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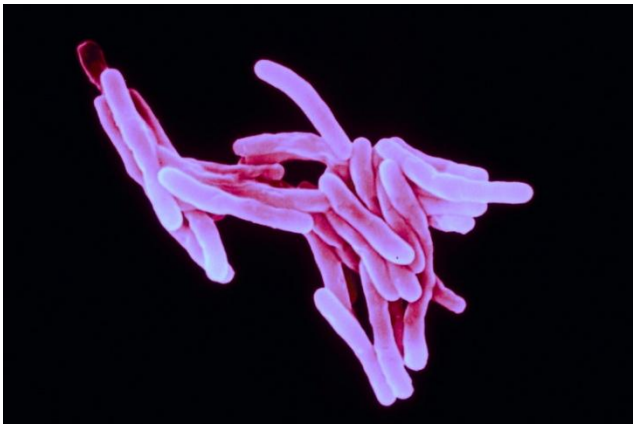
Drug Resistant Tuberculosis



Tuberculosis (TB) is a leading cause of death globally. Progress in the control of TB is threatened by drug-resistant TB strains. This note examines the extent of, and risks posed by, drug-resistant TB. It also gives an overview of national and international TB surveillance, research into treatments and policy options to limit infections.

Overview

- Globally, 1.45 million people died from tuberculosis (TB) in 2010, even though the disease is curable with drug treatment.
- Drug resistant strains are now estimated to account for about 10% of all TB deaths.
- Drug resistance is a man-made problem, resulting from misuse of anti-TB drugs and poor management of the disease.
- Treatment for drug-resistant TB is more expensive, toxic and takes much longer than treatments for drug-susceptible TB.
- Early and rapid diagnosis and treatment completion are essential for controlling TB.
- In the UK, TB is a particular problem among people born abroad and hard to reach groups such as the homeless.
- Funding is required to develop better diagnostics, vaccines and anti-TB drugs.

Background

TB is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* and transmitted via aerosol droplets. The bacteria usually attack the lungs but can affect any part of the body. One third of the world's population carries the bacterium but does not have the disease (latent TB). Only a small proportion of these people will develop the disease and become infectious. In 2010, some 8.8 million people contracted TB causing 1.45 million deaths, including those among HIV-infected persons[1]. Progress has been made in tackling the epidemic. Globally, the number of new/relapsing cases has fallen each year since 2006 and TB death rates have dropped by more than a third since 1990[1].

Medical risk factors include co-infection with HIV; people with HIV are 21 to 34 times more likely to develop TB, and accounted for about 13% of all TB cases globally[1] in 2010. Development of the disease is also linked to certain social risk factors, notably drug or alcohol abuse, poor housing conditions, homelessness and imprisonment.

Drug resistant (DR)-TB

Drug resistant strains have developed through inappropriate use of anti-TB drugs (see Box 1) and poor management of the disease including infection control. Once DR-TB strains develop, they can be transmitted to others. There are several types of DR-TB:

- **drug-resistant (DR) TB** is resistant to any first line drug
- **multidrug-resistant (MDR) TB** is resistant to the two most effective first line drugs, rifampicin and isoniazid;
- **extensively drug-resistant (XDR) TB** is MDR-TB which is also resistant to drugs called fluoroquinolones as well as to at least one of second-line injectable drugs (see TB Treatment section).

In recent years, XDR-TB patients infected with strains resistant to many other anti-TB drugs have been reported.

Box 1. How does drug resistance develop?

Drug resistance develops in bacteria because of naturally-occurring changes in their genes. When bacteria are treated with a drug, these changes allow some to survive. Continued exposure to the drug kills any remaining drug-susceptible bacteria, providing the ideal environment for the resistant forms to flourish. Eventually that strain of bacteria can become completely resistant to the drug in question. Bacteria may develop resistance to more than one drug.

