Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment

L. P. Ormerod

Chest Clinic, Blackburn Royal Infirmary, Blackburn, Lancs BB2 3LR, and Postgraduate School of Medicine and Health, University of Central Lancashire, Preston, Lancs PR1 2HE, UK

Multidrug-resistant tuberculosis (MDR-TB) is an increasing global problem, with most cases arising from a mixture of physician error and patient non-compliance during treatment of susceptible TB. The extent and burden of MDR-TB varies significantly from country to country and region to region. As with TB itself, the overwhelming burden of MDR-TB is in high-burden resource-poor countries. The diagnosis depends on confirming the drug susceptibility pattern of isolated organisms, which is often only possible in resource-rich settings. There should be a strong suspicion of drug resistance, including MDR-TB, in persons with a history of prior treatment or in treatment failure cases. Treatment in developed countries is expensive and involves an individualized regimen based on drug susceptibility data and use of reserve drugs. In resource-poor settings a WHO retreatment regimen may be used, but increasingly the move is to a directly observed treatment based 'DOTS-plus' regimen in a supported national TB programme. However, even where such treatment is given, the outcome for patients is significantly worse than that for fully susceptible TB and has a much higher cost.

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis due to organisms which show high-level resistance to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs. The molecular basis of resistance to isoniazid and rifampicin (and some other drugs) is now largely understood (Table 1). Resistance to isoniazid is due to mutations 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 the *rpo* gene in the beta subunit of DNA-dependent RNA polymerase.[3] These mutations are not directly connected, and so separate mutations are required for organisms to change from a drug-susceptible isolate to MDR-TB. The accurate diagnosis of MDR-TB requires a positive culture of *Mycobacterium tuberculosis* and drug susceptibility

Accepted: May 11 2005
Correspondence to: Professor L. P. Ormerod, Chest Clinic, Blackburn Royal Infirmary, Blackburn, Lancs BB2 3LR, UK. E-mail: Peter.Ormerod@mail.bhrv.nwest.nhs.uk

British Medical Bulletin 2005; **73 and 74**: 17–24
DOI: 10.1093/bmb/ldh047

Table 1 Genetic sites for drug resistance in tuberculosis

Drug	Target	Gene
Isoniazid	Catalase-peroxidase enzyme	*katG*
Isoniazid–ethionamide	Mycolic acid synthesis	*inhA*
Rifampicin	RNA polymerase	*rpoB*
Streptomycin	Ribosomal S12 protein	*rpsL*
	16S rRNA	*rrs*
Quinolones	DNA gyrase	*gyrA*

testing. However, genetic probes which detect drug resistance to rifampicin with >95% accuracy are very suggestive of MDR-TB; <10% of rifampicin resistance is monoresistant, and so rifampicin resistance is a marker for MDR-TB in >90% of cases.[4] Because of its increasing prevalence MDR-TB is now subdivided into 'basic' MDR-TB, with resistance only to rifampicin and isoniazid, and 'MDR-TB-plus', with a similar resistance pattern but with resistance to one or more additional first- and/or second-line drugs.

The global extent of the problem

The extent of the problem of MDR-TB has been examined by the World Health Organization (WHO) in cross-sectional surveys of drug resistance in either clinical series or whole-country cohorts.[5] Cross-sectional surveys almost certainly underestimate the burden and number of cases of MDR-TB because they do not take into account the numerical burden of TB in the high-burden countries. When the exercise is repeated with a mathematical modelling design using drug-resistance estimates and the number of cases of TB, a more accurate picture of the global MDR-TB burden is claimed[6] (Table 2).

Table 2 Estimates of numbers of individuals with MDR-TB[6]

Country	All cases	MDR-TB% (95% CI)	Estimated no. of cases	(95% CI)
England and Wales	6947	(0.5–1.1)	55	(29–88)
Estonia	935	(10.5–17.6)	131	(85–202)
Latvia	2783	(7.0–11.0)	250	(107–363)
Russia	97 223	(4.5–7.6)	5864	(3761–9039)
USA	15 123	(1.0–1.4)	183	(129–275)
Peru	54 310	(2.3–3.1)	1666	(1068–2570)
Mozambique	86 558	(2.4–4.6)	3023	(1798–4774)
South Africa	215 943	(0.6–2.4)	3267	(1098–5809)
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)	4351	(0–11 217)
India	1 864 390	(1.6–5.2)	63 136	(25 885–108 340)

However, even this has been criticized as underestimating the global burden for the following reason. The stated number of cases per year from a country often includes up to 20% of cases which are actually on 'retreatment', i.e. have had a previous course of first-line drugs. The prevalence of MDR-TB in retreatment cases is between 30% and 80% depending on the country. In Gujerat, for example, where there are about 400 000 'new'cases annually, if it is assumed that 20% are being 'retreated' and there is an MDR-TB rate of 30–80% in retreatment cases, this would include 24 000–64 000 cases of MDR-TB [i.e. (400 000 × 0.2 × (0.3–0.8)]. The estimate of the global burden obtained by modelling could be wrong by a factor of 2–4.

