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Drug-resistant tuberculosis

This editorial is based on a conference entitled 'Multi-drug Resistant Tuberculosis—Molecules to Macroeconomics', held at the RSM on March 29–30. Multi-drug resistant tuberculosis (MDRTB) is defined as resistance to the two principal drugs used in treatment—isoniazid and rifampicin—whether or not there is resistance to other drugs. The terms 'primary' and 'acquired' resistance have been changed to 'resistance in new patients' and 'resistance in previously treated patients'. The main causes of MDRTB are poor patient management, non-adherence to the prescribed regimen, a poor national programme or some combination of these three.

Cure rates

MDRTB is much more difficult to treat than fully susceptible disease, requiring expensive second-line drugs for at least eighteen months (compared with cheaper first-line drugs for only six months)[1]. For fully susceptible disease, cure rates will exceed 90% in a well-run programme, and the World Health Organization says that 75% is the minimum necessary to achieve control in the community. Cure rates for drug-resistant disease vary from 60% in Hong Kong to as low as 5% in Russia. There is also much variation in the incidence of multi-drug resistance: in Estonia and Latvia it is found in 14% of new patients, in Northern Ireland 0%[2]. Certain countries such as China, Korea and Vietnam are seeing a decrease in MDRTB; others such as Russia and Eastern European countries an increase. In the UK, despite a 10% increase in total cases last year, mainly as a result of immigration, we have had a slight fall—from about 1.5% (of cases in which sensitivities have been obtained) to 0.8%. This compares with a steady rate of resistance to isoniazid alone of around 6%. About half of these cases develop within the UK and half are imported[3].

Risk factors

The highest rates of MDRTB are found in previously treated patients. For example, in Bombay the incidence proved to be under 10% in new patients but over 50% in those who had had previous treatment[4]. MDRTB has been less common in Africa—under 5% in most countries—perhaps because most programmes could not until recently afford rifampicin.

HIV is the biggest risk factor for tuberculosis, increasing the risk of disease (as opposed to latent infection) at least 100-fold. In sub-Saharan Africa, cases rates have risen up to 10-fold in a decade as HIV has spread through the community, and this increase in caseload imposes a strain on the health systems and their ability to manage tuberculosis effectively. A resultant rise in the number of retreatment cases could mean an increase of drug resistance in the region[5]; and to prevent it, control of tuberculosis and HIV should become a top priority for governments in this part of Africa. In India the probable burden of an HIV-related increase in TB is still greater. The population is at least twice that of sub-Saharan Africa and the prevalence of HIV infection in the community is rising fast; among the commercial sex workers of Mumbai it rose from 5% to 50% in five years.

MDRTB is especially troublesome in prisons, where inmates often experience abysmal living conditions, food and health care. Poverty and overcrowding are almost the rule. TB in these establishments is 100 times more common than in the community. Prisons are not closed systems and what develops within them will spread outwards. In Russia, one million people are behind bars and 10% of these have TB; in some prisons the majority of TB sufferers have MDRTB. A prisoner being treated for a susceptible strain has been known to catch a drug-resistant strain from a cellmate. The most important long-term intervention is penal reform, to reduce the number of prisoners, restructure prison buildings to ensure the passage of light and air, and create a new relationship between prison medical services and health ministries[6].

New methodologies

New molecular methods of rapid diagnosis have offered some help in the management of MDRTB by providing a way to tailor appropriate drug regimens early in the treatment. The techniques apply particularly to rifampicin resistance and include PCR-based methods, DNA sequencing, RNA-based assays, microassays and use of mycobacteriophages[7].