Global trends in TB

Most TB cases today occur in Asia (59%) and Africa (26%). The countries with the highest TB burdens are India, China, South Africa, Indonesia and Pakistan[1]. In 2010, India had the highest figure for incidence of TB cases – about 2.3 million – that is a rate of 185 per 100,000 population (compared with 13.6 per 100,000 in the UK), and accounted for 26% of all cases globally[1]. Headline figures for TB rates are shown in Table 1.

Table 1. Headline TB rates, 2010

	Estimated Global, 2010[1]	Notified UK, 2011[2]
TB Incidence*	8.8 million	8,963
TB prevalence*	12 million	Not reported
MDR-TB cases	650,000 (prevalent* cases)	81 (out of a total of 431 DR-TB cases)

* Incidence is defined as the number of new and relapse cases occurring during a given time period. Prevalence is defined as the absolute number of TB cases.

MDR-TB is estimated to cause about 10% of all TB deaths[3]. Of all MDR-TB cases in the world in 2010, 40% are thought to be in China and India. There were 53,108 MDR-TB cases reported worldwide in 2010 (32,616 of which were reported in Europe, most in Eastern Europe) despite global estimates being much higher[1]. Although more people are being treated for MDR-TB, it is thought that only 16% of MDR-TB patients worldwide that need treatment are receiving it[1].

Figures on the global burden of TB (Table 1) are estimated because of a lack of good quality surveillance data and non-standardised surveillance methods. Many countries have never done surveys of DR-TB. The most recent TB report by the World Health Organisation (WHO) highlighted that by 2010 no high-burden MDR-TB country undertook good quality continuous surveillance for drug-resistance[1].

TB trends in the UK

Data on TB incidence in the UK for 2011 shows an increase of 6.6% from the previous year[2]. Overall, for the past twenty five years there has been a rise in TB incidence but rates appear to have been stabilising since 2005. This increase can be attributed to an increase of TB in non-UK born individuals, and ongoing TB transmission in people born in the UK, particularly those in hard to reach groups such as the homeless and drug users. London accounts for 39% of all UK cases[2]. TB rates in London increased 8% in 2011, and it has the highest TB rates of any capital city in Western Europe[2]. The worst affected borough is Newham, with TB incidence rates of 128 per 100,000 people[4].

The total number of cases with DR-TB in the UK has increased by over 50% in the last 10 years, but is still relatively small. The majority of patients in the UK with DR-TB were born in regions of the world where DR-TB is common, such as the Indian subcontinent or Eastern Europe. The other main risk factors for acquiring DR-TB are a previous diagnosis of TB, and homelessness or drug use[3].

TB Care and Control

WHO works towards reducing the global TB burden, helping national governments build on their progress. The Health Protection Agency (and counterpart organisations in the Devolved Administration) and the Department of Health take the lead in the UK on TB care and control (see Box 2).

Diagnosis

Controlling TB transmission and improving patient outcomes depends on rapid diagnosis and treatment completion. For TB diagnosis, the simplest and most common method is analysing sputum samples using a microscope. It is often the only test available in countries most affected by TB. It detects the most infectious cases, but is not a sensitive test and cannot discriminate between drug-susceptible TB (DS-TB) and DR-TB. Newer diagnostics are costly and unaffordable for many developing countries, so detection rates are low in countries where most TB cases occur[5].

Box 2. Global and UK TB Policies

WHO launched the Stop TB Strategy in 2006 and updated its guidelines on treating TB in 2010. WHO recommendations are produced after experts assess evidence in a standard manner, rating them as "strong" or "conditional" depending on the quality of the evidence and on other factors such as resources. The STOP TB Partnership developed a comprehensive assessment of the action and resources needed to implement the STOP TB Strategy; the Global Plan to Stop TB 2011-2015.

In the UK, the Department of Health (DH) published its TB Action Plan for England in 2004 and a TB Toolkit in 2007 to assist those planning, commissioning and delivering TB services. The National Institute of Health and Clinical Excellence (NICE) has published clinical and public health guidelines to assist the NHS in TB control. The Health Protection Agency (HPA) is responsible for local and national surveillance, laboratory diagnostic and reference services, disease control in the population, international partnership and research.