Why is MDR-TB such a matter of concern?

Understanding the scientific basis of short-course 6 month chemotherapy for tuberculosis helps to explain why the loss of sensitivity to both isoniazid and rifampicin, even without resistance to additional drugs, has such major effects on outcome. Numerous controlled trials have shown that a 6 month regimen of rifampicin and isoniazid, supplemented by pyrazinamide and streptomycin or ethambutol for the first 2 months, will provide a cure in >95% of cases if the medication is taken correctly. Such a regimen also renders infectious cases non-infectious in 2 weeks.[7] Each drug varies in its ability to kill tubercle bacilli (bactericidal ability), to deal with persistent organisms which are only occasionally metabolically active (sterilizing ability) and to prevent the emergence of drug resistance.[7] Isoniazid is the best bactericidal drug and if monoresistance to this occurs, treatment with rifampicin and ethambutol has to be extended for 9–12 months, in addition to 2 months initial pyrazinamide.[8] Rifampicin is the best sterilizing drug, and monoresistance to this drug requires treatment with isoniazid and ethambutol for 18 months, with 2 months initial pyrazinamide.[8] Therefore loss of response to both the main bactericidal drug and the main sterilizing drug means that patients remain infectious for much longer, both in the community and in hospital, that treatment is required for at least 12 and possibly more than 24 months, and that less effective and more toxic second-line drugs have to be used[8] (Table 3).

How do we stop creating new cases (prevention)?

Although some individuals who have not had previous TB treatment are infected by MDR-TB, this is not the case for most patients. Many new cases of MDR-TB are created each year by a combination of physician

Table 3 Second-line anti-TB drugs

Injectable	Oral
Streptomycin	Pro(ethion)amide
Kanamycin	Clarithro(azithro)mycin
Amikacin	Rifabutin*
	Quinolones
	Moxifloxacin
	Gatifloxacin
	Levofloxacin
	Ofloxacin
	Ciprofloxacin
	Cycloserine
	PAS
	Thiacetazone†
	Clofazimine
	Co-amoxiclav
	(Linezolid)

*NOT to be used unless susceptibility confirmed; >70% of cases have rifampicin/rifabutin cross-resistance.
†Avoid if the patient is HIV-positive.

error and poor patient compliance with treatment, which turn fully susceptible organisms, or those with less complex resistance patterns, into MDR-TB. Professor Michael Iseman, the US 'guru' of MDR-TB, has shown that two to four errors are needed to turn a fully susceptible organism into a case of MDR-TB.[9] He has ten commandments for physicians: the first is never to add a single drug to a failing regimen, and the other nine are for the physician to repeat the first commandment nine times to make sure that the message is understood!

Support and funding of national TB programmes, in which treatment is given as directly observed therapy (DOT), is essential for all persons with TB if at all possible. Physicians should always use evidence-based treatment guidelines and drugs of proven bio-availability. The WHO recommend a 6 month initial treatment regimen of rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifampicin and isoniazid for 4 months (2RHZE–4RH). If the patient fails treatment (positive cultures or sputum smears in months 5 or 6 of treatment) or relapses, an 8 month retreatment regimen is recommended. This consists of streptomycin, rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months, followed by rifampicin, isoniazid, pyrazinamide and ethambutol for 1 month, followed by rifampicin, isoniazid and ethambutol for 5 months (2SRHZE–1RHZE–5HRE).[10]

This retreatment schedule is now being re-evaluated, as it may be amplifying the problem. Since patients who fail on or relapse after the initial treatment outlined above have a 10–15-fold increased risk of having MDR-TB,[11] the retreatment regimen 2SRHZE–1RHZE–5RHE,

which, for 7 of the 8 months, adds only one drug to the previous treatment regimen of 2RHZE–4RH, can be said to be failing the first commandment (see above).