The sequencing of the genome of *Mycobacterium tuberculosis* now provides us with perhaps the most important single piece of information to find new drugs, vaccines and diagnostic methods. Isolation of the genes

providing templates for the enzymes responsible for the unique bacterial wall structure of *M. tuberculosis* should allow design of drugs that inhibit these enzymes and so prevent the bacteria from forming walls[8]. The recent discovery that the isocitrate lyase gene is necessary for the bacteria to exist in the persistent (non-dividing state) may provide another way for targeted drugs to work. Another promising approach, both in treatment of disease and in preventive therapy for latent infection, is to exploit synergistic mechanisms between new drugs and vaccines. We shall have to wait between five and ten years for these developments. Yet other possible routes to treatment are offered by discoveries within the human genome. Twin studies point to a genetic susceptibility to tuberculosis, and people who are inefficient at controlling bacterial numbers may be at excess risk of MDRTB. The vitamin D receptor gene *tt* seems to be associated with protection against disease[9], and likewise *HLA-D2* and *NRAMP1*. But the hunt is still on for a major gene that mediates either protection or high susceptibility. A linkage of a susceptibility gene to the X chromosome may explain why men, especially older men, have higher rates of disease than women. Unravelling of the human genome may provide ways to find new vaccines or drugs which could modulate the human control mechanisms for inhibiting bacterial growth and thus reduce the likelihood of infection leading to disease.

Management

Until new drugs become available, the best hopes lie in a more rational approach to managing existing agents. The World Health Organization now insists on the practice of directly observed therapy (DOT)—i.e. supervised swallowing. This should not only cure the patient but also prevent development of drug-resistant disease, since the patient will have no opportunity to give himself or herself monotherapy. But WHO declares that DOT is only one part of a five part strategy, the others being government commitment to provide resources, use of drugs with proven bioavailability, immaculate record-keeping and reliable microscopy smear services. No DOTS programme is complete without all five components.

Where a sophisticated laboratory service is available, culture and sensitivity testing can be done, but this will be a luxury for most services where tuberculosis is common. In resource-rich countries drug levels can be monitored on the rare occasions when there is concern about them (for instance, in a patient with renal failure). A few rules here can help rational therapy. First, treat the whole patient, not laboratory-generated numbers. Second, go for the highest dose of drug to achieve the desired response with an acceptable level of toxicity. Third, beware of drug/drug interactions. Only two-drug interactions have been studied. When a whole cocktail is being given—as when HIV is being treated simultaneously with TB—the patient and health professional are sailing in uncharted waters.

The treatment of MDRTB should be supervised by an expert centre. Second-line drugs are less effective than first-line drugs, and are more likely to cause adverse effects. At least two and preferably three drugs should be given to which the bacterium is known to be susceptible on sensitivity testing. If sensitivities are not known at the time treatment is started, the drugs should be chosen from agents that the patient is not known to have received previously. Risk factors for drug resistance include previous treatment (especially if lengthy), exposure to another patient with MDRTB, immigration from a country with a high incidence of MDRTB, substance abuse (including alcohol) and, in the setting of an outbreak of MDRTB, HIV infection or being a child. The older second-line drugs include cycloserine, ethionamide and prothionamide, amikacin, kanamycin and capreomycin, PAS and thiacetazone. By serendipity not design, several newer drugs have been found to be active against tuberculosis. These include the quinolones, the macrolides, clofazimine and the combination of amoxicillin and clavulanic acid[1].

In the presence of HIV infection MDRTB has a very high mortality. Special precautions should be taken in the hospital setting to ensure there is no cross-infection. In resource-rich countries MDRTB patients should be nursed in an isolation room under negative pressure and staff should wear special sealant face-masks. Patients suspected of having MDRTB should be cared for under these conditions until proved not to have it[10].

There is much debate as to whether the WHO DOTS strategy could lead to drug resistance. In resource-poor settings where sensitivity tests cannot be done, a four-drug regimen consisting of isoniazid, rifampicin, pyrazinamide and ethambutol is given to all new patients and the sensitivity of the bacterium will remain unknown. These agents are given under direct observation for two months followed by two drugs, usually isoniazid and rifampicin, for a further four. Patients who relapse or do not respond to this regimen are given these four drugs plus streptomycin as a fifth drug. This appears to break a cardinal rule of TB treatment which is that a *single drug should never be added to a failing regimen* in case the regimen is failing because there is resistance to all the drugs used. Thus the addition of a single drug would result in resistance arising to the newly added drug.

