TBERCULOSIS

THE LAST MILE
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Mbali lives in a Southern African country with her husband Thando and 18-month-old daughter Aya. They live four hours from the nearest major town. Mbali runs a market stall and Thando works on a sugarcane plantation. One of Mbali’s co-workers has had a cough and fever for several months. This is where the stories diverge – with a vision of tuberculosis (TB) treatment in 2025 that will be safer, simpler and more effective than TB management today.

**Tuberculosis in 2014**

After a month of coughing, chest pains and fever, Mbali’s husband takes her by motorbike to the local primary healthcare centre, 30 minutes away. The nurse asks Mbali to cough up a sputum sample so that she can test it for TB by adding a coloured dye to the sputum and examining it under a microscope – the same test used for the past 100 years. She asks Mbali to return for the results in two days.

When they return, the nurse tells Mbali she has TB. The clinic cannot test for drug-resistance so Mbali is commenced on the six-month treatment for ‘standard TB’. She takes her medication but, at the end of that time, and with little change to her condition, the nurse suspects Mbali has multidrug-resistant TB (MDR-TB) and refers her to the district hospital, four hours away. The doctor takes another sputum sample, and tells Mbali they will have the results in 2-3 months. When they return to the hospital, Mbali is told she has MDR-TB. She is admitted to the MDR-TB isolation ward for two months, and is started on MDR-TB treatment with painful daily injections and many tablets. Thando’s family help with Aya but he still misses many days of work, with significant loss of income.

When she returns home, Mbali must continue taking the TB drugs for another 22 months. The pills cause Mbali nausea, vomiting and dizziness but, more worryingly, she notices that Aya is losing weight – is it TB? Going straight to the hospital this time, Aya is unable to cough up sputum for the test so the doctor puts a tube down her nose into her stomach to collect a sample. After two months they are told that Aya also has MDR-TB and she is started on treatment. There are no child formulations for many of the tablets, so the doctor tells Mbali to cut up adult medications based on Aya’s weight – she does so, but is worried she is giving too much, or not enough. The doctor also warns them that the daily injections Aya needs can cause permanent hearing damage in a child her age.

After another year of MDR-TB treatment – totalling thousands of pills – and daily contact with healthcare providers, the burden on the family is simply too great. They worry about how much time Thando is taking off work – the family is already struggling now that he is the sole source of income and he cannot afford to lose his job – and another year of tablets and medical visits would just be too much. Mbali does not finish her treatment, which increases the risk of her TB reactivating as extensively drug-resistant TB (XDR-TB).
Tuberculosis in 2025

Mbali feels perfectly well but the local health worker visits and tells her she should come in for a TB test; her co-worker on the market stall has been diagnosed with TB and they need to make sure Mbali is clear. Her husband takes her by motorbike to the local primary healthcare centre, 30 minutes away. At the centre, she is screened for TB by a basically-trained health worker using a simple, reliable diagnostic test. Mbali tests positive for TB. After delivering the result, the health worker conducts a second simple test for drug resistance, and within another hour confirms that Mbali has MDR-TB.

Mbali is started on treatment immediately. She needs to take 1-2 pills a day for eight weeks, which will cure her TB. Unlike the MDR-TB treatments used in the past, Mbali’s treatment requires no injections. It also rapidly stops her from being infectious, so there is no need for her to be admitted to hospital to stay in a TB isolation ward. She is able to take her TB treatment at home, which means she can look after Aya, and there is less strain placed on Thando, who does not have to take time off work to care for his family.

There is low risk of Thando or Aya contracting MDR-TB from Mbali, as both had already received vaccinations that, unlike the previous BCG vaccine, provide reliable protection against TB.

