With around nine million new cases and nearly two million deaths every year – almost four lives claimed every single minute – tuberculosis is far from defeated. TB has also become the number one killer of people living with HIV/AIDS. And with almost half a million people developing drug-resistant strains of TB, the time to act is now.

TB is a contagious disease and spreads mainly through the air like a common cold. Only one in ten people infected by the germ will actually develop the disease, as a healthy immune system will keep the infection dormant. These infections can reactivate years, even decades later, if the immune system is weak. Poor populations are most at risk to TB due to cramped living conditions, which favour disease transmission and due to weaker immune systems because of less nutritious diets.

*Mycobacterium tuberculosis* usually affects the lungs. Called pulmonary TB, this form of the disease is characterised by a persistent cough, shortness of breath and chest pain. Other symptoms include weight loss, fever and night sweats. Left untreated, each person with active pulmonary smear positive TB will infect on average between 10 and 15 other people every year. The mycobacteria can also infect almost any part of the body, such as the lymph nodes, bones, the brain and heart. This “extra-pulmonary” form, most common in HIV co-infection, may not be contagious but is equally vital to diagnose and treat rapidly, as all forms of TB are deadly if left untreated.

**Diagnosis**

“What we need urgently is a simple, field adapted and effective test that can tell us, almost instantly and without doubt, if the patient is infected with active tuberculosis. At the moment there’s nothing even remotely like this. Until we have a simple reliable test, many TB patients will keep falling through the net and die untreated.”

Dr. Francis Varaine, MSF TB Coordinator

The tools available to diagnose TB have changed little in the last 100 years, due to lack of research and development. The most widely used techniques to examine a suspected patient’s sputum sample is using a microscope. Although this means diagnosis is cheap and possible even in remote areas provided you have trained staff, there are serious shortcomings associated with this method. Many people with active TB will not have sufficient TB.
mycobacteria in their sputum. In some cases, there is no presence of mycobacteria at all. This is especially true for patients suffering from extra-pulmonary TB and co-infected with HIV. Microscopy is also of limited use for detecting TB in children, because they often do not produce enough sputum to make a reliable sample. Even in the best of hands, microscopy will only detect around half of all TB cases.

Another technique, known as culture, consists of incubating a sputum sample over a few weeks to see whether it contains live TB mycobacteria. Although this is a more sensitive method when performed correctly, it is unfortunately slow, as you need to wait at least three weeks and sometimes up to eight weeks, to be sure no mycobacteria are present. Improvements to culture, such as Thin Layer Agar or MODS (microscopically observed drug sensitivity) are reducing the time to diagnosis and are simplifying the techniques, but culture remains logistically difficult, requiring incubators, a continuous power supply, and skilled staff. More modern methods such as those relying on DNA tests, for example, are too sophisticated to be used widely in developing countries, precisely where tuberculosis takes its heaviest toll.

Treatment

Although TB can be cured, current treatment is complex, lengthy and involves a combination of antibiotic drugs that were developed over 35 years ago. To prevent the emergence of resistance, the drugs are taken in combination. It is therefore recommended that TB drugs be produced in fixed-dose combinations (different drugs combined in a single pill). Treatment must be continued until all the mycobacteria are dead, which takes at least six months. Interruption of treatment before its completion, an irregular compliance to treatment as well as bad quality or insufficient drugs can trigger the selection of mycobacteria that are resistant to the drugs in use, leading to the development of drug-resistant forms of TB (DR-TB) that are more complex and lengthy to treat.

The drugs must also be of quality. This is often not the case, as substandard anti-tuberculosis drugs are widely available on the market in many countries. The World Health Organization is currently assessing the quality of drugs produced by different manufacturers, a valuable exercise which should enable developing countries to purchase “WHO prequalified” drugs of guaranteed quality. Today, only some first-line drugs for TB are “WHO prequalified”. There are no prequalified sources of anti-tuberculosis drugs in formulations suitable for children, nor are there any prequalified sources of streptomycin, one of the drugs used against TB.

