

Anti-tuberculosis drug resistance – a major public health problem

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Although caused by vastly different pathogens, the world's three most serious infectious diseases, tuberculosis, malaria, and HIV-1 infection, share the common problem of drug resistance. The pace of new drug development has been very slow for tuberculosis.

Tuberculosis, is a contagious disease that thrives in overcrowded places. It is caused usually by *Mycobacterium tuberculosis* which typically attacks the lungs, but also affects other parts of the body. It is spread by air transmission when affected people cough, sneeze and pass respiratory aspirate through the air. Most infections remain latent, but about one in ten of these cases eventually progresses to active disease. Once the infection becomes active, if left untreated, the mortality rate is high with the disease killing half of those infected. About one third of the world's population has probably been infected with *M. tuberculosis*,¹ with an estimate of 9 million new cases and 1.5 million associated deaths annually, mostly occurring in developing countries.² Up to 80% of the population in many Asian and African countries test positive in tuberculin tests. The absolute number of tuberculosis cases has been decreasing since 2006. More people in the developing world contract tuberculosis because of compromised immunity, largely due to high rates of HIV infection and the corresponding development of AIDS.³

The global burden of TB remains enormous. In 2011, about an 1.4 million people died from TB, including almost one million deaths among HIV-negative individuals and 430 000 among people who were HIV-positive. TB is one of the top killers of women, with 300 000 deaths among HIV-negative women and 200 000 deaths among HIV-positive women in 2011.²

Classic symptoms are chronic cough, blood-tinged sputum, fever, night sweats, and weight loss. Diagnosis of active TB depends on chest X-rays, microscopic examination and examination of body fluids, with latent TB identified by tuberculin skin test. Prevention relies on screening programs and vaccination with the bacillus Calmette-Guerin vaccine. Treatment requires administration of multiple antibiotics over a long period of time.

Development of resistance to antibiotics is common in many bacterial infections. Resistance is often due to transmission of infrequently-arising resistant clones, generated through mutation. Cure of an uncomplicated Tb infection may require at least six months, on up to four different drugs, allowing the bacteria ample opportunity to develop resistance. Anti-tuberculosis drug resistance is a major public health problem which threatens progress made in TB care and control worldwide. It arises from improper use of antibiotics in chemotherapy of drug-susceptible TB patients, the result of improper treatment regimens and failure to ensure that patients complete the whole course of treatment. Drug resistance arises in areas with weak TB control programmes. A patient who develops active disease with a drug-resistant TB strain can transmit this form of TB to others.

Increasing antibiotic resistance has brought multiple drug-resistant tuberculosis (MDR-TB) infections. Poor diagnosis, misuse and mismanagement of powerful drugs have created strains progressively harder to combat. When a TB patient is given an ineffective prescription or, starts but does not complete the full course of drugs, the bacterium can grow stronger and resistant to medication.⁴ Nearly 4% of new TB patients have MDR strains of TB. Among patients who had been treated for TB before, about 20% have MDR TB. According to the World Health Organization, worldwide rates of MDR and extensively drug-resistant (XDR) tuberculosis are probably higher than reported.⁵ Complete drug resistance in TB has not been clearly defined but the evolution of resistant variants has made some Tb infections virtually untreatable. XDR is reported by WHO in 84 countries.⁵ East and Southeast Asia, Eastern Europe, South Africa, Russia and India have alarmingly high rates of drug resistance but only India, Italy and Iran have reported cases of TB that do not respond to any drugs.

Multidrug resistant TB strains (MDR-TB) cause 3.6% of all TB cases and require at least two years of treatment with as many as six potentially toxic drugs.⁶ Extensively drug resistant strains (XDR-TB), which may be nearly impossible to cure, have been isolated in all countries that have adequate diagnostic capability to recognize them.⁷ Within a year of the first reports of extensively resistant TB (XDR-TB) in 2006, isolated cases were reported in Italy that had resistance to all first-line anti-TB drugs (FLD) and second-line anti-TB drugs (SLD) that were tested. In 2009, a cohort of 15 patients in Iran was reported which were resistant to all anti-TB drugs tested. The terms 'extremely drug resistant' ('XXDR-TB') and 'totally drug-resistant TB' ('TDR-TB') were given by authors reporting this group of patients. Recently, a further 4 patients from India with 'totally drug resistant tuberculosis' ('TDR-TB') were described, with subsequent media reports of a further 8 cases.⁷

Reports of tuberculosis patients with these severe patterns of drug resistance are increasing. The term 'totally drug resistant' has not been clearly defined for tuberculosis. A new definition of resistance beyond extensively drug-resistant TB (XDR-TB) is not recommended by WHO. While the concept is easily understood, in practice, in vitro drug susceptibility testing (DST) is technically challenging, with problems in drug susceptibility testing of many anti-TB medicines, insufficient evidence to link such DST results to treatment outcomes of patients, and lack of standardised DST methods for several anti-TB drugs (including new ones). XDR-TB severely reduces the options for treatment. Patients who have resistance to additional second-line anti-TB drugs have even more limited therapeutic options.⁷