In practice most centres have reported success with this five-drug retreatment regimen. But some areas, notably Peru, have seen an increase in drug resistance and believe the WHO treatment policy to be a possible cause. Doctors working at such centres have therefore called for a 'DOTS plus' strategy whereby patients who do not respond to the

first-line drugs are treated with second-line drugs such as amikacin and ciprofloxacin.

Costs, stigma and poverty

What of costs? The drug costs of first-line treatment can be as little as $10 for a six-month course. In the developed world the cost of second-line treatment can be in the $10 000s—clearly beyond the scope of most countries. The proponents of 'DOTS plus' point out that unless we aim to treat and cure MDRTB patients wherever they are, we may be building up an unmanageable burden of MDRTB for the future. They also point out that the costs of second-line drugs have come down, in some instances by 90%, and more pressure on the pharmaceutical companies might force prices down even more, as has now happened with drugs for HIV infection. After all, they argue, these drugs have been off patent for decades. But there are others who argue that second-line drugs will always be too expensive for the poorest countries where TB is endemic, and treatment of MDR has a low success rate even in the best hands.

The main difficulty with lengthy treatment is that patients default. Completion of treatment requires a team of carers including specially trained nurses. In many cultures TB carries a stigma that has to be overcome. Patients may be afraid they will lose employment and income as a result of the disease; they may not appreciate the threat they pose in spreading disease to the rest of the community; and they may see the insistence on their taking tablets as an infringement of rights. Patients who default from treatment can usually be helped: a skilled and motivated staff will find ways to combat their practical or emotional difficulties. Also, most countries have laws to enable compulsory detention when an individual with a dangerous infectious disease such as MDRTB refuses treatment. In practice this is seldom used, though some countries such as the USA have employed compulsory detention in as many as 1% of cases[11].

Tuberculosis is a disease of poverty, and world poverty is worsening, both in terms of inequality of wealth distribution and the numbers in absolute poverty. Whether by omission or commission, those of us in the developed world are benefiting materially from deprivation in the rest of the world[12]. John le Carré, in his latest novel *The Constant Gardener*, which includes an account of the trial of a new TB drug in East Africa, remarks that 'the problem with the poor is always the same. They are not rich enough to buy expensive medicines'. More prophetically he adds, '[The plan] is to test the pill in Africa for two or three years, by which time [the pharmaceutical company] calculate the TB will have become a *big problem* in the West'[13]. For two to three years read twenty to thirty. We have been warned.

P D O Davies

Cardiothoracic Centre, Thomas Drive, Liverpool L14 3PE, UK

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Foot and mouth disease: why not vaccinate?

At the time of writing (May 4), the Government believes the massive outbreak of foot and mouth disease in Britain to be under control. The option of a limited vaccination programme, in severely affected areas, has therefore been shelved. The aim is to reinforce the slaughter programme, to ensure that all infected animals are destroyed within 24 hours of detection. The main reason for the Government's earlier hesitancy about selective vaccination was opposition from farmers. What are the facts on vaccination, for control or prevention?

Foot and mouth disease (FMD) virus comes in seven major types (O, A, C, Asia 1, and SAT 1, 2 and 3). Unfortunately, variants within a type arise which are not

cross protective, so the variant of the type in the vaccine must be matched as closely as possible with the strain circulating in nature. The Pan Asian O strain, the cause of the present outbreak, differs from the previously prevalent strains in Europe (e.g. OBFS, OLausanne, OKaufbeuren) but is closely similar to OManisa, a widely used vaccine strain first isolated in 1969. The latest FMD vaccines are purer and more potent than their forerunners and give at least partial protection even if the match is not perfect. Cross-neutralization studies indicate that the vaccine in the strategic reserve (OManisa) would give good protection against the outbreak strain. Another aspect of modern vaccines is the speed at which protection is generated[1]. Thus in cattle a single dose begins to protect by 4 days—although in pigs it takes longer, about 21 days.