Drug-resistant tuberculosis

An inadequate or incomplete treatment course and poor quality drugs are the major factors favouring the emergence of mycobacteria that are resistant to anti-tuberculosis drugs. Drug-resistant TB (DR-TB) has reached alarmingly high levels in many countries around the world and is a serious global health problem. The World Health Organization estimates that there are around 450,000 new cases of MDR-TB every year and 25,000 of these cases are expected to develop XDR-TB. DR-TB is a particularly pressing emergency in Eastern Europe and Central Asia, but it is also growing in incidence in Africa.

What's what in TB Drug Resistance: Some definitions

When the most commonly used drugs are effective against the disease, the patient is said to have drug susceptible TB, or standard TB. Drug-resistant TB (DR-TB), on the other hand, is a strain of TB that presents resistance to one or more anti-tuberculosis drug. A more serious form of this is known as multi-drug-resistant TB (MDR-TB), when patients are resistant to the two most powerful first-line antibiotics, isoniazid and rifampicin. Extensively drug-resistant TB (XDR-TB) is a form of TB where the strains are, in addition, resistant to certain second-line drugs.

The increasing numbers of MDR-TB cases, and the growing body of data showing the poor outcomes of patients taking inappropriate first-line therapy when they have MDR/XDR-TB, reinforces the urgency for access to good diagnostic tools. It is no longer sufficient to just diagnose TB. We need simultaneous, rapid drug sensitivity information, which is necessary to guide treatment. Without this information, a doctor risks treating a patient with drugs that are ineffective and that further fuel resistance.

Treating DR-TB is difficult. Only one of the second-line drugs used against MDR-TB is WHO prequalified. There are very few manufacturers of these drugs, and those

Tuberculosis and HIV: a lethal duo

Most people infected by TB mycobacteria will not develop active TB as their immune response works to keep the disease dormant. But as a person’s immune system weakens, which is what happens with HIV infection, the tuberculosis infection can reactivate. An estimated one third of the 40 million people living with HIV/AIDS worldwide are co-infected with TB.

Tuberculosis is now the leading cause of death among people who are HIV positive: without treatment, about 90% of them will die within months of contracting the disease. Current TB drugs negatively interact with ARVs, making co-treatment of TB/HIV co-infected patients very complex.

We need to adapt our strategies to face this lethal combination, by offering counselling and voluntary HIV testing to TB patients, by actively screening HIV positive patients for TB and by integrating health services for the two diseases.

We also need better tools for diagnosis and treatment of TB in HIV positive patients. Indeed, diagnosis of TB cannot rely on microscopy alone and a more sensitive test is urgently needed so that patients can be started on treatment as early as possible.

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that exist have a limited production capacity, which endangers the regular supply that is necessary to ensure continuous treatment. MDR drugs are less effective than first-line drugs and must be taken for at least 18-24 months. They are also highly toxic and can cause a range of serious side-effects including hepatitis, depression and hallucinations. The patient is often hospitalised for long periods, in isolation.

“We explain that the treatment is very long, with very violent side-effects, and very serious constraints. Those who start this treatment have to know that they will neither be able to work nor sleep with their partner, nor play with their children for a long time whilst infectious... The intensive phase under hospitalisation lasts a minimum of six months. The patient takes a cocktail of five molecules, which means a painful injection every day and a handful of pills every morning and every afternoon.... Side-effects are not only unpleasant, but are, in fact, often unbearable, and can actually be dangerous... it is a treatment that is as violent and toxic as cancer chemotherapy.”

Dr. Cathy Hewison, MSF TB Specialist

In addition, the drugs are extremely expensive: depending on the choice of drugs, a treatment course for MDR-TB can cost up to US$ 15,000 per patient; and sometimes up to 3,000 times more than a treatment course for standard TB. Finally, because of their limited production and the absence of a central buffer stock, due to their short shelf-life, and given the customs and registration barriers, the supply of second-line drugs is extremely complex and erratic.

