THE GLOBAL THREAT OF MULTI-DRUG RESISTANT TUBERCULOSIS*

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Multi-Drug Resistant Tuberculosis (MDR-TB) is a form of tuberculosis with high-level resistance to both isoniazid and rifampicin, with or without associated other anti-tuberculosis drug resistance. It is now subdivided into 'basic' MDR-TB, with resistance only to isoniazid and rifampicin, and 'MDR-TB-plus' with a similar resistance pattern but often with resistance to several additional drugs. The molecular basis of resistance to both isoniazid and rifampicin are now largely understood. Resistance to isoniazid is due to mutation at one of two main sites, in either the katG or inhA genes.[1,2] Resistance to rifampicin is nearly always due to point mutations in *rpo*-gene in beta subunit of DNA-dependent RNA polymerase.[3] These mutations are not directly inter-connected. The diagnosis of MDR-TB strictly depends on a positive culture of *Mycobacterium tuberculosis* (*M. tuberculosis*) and drug susceptibility testing. Genetic probes which detect drug resistance to rifampicin, with over 95% accuracy, however, are very suggestive of MDR-TB because less than 10% of rifampicin resistant strains are mono-resistant, and so in over 90% of cases rifampicin resistance is the marker for MDR-TB.[4,5]

WHY IS MDR-TB SUCH BAD NEWS?

To understand why the loss of both isoniazid and rifampicin has drastic effects of treatment, the scientific basis of short-course six-month chemotherapy for tuberculosis has to be examined. Multiple controlled trials have shown that a six-month regimen of rifampicin and isoniazid, supplemented by pyrazinamide and streptomycin or ethambutol for the initial two months, will provide a cure in over 95% of cases if this medication is taken correctly, and also render infectious cases non-infectious in two weeks.[6] Each of the drugs vary in their ability to kill tubercle bacilli (bactericidal ability), in their ability to deal with persistent organisms which are only occasionally metabolically active (sterilising ability), and in their ability to prevent the emergence of drug resistance.[6] Isoniazid is the best bactericidal drug and if mono-resistance to this occurs, treatment has to be for between nine to 12 months with rifampicin and ethambutol, in addition to two months initial pyrazinamide.[4] Rifampicin is the best sterilising drug, and mono-resistance to this drug requires treatment with isoniazid and ethambutol for 18 months, with two months initial pyrazinamide.[4] The loss of response to both the main bactericidal and the main sterilising drugs therefore means that patients remain infectious for much longer, both in the community and in hospital, that treatment will be for at least 12, and possibly more than 24 months, and that less effective and more toxic reserve drugs have to be used.

HOW SHOULD SUCH CASES BE MANAGED IN THE UK?

The principles of managing such cases in the UK have been set,[4] and are:

1. Such cases should only be treated by physicians experienced in treating complex resistant cases.
2. Infectious cases should only be treated as an in-patient in full negative pressure facilities.
3. These cases should be managed in close collaboration with the Mycobacterium Reference Units.

The drug regimens used will have to be individualised to the patient's drug resistance profile and will include reserve drugs (Table 1). A *minimum* of five drugs (preferably including one injectable form) to which the patient is known, or thought likely, to be susceptible should be used until cultures are negative. After cultures become negative, a *minimum* of three drugs should be continued for a *minimum* of nine further months.[4] In selected cases,[4] particularly with localised unilateral pulmonary disease, surgical resection under drug cover may be an option.[7] Costs per case are high, being conservatively estimated at a minimum of £50–70 thousand in the UK.[8]

TABLE 1
Reserve anti-TB drugs.