The main method of drug-resistant TB detection is by growing TB bacteria in the presence of the drug. This is costly, time consuming and requires bio-secure laboratories. Diagnosis of DR-TB is thus unavailable in many countries and remains clinically challenging and logistically difficult[5,6] A lack of laboratory capacity means that many people in the high-burden TB countries have poor access to good-quality diagnostics for DR-TB. This is a problem in much of Africa and Asia as well as parts of Eastern Europe, and means that the true global burden of DR-TB may be higher than current estimates. Since 1994, 114 countries have reported surveillance data on MDR-TB. But only 42 of these perform continuous surveillance based on testing of all TB patients. The others rely on periodic surveys of samples of patients[3].

With the exception of high-income countries, an extremely low number of people receive DR-TB testing elsewhere. In the 27 countries which account for over 85% of MDR-TB cases in the world, only 1.5% of new TB cases and 5.5% of previously treated cases are laboratory-screened for MDR-TB[1]. Failure to detect resistance may result in inappropriate treatment, premature death and increased rates of resistance (see Box 1) and transmission[5,6].

Most TB-related deaths arise from undiagnosed cases or delayed treatment. Inadequate access to newer diagnostic technologies and inaccuracy of sputum microscopy means patients may have to make multiple visits to health providers[5], with diagnosis often taking months. Many people cannot afford to take time off work, meet the costs of travel to the health centre or pay for treatment. Patients may also fail to seek medical help because of a lack of awareness, limited access to health services or geographical and economic disadvantages[5]. They may also fear the stigma and social exclusion often associated with a diagnosis.

TB treatment

Front line treatments

TB bacteria are very hard to kill. The standard WHO regimen is a combination of four (front-line) drugs taken for six months. The drugs used are isoniazid and rifampicin supplemented by two further drugs (pyrazinamide and ethambutol) for the first two months. DR-TB can develop if:

- patients do not complete the full course of treatment;
- the correct therapies are not prescribed/available;
- the drugs are of sub-substandard quality.

The length and complexity of treatment means that many patients forget to take a drug every day or fail to complete courses once their symptoms improve. Clinical management techniques, such as Directly Observed Treatment (where the patient is watched taking every dose) and patient support can improve treatment completion. Non-adherence results in the rise of resistant strains (see Box 1), poor health outcomes and increased transmission. Average public sector health care costs of treating a case of TB vary worldwide, but in the UK it costs around £5000 per patient[7].

Second line treatments

A range of second line drugs can be used to supplement the front line regimen where DR-TB is encountered. MDR-TB treatment typically lasts about 20 months (compared with 6 months for DS-TB), often with less chance of long-term cure. The second-line drugs used often have severe side effects making it more difficult for patients to adhere to treatment. Current treatment guidelines are mainly based on medical opinion rather than evidence from clinical trials. The overall costs for treating DR-TB in the UK are £50,000-£70,000 per patient[7].

Second-line TB drugs are expensive to manufacture, are produced in low quantities and often have short shelf-lives. Funding agencies such as UNITAID are working to improve affordability, access to and control of these drugs[2,5]. A further concern is that such drugs are often used where they are not required, for instance to treat DS-TB, and this stimulates the emergence of DR-TB (see Box 1). This is a particular problem in India where many anti-TB drugs are available over the counter without prescription.

UK TB Issues

Detection and Treatment Targets

WHO has two global targets for TB control and care:

- **Detection rates of 70%.** The UK meets this target. Early diagnosis is important as late detection leads to poor health outcomes and increased onward transmission. Late detection may be caused by low levels of TB awareness among the public and primary healthcare professionals[7].
- **Treatment completion rates of 85%.** The UK is not meeting this target although rates have improved from 78.4% in 2001 to 83.8% in 2010[2]. Treatment completion at 24 months for MDR-TB cases notified in 2009 was 80%[2]. Failure to complete treatment stimulates resistance and if no improvement is seen DR-TB is likely to rise.