Although the feasibility and cost-effectiveness of treating patients with MDR-TB in resource-constrained countries is well established, outcomes of MDR-TB treatment remain sub-optimal. MDR-TB can be lethal; 5-20% of HIV-negative patients and 66% of HIV-positive patients die during treatment. The combined frequency of cure and completion often remains below 50%.

Moreover, the poor outcomes of current regimens mean that many of those treated will develop chronic, highly resistant forms of TB that have a high mortality rate and can be transmitted to others. XDR-TB has been reported in at least 37 countries, with very poor treatment outcomes.

The need for better tools

TB has suffered from decades of neglect from pharmaceutical companies, researchers and policy makers, because it offered no lucrative rewards and incentives for investment into R&D. Funding has been running at a disgracefully low level: the annual shortfall for TB R&D has recently been estimated at around US$800 million. MSF is calling for governments and international bodies to step up and reinvest in this killer disease.

After decades of virtually no TB drug R&D, we welcome today the existence of a TB drug pipeline that counts approximately 40 compounds. But, chances are low that a multiple therapies will emerge from the current pipeline, as only about one compound in 20 successfully emerges from an anti-infective drug discovery programme. Since new drugs for TB should only be used in combination, to prevent resistance, it is necessary to attract approximately 60 new lead compounds into the pipeline as quickly as possible. Nothing less will avert the escalation of what is already a major public health catastrophe.

Few of the compounds in the pipeline are in the clinical phase of development. Some of these candidate drugs have been shown to be active against
MDR-TB strains in vitro and can be potentially effective against MDR-TB in human patients. There is an urgent need for innovative thinking in the field of clinical trials for new TB drugs in order to speed up the development of these new tools and accelerate their delivery to patients.

MSF and TB

MSF has fought against tuberculosis since its first day of operations more than 30 years ago and in 2006 treated around 29,000 patients in 40 countries worldwide.

The settings in which MSF provides TB care vary widely. They include areas of chronic conflict, such as Chechnya; refugee camps in Chad or Thailand; prison settings as in Kyrgyzstan. The focus of the projects also vary: some concentrate on integrating HIV and TB services, such as in South Africa and Kenya; others offer treatment to patients suffering from drug-resistant tuberculosis, as in Uzbekistan and Georgia; others reach out to particular populations who have little access to medical care, such as migrants in Thailand. MSF is striving to improve diagnosis of all TB patients, by introducing culture and other tools where possible and assessing the feasibility of other diagnostic methods. In terms of treatment, MSF is currently exploring different ways of ensuring patient adherence, and is committed to using fixed-dose combinations and quality-assured drugs in its programmes. MSF also aims to integrate TB and HIV services where possible, and to treat drug-resistant tuberculosis in appropriate settings.

What needs to be done?

There is a desperate need for:

- New diagnostic tools that are simple, reliable, and field adapted to resource-poor settings;
- Better drugs to shorten the length of treatment, address drug-resistant TB and make possible the integrated treatment for HIV/TB co-infected patients;
- An effective vaccine.

Until that time:

- Governments and pharmaceutical companies must commit to funding research and development programmes that address these needs;
- Pharmaceutical companies must actively participate in the WHO prequalification process to ensure that prequalified sources for paediatric formulations, for streptomycin, and for second-line drugs, are identified. Access to prequalified drugs should be ensured through procurement agencies;
- Manufacture and procurement of second-line drugs should be facilitated to ensure a constant easily accessible supply of drugs for DR-TB;
- WHO and the Stop TB Partnership must keep sounding the alarm: tuberculosis is not under control and more resources and commitment are needed.

[1] Source: Global tuberculosis control: surveillance, planning, financing; World Health Organization; March 2005