Mass migrations, urban overcrowding, increasing global air travel, national conflict and civil wars ensure that the disease is spread rapidly. If TDR strains take hold in global populations, the resulting contagion could be catastrophic and in some areas it is already difficult for health authorities to contain. Zimbabwe for instance is grappling with multi-drug resistant tuberculosis (MDR-TB) as patients fail to respond to traditional first-line TB drugs. According to the Ministry of Health and Child Welfare, cases of MDR-TB nearly doubled last year from 156 in 2011 to 244 cases. This was despite the fact that notifications for ordinary TB drastically declined from 47,000 in 2010 to 38,367 in 2012.⁸

Since 2006, India's government has provided free TB medication nationwide. In Hinduja (where the first Indian cases of totally drug-resistant TB were reported) victims get free medications but patients need to go to a clinic, hospital or government drug provider three times a week to acquire them. For day labourers, this is impracticable and they do not take up the offer, take the drugs intermittently, or discontinue treatment prematurely. In the slums, as many as a third of TB patients stop taking their drugs before the standard six-month treatment is complete. New patients are given a combination of four medications, with two months of intensive treatment followed by four months of continuing care. Following the regimen is crucial. If patients do not respond to that treatment, or if they test positive for drug resistance, they are given other, more powerful second-line drugs, which can be highly toxic and are part of a gruelling two year pro-gram very demanding on the ability of poor patients to follow. If a patient stops treatment the bacterium becomes even more resistant to a concoction of ever more toxic drugs.

While the overall incidence of tuberculosis world-wide has gone down in recent decades, the rise of TB in North Korea has been swift. According to a 2012 report by the World Health Organization, between 1994 and 2011, reported cases went from fewer than 50 per 100,000 people to 380 cases. Today, the incidence of TB in North Korea is second only to that in sub-Saharan Africa. Several factors have allowed TB to take a hold, firstly a four-year famine that left malnourished survivors highly susceptible to TB infection, secondly, a shortage of TB drugs at the time and a tendency of locals not to comply with therapy recommended by doctors.⁹ Today, the country's health ministry estimates that up to 15% of patients with TB fail to respond to commonly used first-line TB drugs, which suggests they are carrying drug-resistant strains. Neighbours, like China, are worried as MDR is difficult to treat even with top-tier health programs and North Korea's health responses are politically compromised.

The anti-TB arsenal of drugs is decades old and is being quickly depleted due to resistance. The US Food and Drug Administration has recently approved the first new drug for a long time and several other drugs are also in the pipeline that could help fight resistant strains. Faster and more accurate diagnostic tools are also on the way, including GeneXpert, a machine already in use in India which tests for drug-resistant TB in hours, rather than days.¹⁰

Another approach is to repurpose existing drugs approved for other infections such as the MRSA drug linezolid and the antibiotic metronidazole. New research on genes essential for MTB survival in the host has prompted the search for inhibitors of the products of these attractive targets. These developments are puny considering the enormous challenge of drug resistant TB and the concurrence of HIV-1 plus TB epidemics. As with HIV-1, it is increasingly clear that no single drug can act against TB. It is essential to develop new drug combinations for TB, using new and existing compounds to provide shorter, effective therapy.¹¹ WHO is promoting initiatives for early collaboration among pharmaceutical companies producing investigational new TB drugs, to use these drugs in novel combination regimens and to facilitate their introduction into clinical settings.

Increasing antibiotic resistance resulting in multi-ple drug-resistant tuberculosis (MDR-TB) infection is a major global health challenge and so far there has been an ineffectual response by world health organisation to combat it. If TDR strains take hold in global populations, the resulting contagion and spread of the disease could be catastrophic. The hope is that new drugs and new combination therapies will stem the resurgence of this potentially fatal disease.

Conclusions

Anti-tuberculosis drug resistance is a major public health problem

The pace of new drug development for tuberculosis treatment has been very slow.

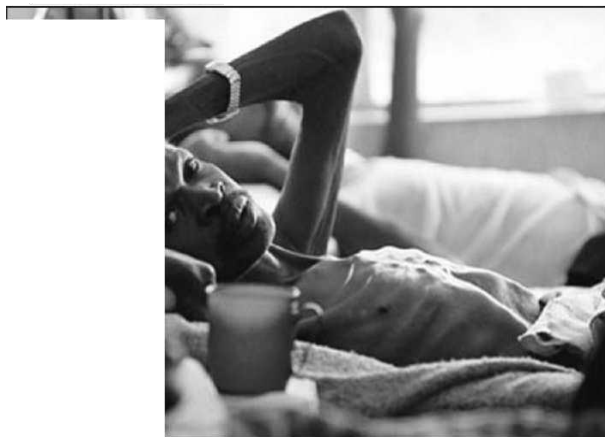
There is a pressing need for properly conducted studies evaluating head-to-head comparisons of available DST methods, in different epidemiological settings, and linked to patient management and clinical outcomes.

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Emaciated tuberculosis patients undergoing treatment in Africa and India