Injectable	Tablet	Frequency
Streptomycin	Pro(Ethion)amide	bd
Kanamycin	Cipro(O)floxacin	bd
Amikacin	Clarithro(azithro)mycin	bd
	Cycloserine	bd
	PAS	bd
	Thiacetazone+	od
	Clofazimine	od
	Co-Amoxiclav	tds
	Rifabutin*	od

\+ Avoid if patient HIV-positive
* Not to be used unless susceptibility confirmed 70% of cases have cross rifabutin/rifampicin resistance

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UK RISK FACTORS

Previous drug treatment is the biggest risk factor for the presence of MDR-TB. In an international comparative study the rates of isoniazid resistance and MDR-TB in England and Wales in 1995 and 1997 were 6·9–7·2% and 0·9–1·1% respectively for all patients, but 22–32% and 13–17% for those patients with a history of prior treatment.[9] A further study in England and Wales showed the following independent risk factors for MDR-TB: previous treatment (x12), HIV-positivity (x8), birth in the Indian Subcontinent (x4), birth in sub-Saharan Africa (x3), male sex (x3) and residence in London (x2).[10]

THE GLOBAL EXTENT OF THE PROBLEM

The extent of the problem of MDR-TB has been examined by cross-sectional surveys of drug resistance on either clinical series or whole country cohorts by the WHO.[9] Using this method of analysis, results for the countries of the UK, some in Europe, the Americas, sub-Saharan Africa and Asia are given in Table 2. Such cross-sectional surveys, however, underestimate the burden and number of such cases because they do not take into account the amount of TB in high-burden countries. When the exercise is repeated with a mathematical modelling design using the drug-resistance estimates and the number of cases of TB, a more accurate global picture is given (Table 3).[11] We are now living in a global village, and what happens in one country can affect disease in another. One example of this is from my own recent practice: some years ago a 13-year-old boy of Indian ethnic background, born locally and given BCG at birth, presented with TB of the spine and mediastinal lymph nodes; positive cultures were obtained from a psoas abscess and sputum. These showed resistance to rifampicin, isoniazid, streptomycin, cycloserine and para-amino-salicylic acid. No local cases had had that resistance pattern, no family case was found, his ethnic origin was the only risk factor, and where we presumed he was infected was India during a six-month visit at the age of seven. The majority of UK cases occur in the foreign-born,[10] but residence in or travel to high-burden countries is also a risk factor.

SO HOW DO WE RESPOND TO THE PROBLEM?

First, we can stop new cases of MDR-TB being created. Some cases are due to infection with MDR-TB, but many are created each year by a combination of physician error and poor patient adherence to treatment. We need to support and fund national TB programmes, in which treatment should be by directly observed therapy (DOT) if possible. Individual physicians should stick to evidence-based treatment guidelines and use only drugs with proven bio-availability. Professor Michael Iseman, the US 'guru' on MDR-TB, has shown that two to four errors are needed to turn a fully susceptible organism into MDR-TB.[7] He has ten commandments for physicians, the first being never to add a single drug to a failing regimen; the other nine are for the physician to repeat the first nine times to make sure they get the message! The WHO recommend a six-month initial treatment regimen of rifampicin, isoniazid, pyrazinamide and ethambutol for two months followed by rifampicin and isoniazid for four months (2HRZE/4HR). If the patient fails treatment or relapses, an eight-month re-treatment regimen of streptomycin, rifampicin, isoniazid, pyrazinamide and ethambutol for two months followed by rifampicin, isoniazid, pyrazinamide and ethambutol for one month followed by rifampicin, isoniazid and ethambutol for five months (2SHRZE/1HRZE/5HRE) is advised.[12] Patients failing this are by definition chronic cases with a high probability of MDR-TB.

TABLE 2
Estimates of MDR-TB rates from cross-sectional surveys[9]

Country	Percentage MDR-TB	(95% CI)	Sample size
England	0·8	0·5–1·2	3,053
Scotland	0·3	0·0–1·8	299
Northern Ireland	0	0·0–6·6	41
Estonia	14·1	10·7–17·8	377
Latvia	9·0	7·1–11·2	789
Russia (Tomsk)	6·5	4·3–9·3	417
(Ivanova)	9·0	5·6–13·6	222
US	1·2	1·0–1·4	12,063
Peru	3·0	2·3–3·9	1,879
Mozambique	3·5	2·3–3·9	1,028
India (Tamil Nahdu)	3·4	2·5–4·5	384
China (Zhejang)	4·5	3·2–6·2	802