Active Case Finding

Experts agree health services should focus more effort on actively seeking out cases. This can be done by testing people the patient has come into contact with, screening high risk groups and systematically reviewing the outcomes of all cases in an area. It requires multidisciplinary teams capable of delivering all elements of TB services from diagnosis to cure. Find and Treat (Box 3) is an example of one such UK NHS service which screens homeless people and drug users. TB incidence among the homeless in London is 50 times higher than the national average. The homeless are also very likely to present late for treatment and much less likely to complete treatment, creating the perfect conditions for development and transmission of DR-TB. Other important steps in the fight against TB in the UK include identification and treatment of latent infection, and increased awareness-raising activities, such as *The Truth About TB* programme of the UK charity TB Alert.

Box 3. Find and Treat

Find and Treat is a London-based NHS initiative that uses a mobile x-ray unit to screen almost 10,000 homeless people and drug users a year for active TB. It provides early diagnosis and supports patients to take a full course of treatment and get cured. In recognition that TB is not just a medical problem but a socially complex disease, Find and Treat is a multidisciplinary team of TB nurse specialists, social and outreach workers, radiographers and technicians. The service has been shown to be extremely cost-effective because it limits onward transmission and the high treatment costs of late diagnosis.

Variations in Screening and Care

A 2011 report highlighted that current TB screening and control guidelines are not applied consistently across London and that standardisation of TB services is urgently required[7]. There is significant variation in the configuration and governance of the 5 London TB networks and no performance management role[6]. Notably, staffing profiles and provision of Directly Observed Treatment vary but not in relation to need. The NHS in London has developed a TB Model of Care report to tackle TB more effectively.

Commissioning of TB services

Public health groups are concerned that the health service reforms in the Health and Social Care Act 2012 could potentially result in a fragmented approach to TB care and control[7]. Under the Act, clinical commissioning groups (CCGs) will commission the majority of NHS services, including TB services. However, such concerns could be allayed if CCGs commission TB services collectively and at scale, and if services for complex cases of TB such as MDR and XDR-TB were commissioned by the NHS Commissioning Board as a specialised service.

TB and Immigration

The rise in UK TB rates is largely due to TB in non-UK born individuals[2]. Chest x-ray screening for active TB at Gatwick and Heathrow airports is to be discontinued as it is expensive and ineffective. The UK Borders Agency is now rolling out pre-entry screening following a pilot scheme started in 2005 covering 15 countries. Migrants (staying >6 months) from 82 countries with high incidence of TB will be required to be tested for active TB in their own country

before being granted a visa. This will not detect latent TB, even though evidence suggests that most cases of TB among non-UK born people develop from latent TB. Some experts have thus argued that the new pre-entry screening system will only be fully effective if combined with screening for latent TB in high-risk new arrivals.

Global TB Issues

Funding to fight TB

Total funding to diagnose and treat TB globally is expected to be $4.4bn in 2012. Of this, $0.6bn is expected to come from donors and the remainder from national governments. In comparison, donor funds for malaria ($1.8bn) and HIV ($6.9bn) are much higher[1]. The Global Fund to Fight AIDS, Tuberculosis and Malaria is a public-private partnership that funds treatment of these diseases. It accounts for 12% of all TB funding worldwide and 82% of all international funding. In November 2012, the Global Fund Board decided to cancel a round of funding but still expects to spend between $9-10bn from 2011-13. The UK government has said that it will significantly increase funding to the Global Fund, subject to continued good progress on its reform. However, the International Development Select Committee has pointed out that the extent and timing of the increase has yet to be confirmed. Most low-income countries rely on the Global Fund for TB control funding and the Committee suggested that increased funding from the UK could act as catalyst to encourage other funders[8].

An estimated 1 million cases of MDR-TB will need treating in the world between 2011 and 2015 at a cost of $7.1bn. Current funding levels are much too low to cover this. According to the WHO, if middle income countries were to fully finance their own MDR-TB treatments, donor financing could be re-directed and would almost fund the scale up of DR-TB services needed in low-income countries[1]. As well as financing for TB control, an estimated $2bn is needed each year to advance the development of new drugs, diagnostics and vaccines for TB and conduct other essential research to improve treatment and care. However, financing slowed in 2010, reaching only one-third of the estimated target.

