in 2006), and again stable over a number of years.[5] However, with increasing numbers of cases imported from resistance hot spots around the world, for example the Baltic states, parts of China, and Southern Africa,[6] comes the real possibility that rates of drug resistance in the UK will also increase. Not only will this bring huge additional costs (treating a case of MDR-TB costs around 10 times as much as a drug-sensitive case[3]), but also major challenges relating to infection control and the management of contacts of these cases.

The issue has become topical with the February 2008 publication of the fourth report on global antituberculous drug resistance by the World Health Organization (WHO), based on data collected between 2002 and 2006 on 91,577 TB patients in 81 countries.[7] There appears to have been a significant increase globally in drug resistance in general, and MDR-TB in particular: around 5% of the estimated nine million cases of TB annually throughout the world are MDR, which equates to around half a million cases per year. MDR rates vary enormously, the highest rate being reported from Azerbaijan, where 22.3% of new cases are MDR, compared to 14.2% in 2004. Other areas of high resistance include most of the former Soviet Union countries, and several regions of China. The prevalence of drug resistance is higher in patients who have previously been treated for TB: in Uzbekistan and Azerbaijan up to 60% of cases of TB in individuals who have had prior TB treatment are MDR, an astonishingly high level of resistance with major implications for management of individual cases and national TB control. India, the origin of much TB imported into the UK, reported a prevalence of MDR-TB of 5% overall and 17.2% in previously treated cases.

Trend data were presented for a number of countries and several patterns emerged. Most countries of West or Central Europe have stable rates of resistance, and the USA reported a decline in TB notifications and rates of MDR-TB. Most TB in the USA has in the past been 'home-grown', as previously in the UK, and with increasing immigration, this pattern is likely to change. MDR-TB rates are stabilising in Latvia and Estonia, two areas with previously high rates where there has been huge effort to bring this problem under control. However rates are continuing to increase in many parts of Russia and China. It is recognised that this survey does not cover some key areas: only six African countries provided data, which reflects the widespread lack of mycobacterial culture facilities available. Since Africa has the highest incidence of TB in the world, this is an important omission. The information that has been available has suggested low rates of drug resistance in Africa in the past, but this is clearly increasing, particularly in Southern Africa.

In addition to the rise in MDR-TB, there has been increasing concern about the global emergence of extensively drug-resistant TB (XDR-TB).[7,8] These strains are not only resistant to rifampicin and isoniazid, but also demonstrate extensive resistance to second-line antituberculous drugs. XDR-TB has now been reported from 45 countries worldwide, although it is likely to be much more widespread because many countries do not have the facilities to detect it routinely. The major impact appears to be on resource-limited countries with high HIV prevalence, where alarmingly high and rapid mortality has been reported.[9] XDR strains have been reported to cause major nosocomial outbreaks, again a particular issue where infection control facilities and

practices may be limited, and where patients are particularly susceptible to primary progressive disease, for example where there is co-infection with HIV.

In recognition of this new challenge the WHO has set up a global task force on XDR-TB. Key areas for action include the expansion of laboratory facilities for mycobacterial culture and sensitivity, which will aid detection/management of individual cases and the collection of epidemiological data; action to strengthen TB control programmes to increase treatment completion rates; increased availability of second-line antituberculous agents; and strategies to reduce transmission, particularly in healthcare settings. Recent advances in the field of TB may in the future provide weapons with which to fight XDR strains, for example rapid testing for drug resistance, interferon-gamma release assays for earlier detection of active/latent disease, and strain typing methods to confirm outbreaks at an earlier stage and thus facilitate more rapid control. However, on a global level, these expensive and often technically challenging techniques are unlikely to be available in the areas that need them most for some considerable time. More immediate advances may be made through the development of new antituberculous drugs,[10] and/or an effective TB vaccine: a number of vaccine candidates are in development including MVA85A, which is currently undergoing phase 2 clinical trials.[11]

In the UK, this degree of resistance is, as yet, unusual. However, the massive expense and logistical burden of treating such patients, and their contacts, necessitate advanced planning for its arrival. At the level of the individual patient, as always with TB, awareness is key, not only of the possibility of TB as a differential diagnosis in an ill patient, but also of the existence of drug resistance in different parts of the world, and the need to consider resistance as part of the initial assessment of any patient with possible TB,[3] with institution of appropriate infection control procedures including isolation in a negative pressure room.

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