TABLE 3
Estimates of number of individuals with MDR-TB.[11]

Country	All cases	95% CI MDR-TB%	Estimated NUMBER cases	(95% CI)
England	6,947	0·5–1·1	55	(29–88)
Estonia	935	10·5–17·6	131	(85–202)
Latvia	2,783	7·0–11·0	250	(107–362)
Russia	97,223	4·5–7·6	5,864	(3,761–9,039)
USA	15,123	1·0–1·4	183	(129–275)
Peru	54,310	2·3–3·1	1,666	(1,068–2,570)
Mozambique	86,558	2·4–4·6	3,032	(1,798–4,774)
South Africa	215,943	0·6–2·4	3,267	(1,098–5,809)
China (DOTS)	650,502	2·0–3·7	18,520	(11,305–28,936)
China (non–DOTS)	650,502	6·3–9·0	49,844	(34,515–75,216)
Pakistan	273,099	0–21·6	26,201	(0–62,249)
Bangladesh	308,271	0–3·3	4,351	(0–11,217)
India	1,864,390	1·6–5·2	63,136	(25,885–108,340)

Such cases, however, have a high mortality and morbidity, particularly if HIV-positive. Human immunodeficiency virus negative cases in the US have had response rates between 56%[13] and 69%,[14] HIV-positive cases initially have 100% mortality,[15] although better initial response rates of 50% are subsequently reported.[16] Nosocomial outbreaks, often in a HIV-setting are well documented, not just in the US. An outbreak in Spain between 1991–5 killed 47 out of the 48 patients infected,[17] and in two outbreaks in London (Kensington Chelsea & Westminster and St Thomas' Hospitals) both had a mortality of >50% in HIV-positive patients.

IS TREATMENT POSSIBLE OR AFFORDABLE IN RESOURCE POOR SETTINGS?

The WHO is looking at a strategy of supervised treatment for MDR-TB – so called 'DOTS-plus' to see if this is deliverable and affordable. One example of this is a study from Peru recently reported.[18] In it 298 patients with MDR-TB, were treated with a fixed regimen of kanamycin for three months, and pyrazinamide, ethambutol, ethionamide and ciprofloxacin for 18 months: 12% died, 48% were cured, 11% defaulted and 28% did not respond. The cost was $600,000 (US dollars), which was 8% of the cost of the whole national TB programme. The cost per patient completing treatment was $2,381 and the cost per death adjusted life year (DALY) was $211. Peru, however, is a middle income country, with a strong TB control programme, and (as yet) little HIV. Such results and costs may only be applicable in such settings. Where there is a poor TB control programme, more HIV or less national income, even such modest results may not be possible.

WHAT HAPPENS NEXT?

It is clear that without both money and political will from resource-rich countries the number of cases of MDR-TB *will* continue to rise. Increasing globalisation and population mobility *will* mean an increase in cases in developed countries without this input. It is equally clear that the costs of inaction are likely in the long term to be considerably more than the costs of action. An example of this is the experience in New York from 1980–2000. In the early 1980s case numbers were dropping, so as a health economy, regular drug susceptibility testing was stopped and a lot of the TB control infrastructure dismantled. Case numbers started to rise again from 1985, and by 1990 19% of cases had MDR-TB, and as few as 10% of patients were completing treatment. A huge and expensive effort was made, which has reduced MDR-TB to below 5% incidence, and case numbers have been falling substantially. This effort, however, has cost more than $1 billion for New York alone, to recover the ground lost by savings which 'gained' $50 million in the 1980s.

Tuberculosis was declared a Global Emergency by the WHO in 1995. The Group of Seven signed up to the Amsterdam Declaration to fund the fight against the 'big three' killers, TB, HIV and malaria, but so far action and money lag well behind promises. Both humanity and self-interest dictate action. The most effective way to reduce cases of tuberculosis, both susceptible and drug-resistant, including MDR-TB, in the UK, is to support and to help fund TB programmes in the Developing World.

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