Treatment and management of cases in developed (resource-rich) settings

Previous drug treatment is the largest single risk factor for the presence of MDR-TB. In an international comparative study, the rates of resistance in England and Wales in 1995 and 1997 were 6.9–7.2% for isoniazid resistance and 0.9–1.1% for MDR-TB for all patients, but 22–33% and 13–17%, respectively, for those patients with a history of prior treatment.[5] Therefore physicians should suspect that any patient with a prior treatment history, or failure during treatment (defined earlier), could have acquired resistance. Urgent gene probes for rifampicin resistance should be carried out on material which is either microscopy or culture positive. The suspicion of MDR-TB, and the appropriate isolation of suspected cases until they are either effectively treated or MDR-TB is disproved, is also important because of the potential for nosocomial outbreaks if there is inadequate isolation and/or immunocompromised (mainly HIV-positive) patients are exposed. In the USA, HIV-positive MDR-TB cases initially had a 100% mortality,[12] but with greater awareness and earlier diagnosis an improvement in initial survival rates to up to 50% has been reported.[13] HIV-negative cases in the USA have had better response rates of between 56%[14] and 69%[15]. Nosocomial outbreaks, often in an HIV setting, are well documented in other countries as well as the USA. An outbreak in Spain between 1991 and 1995 killed 47 of 48 patients infected,[16] and in two outbreaks in London (Chelsea and Westminster Hospital and St Thomas's Hospital[17]) the mortality was over 50% in HIV-positive patients. Algorithms for correct isolation, which make use of sputum microscopy, a suspicion of MDR-TB and whether immunocompromised patients are on the same ward, are available.[18]

Principles for managing cases of MDR-TB in developed countries have been set out. Those recommended by the British Thoracic Society[8] are similar to those recommended by the European and American Thoracic Societies and the WHO with the International Union Against Tuberculosis and Lung Disease (IUATLD).[10] The main features are as follows.

1. Such cases should only be treated by physicians experienced in treating complex cases with drug-resistant organisms.
2. Infectious cases should only be treated as inpatients and in facilities with full negative pressure ventilation.

3. Cases should be managed in close collaboration with national/regional mycobacteriology services utilizing drug susceptibility data.

The drug regimens used will have to be individualized to the patient's drug resistance profile and will include reserve drugs, as well as any remaining first-line drugs to which the organism remains susceptible (Table 3). 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 a further 9 months.[8] The cost per case of such treatment is very high, and has ben conservatively estimated at a minimum of £50000–70000 ($85 000–120 000) in the UK.[19]

Specialized centres in the USA have suggested that surgical resection under drug cover is an option in selected cases,[14] particularly those with unilateral disease. Their experience with this approach, coupled with the availablity and use of fluoroquinolones, particularly moxifloxacin and levofloxacin, in the drug regimen, has improved the survival in such patients.[20] The long-term success rate was increased from 56% in the prior cohort[14] to 75%, and the TB death rate fell from 22% to 12% as quinolones and surgery were used increasingly. However, these outcomes are still significantly worse than for unselected tuberculosis, which is largely fully drug susceptible and for which death rates of 5% and cure/completion rates of 89% for respiratory disease and 94.4% for all forms of disease in programme conditions are reported.[21]

Treatment and management of cases in resource-poor settings

There have been concerns that the WHO retreatment regimen could be exacerbating the MDR-TB problem, particularly where there are failures in the national TB programme (see above). Therefore the WHO has considered a strategy of supervised treatment of MDR-TB cases, the so-called 'DOTS-plus' programme, to try to contain the problem. This approach requires a sustainable and functioning national TB programme, drug availability at a reasonable cost via the Global TB Alliance and some support for drug-resistance monitoring either within the country, or provided outside the country via a partnership with a resource-rich country. This strategy has been tested in settings with a moderate MDR-TB problem, but with a good TB programme, wide DOT provision and a good infrastructure for monitoring and delivery of treatment.

For example, 298 patients in Peru were treated for MDR-TB with a fixed regimen of kanamycin for 3 months, and pyrazinamide, ethambutol,

ethionamide and ciprofloxacin for 18 months.[22] Twelve per cent died, 48% were cured, 12% defaulted and 28% did not respond. The total cost was $600 000, which was 8% of the cost of the whole national programme. The cost per patient completing treatment was $2381 and the cost per death-adjusted life year (DALY) was $211. Peru is a middle-income country, with a strong TB programme and little HIV at present. Such results and costs may only be applicable if these conditions are met. Where there is a poor TB control programme, even such modest results may not be possible.

Treatment modified by drug susceptibility tests may improve the outcome in such DOTS programmes, provided that there is drug availability and continuity at affordable prices. The WHO is carefully vetting DOTS-plus applications and monitoring them where they are implemented. By amplifying drug resistance without improving outcome, poor treatment can be worse than no treatment.

What is the future?

As with all TB, 99% of MDR-TB occurs in high-burden resource-poor countries. However, increasing globalization and population mobility will mean an increase in MDR-TB cases in developed countries. It is clear that without both political will and money, the number of cases of MDR-TB in both developed and developing countries will continue to rise. It is also clear that, in the long term, the costs of inaction are likely to be greater than those of action.