One often-mentioned drawback of vaccination strategies is the difficulty of establishing whether antibodies found are due to infection or vaccination. In fact, these two sorts of response can now be distinguished: a method that seems convenient and reliable[2] is to use an enzyme-linked immunosorbent assay (ELISA) for antibodies to a long B peptide from one of the nonstructural proteins of FMD virus that are present only in infected animals. A second worry is that infected vaccinated animals can become carriers. In experiments such as those described by Doel *et al.*[1] about half the animals became carriers of virus in the pharynx, but these were exposed to massive challenge from contact with infected pigs soon after immunization. Under natural conditions carrier rates would be lower because of less intense and later challenge. Moreover, carrier animals in most experiments did not transmit infection to controls[3], though clearly there is a risk. A third concern is food safety. However, there is plenty of evidence that products from vaccinated (and even infected) animals are safe. In Continental Europe vaccination was for many decades the general policy to control the disease, before the slaughter policy was introduced in 1992; no human-health issues arose. In the wake of the BSE fiasco, assurances that there is no danger might not be believed by a disillusioned public, but the level of anxiety does not seem high—an opinion poll in April suggested that most people would buy meat that came from a vaccinated animal.

If vaccine is used to control an epizootic, what happens to vaccinated animals once the outbreak has been dealt with? It would seem logical to slaughter all animals shown by a test such as that proposed by Shen *et al.*[2] to be infected. Before the idea of vaccination was effectively shelved, Government policy (according to its website) was to vaccinate cattle in infected areas before they were turned out to grass and then let them live out their commercial lives whether they had been infected or not. Clearly this policy would have postponed the country's return to an FMD-free state; but one can understand the opposition of farmers to vaccination of healthy animals if this merely offered a stay of execution when without vaccination an uninfected animal might be allowed to survive. Another control strategy in infected areas would be to supplement existing measures by vaccination within 3 km of an infected farm, thus buying time for the hard-pressed authorities to slaughter animals and safely dispose of their carcasses. But if the country wished to regain its FMD-free status, these animals would ultimately have to be slaughtered.

When the British epizootic comes to an end, policies on FMD will need to be reconsidered. In particular, the review should include cost-benefit analyses such as were done before the European Commission adopted its import control and slaughter policy in 1992. The picture may have changed. With the continuing increase in international exchange of people and goods, more importations of FMD into disease-free areas seem inevitable. These trends, coupled with advances in vaccine technology, particularly the possible development of synthetic peptide vaccines that allow very rapid production in response to new strains, have strengthened the case for vaccination as the bedrock of control. But vaccination is not a trivial exercise. Though a single dose is recommended for outbreak control, routine immunization requires a primary course of two doses 3–4 weeks apart, a booster at 4–6 months and thereafter, for cattle, an annual booster; sheep have the same schedule but lower doses, and for pigs the question of boosters depends on the husbandry and the time to slaughter. The next consideration is the type and strain to use. In Europe, with O virtually the only type likely to arise, vaccination could safely be confined to this single type, but global monitoring of strains and types is clearly essential, as already done by the World Reference Laboratory at the Institute for Animal Health, Pirbright. A vaccination programme will be most effective if it incorporates modern techniques of diagnosis—differential serology to distinguish vaccinated animals from those infected, and a rapid PCR-based test on the farm for current infection. The decision whether to vaccinate routinely must take account of commercial factors; but if we simply consider animal welfare and the previous successes of vaccination as a component of programmes to eradicate the disease from large geographical areas, the choice is clear.

John Beale

The Priest's House, Sissinghurst Castle, Cranbrook TN17 2AB, UK

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