Drug research and development

Anti-TB Drugs

There have been no new TB drugs in over 50 years, as there is limited market incentive for companies to develop them. However, donors, governments and not-for-profit organisations are investing in research and development of new TB technologies. New drugs, to which there is little pre-existing resistance, could potentially treat both DS and DR-TB more quickly, cheaply and effectively, and prove vital to global TB control efforts. Worldwide there are 10 TB drugs in clinical trials. The most advanced of these are bedaquiline (Tibotec) and delamanid (Otsuka). Bedaquiline has been approved for use under compassionate-use criteria for DR-TB patients for whom there are limited treatment options. Use of new drugs requires careful control to avoid inappropriate prescribing that could result in early emergence of resistance[6].

Box 4. New diagnostics

Over the past five years, several new tests have become available for detecting active TB, screening for latent TB infection, and identifying resistant strains. The GeneXpert system has been a major step forward for DR-TB diagnosis. It is suitable for use in peripheral healthcare facilities and requires minimal expertise, delivering results within 2 hours. It detects both TB and its resistance to rifampacin, one of the major first-line TB drugs. However, there is still real need for a Point of Care (POC) test. POC tests can be carried out at the location at which care is provided, with no specialist expertise required giving immediate results without referral to a laboratory[5]. Some POC tests are now in the pipeline. Such devices are already used in developing countries to detect diseases such as hepatitis B, HIV, malaria and syphilis.

There is a need for DR-TB regimens that are shorter, more tolerable and effective than current regimens and that have undergone rigorous trials. While such trials are difficult to conduct, the Medical Research Council, will is initiating one in 2012. The Global TB Alliance for TB Drug Development, a not-for-profit drug development organisation, is trying to reduce the time taken to develop full regimens. It works with public health experts, drug companies, civil society organisations and regulatory authorities to encourage testing of promising combinations of TB drug candidates from different sources early in the pipeline. This identifies the best new treatment regimens, regardless of the sponsor.

Vaccines

The current vaccine Bacille Calmette-Guérin (BCG) protects against severe forms of TB in children. But it is inconsistent in protecting against the predominant form of TB that affects adolescents or adults. UK data from 2011 showed that 71% of all TB patients were vaccinated[2]. Developing an effective new vaccine is vital to TB and DR-TB control and eventual eradication. Ten vaccine candidates are in Phase I or II clinical trials. It is hoped that one or two of those currently in Phase II will enter a Phase III trial in the next 2-3 years, with the possibility of licensing at least one new vaccine by 2018.

Diagnostics

The development of cheap, accurate and rapid Point of Care (POC) TB tests is key to early diagnosis (Box 4). POC tests under development could have a big impact on global detection but this will depend on the accuracy, cost, and complexity of the test as well as the political will to ensure delivery and treatment. Technologies that are not affordable outside of well-funded aid programs or require laboratory support are unlikely to reach the mass of undiagnosed TB in high-burden African and Asian countries[5].

Endnotes

1 Global Tuberculosis Control, WHO report, 2011
2 Tuberculosis in the UK, HPA Report 2012
3 Multidrug and extensively drug-resistant TB, WHO, 2010 Global Report
4 Tuberculosis in London, HPA Report 2010
5 Tuberculosis Diagnostics and Biomarkers: Needs, Challenges, Recent Advances, and Opportunities, Ruth McNerny et al, J. Infect. Dis., 2012
6 Drug-Resistant Tuberculosis-Current Dilemmas, Unanswered Questions, Challenges and Priority Needs, Zumla et al, J. Infect. Dis. 2012
7 Case for Change: TB Services in London, London Health Programmes, 2011
8 DFID's contribution to the Global Fund to fight AIDS, Tuberculosis and Malaria, House of Commons International Development Committee, 2012

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