In the early 1980s TB case numbers were dropping in the USA, including in New York. Therefore regular drug susceptibility testing was stopped and much of the TB control infrastructure was dismantled as a 'health economy measure'. By 1985 case numbers were starting to rise again, and by 1990 19% of patients had MDR-TB, and in some parts of New York as few as 10% of patients were completing treatment. An expensive and extensive effort was made, which has reduced the incidence of MDR-TB to <5% and has also significantly reduced case numbers, but at a cost of $1 billion in New York alone.

In 1995 the WHO declared tuberculosis to be a global emergency, and in 1998 the Group of Seven signed up to the Amsterdam Declaration to fund the fight against the 'big three' infectious killers: TB, HIV and malaria. So far action and money lag well behind the promises. Continuing pressure and resources will be needed to ensure that the DOTS-plus strategy is funded and monitored, but only introduced into national programmes when these are robust.

References

1 Zhang Y, Heym B, Allen B *et al.* (1992) The catalase-peroxidase gene and isoniazid resistance in *M.tuberculosis*. *Nature*, **358**, 591–3.
2 Piatek AS, Telenti A, Murray MR *et al.* (2000) Genetotypic analysis of *Mycobacterium tuberculosis* in two distinct populations using molecular beacons: implications for rapidsusceptibility testing. *Antimicob Agents Chemother*, **44**, 103–10.
3 Telenti A, Imboden P, Marchesi F *et al.* (1993) Detection of rifampicin resistancemutations in *Mycobacterium tuberculosis*. *Lancet*, **341**, 647–50.
4 Drobniewski FA, Pozniak AL. (1996) Molecular diagnosis, detection of drug resistance and epidemiology of tuberculosis. *Br J Hosp Med*, **56**, 204–8.
5 Espinal MA, Laszlo A, Simonsen L *et al.* (2001) Global trends in the resistance to antituberculosis drugs. *N Engl J Med*, **344**, 1294–1303.
6 Dye C, Espinal MA, Watt CJ *et al.* (2002) Worldwide incidence of multidrug-resistant tuberculosis. *J Infect Dis*, **185**, 1197–2002.
7 Ormerod LP (1997) Chemotherapy of tuberculosis. *Eur Resp J*, **2**, 273–97.
8 Joint Tuberculosis Committee of the British Thoracic Society (1998) Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax*, **53**, 536–48.
9 Iseman MD (1993) Treatment of multi-drug resistant tuberculosis. *N Engl J Med*, **329**, 784–91.
10 WHO (1996) *Guidelines on the Management of Drug-Resistant Tuberculosis*. WHO/TB/96.210. Geneva: WHO.
11 Hayward AC, Bennett DE, Herbert J *et al.* (1996)Risk factors for drug resistance in patients with tuberculosis in England and Wales 1993–4. *Thorax*, **51** (Suppl 3), A8.
12 Small PM, Shafer RW, Hopewell PC *et al.* (1993) Exogenous re-infection with multidrug resistant *Mycobacterium tuberculosis* in patients with advanced HIV disease. *N Engl J Med*, **328**, 1137–44.
13 Salomon N, Perlman DC, Fiedman P *et al.*(1995) Predictors and outcome of multidrug resistant tuberculosis. *Clin Infect Dis*, **21**, 1245–52.
14 Goble M, Iseman MD, Madsen LA *et al.* (1993) Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med*, **328**, 527–32.
15 Telzak EE, Sepkowitz K, Alpert P *et al.* (1995) Multidrug resistant TB in patients without HIV infection. *N Engl J Med*, **333**, 907–11.
16 Herrera D, Cano R, Godoy P *et al.* (1996) Multidrug resistant tuberculosis outbreak in a HIV ward—Madrid, Spain, 1991–95. *MMWR Morb Mortal Wkly Rep*, **45**, 330–3.
17 Breathnach AS, de Ruiter A, Holdsworth GM *et al.* (1998) An outbreak of multi-drug-resistant tuberculosis in a London teaching hospital. *J Hosp Infect*, **39**, 111–17.
18 Joint Tuberculosis Committee of the British Thoracic Society (2000) Control and prevention of tuberculosis in the United Kingdom: recommendations 2000. *Thorax*, **55**, 887–901.
19 White VL, Moore-Gillon J (2000) Resource implications of patients with multidrug resistant tuberculosis. *Thorax*, **55**, 962–3.
20 Chan ED, Laurel V, Strand M *et al.* (2004)Treatment and outcome analysis of 205 patients with multidrug resistant tuberculosis. *Am J Respir Crit Care Med*, **169**, 1103–9.
21 Ormerod LP, Horsfield N, Green RM (2002) Tuberculosis treatment outcome monitoring: Blackburn 1988–2000. *Int J Tuberc Lung Dis*, **6**, 662–5.
22 Suarez PG, Floyd K, Portocarrero J *et al.* (2002) Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet,* **359**, 1980–9.