With the availability of safe, effective, and affordable products, Mbali and her family are able to recover quickly and to avoid catastrophic health outcomes and costs associated with TB.
DOTS AND THE PLAN TO HALVE GLOBAL TB

In 1994, the World Health Organization (WHO) launched its new TB control approach – the Directly Observed Therapy Short-Course (DOTS) Strategy. DOTS is designed for patients with infective TB of the lungs (pulmonary TB) whose infection is responsive to the standard TB drugs.

A central principle of DOTS is a standardised treatment regime, with direct observation of patients to ensure they take the full course of treatment. TB is diagnosed by examining coughed-up sputum under a microscope, followed by six months of treatment with a combination of the standard TB drugs, multiple times daily. A complete DOTS strategy also includes political commitment, reliable TB drug supply, and strong monitoring and evaluation mechanisms.

In 2006, the WHO ramped up DOTS with the launch of the Stop TB Strategy. The Strategy aimed to halve TB prevalence and mortality between 1990 and 2015, and to eliminate TB by 2050, by expanding and enhancing DOTS.

Since its adoption 20 years ago as the accepted best practice for TB treatment, DOTS has made good progress. Global TB deaths have nearly halved (down 45%) since 1990. Since 1995, 56 million people have been successfully treated for TB, and 22 million lives saved. And TB prevalence has dropped by 50% or more in seven of the 22 highest burden TB countries, such as Cambodia (80% of TB cases globally occur in only 22 countries, with India and China alone making up nearly 40% of cases).

Unfortunately, it proved to be impossible to meet the Stop TB targets using only DOTS. Many diseases are difficult to manage in developing countries, but TB is particularly challenging. This is partly due to the persistent nature of the TB bacterium itself, but the main reason is that our TB tools are old and ineffective – far older than the treatments available for malaria, pneumonia, AIDS and many other tropical diseases. And DOTS did not take into account the prevalence of AIDS and the potential spread of MDR-TB.

Today’s main TB test was developed in 1882. It only detects 45-60% of active TB cases, and far less than that in children and AIDS patients. It cannot detect MDR-TB at all. The current vaccine, the BCG vaccine, was developed in 1921 but is largely ineffective in preventing adult TB. The current TB drugs are from the 1940s-1970s: they work, but only if given in multiple daily doses for months or even years.

At the time DOTS was developed, these old tools were all we had but, because of their weak effectiveness, they require lengthy treatment times that impose a high burden on patients, their families and health
systems. Poor countries often struggle to monitor and evaluate DOTS programmes, to reliably supply a patient with their drugs over many months or years, and to provide the health workers needed to directly observe TB treatment for many thousands of patients. TB management under DOTS is particularly difficult for children and AIDS patients, and can be impossible in situations of conflict or mass migration, where lengthy access to patients is unlikely.

These difficulties mean that, while some countries are doing well, many others are not – particularly countries with less effective central governments, weaker infrastructure or higher rates of AIDS. Fifteen out of the 22 countries with the highest TB burden have not reached the Stop TB prevalence or mortality targets, and 11 of these are not on track to do so.

In response, in May 2014, the WHO announced a new Post-2015 TB Strategy. The new strategy addresses many of the weaknesses of DOTS that afflicted Mbali in the story above: it will actively screen for TB in patients like Mbali, rather than waiting for them to turn up with symptoms; it will rapidly diagnose and treat their MDR-TB rather than waiting for failed treatment; and it will collaborate with HIV care groups for those TB patients who also have AIDS. The Strategy also sets out new and more ambitious targets for the next 20 years, in particular a 95% reduction in TB deaths and 90% reduction in TB incidence.

The key point though – and the Strategy acknowledges this – is that none of these targets can be met with the current TB tools.

**TB and HIV/AIDS**

Without HIV, the TB epidemic would now be in decline almost everywhere.

In countries where the AIDS burden is high, such as Russia and South Africa, TB prevalence has even increased over the past 20 years. In South Africa’s case, there has been a 75% increase since 1990.

TB patients who also have HIV (co-infected patients) are the most rapidly growing group of TB patients, accounting for 13% of TB cases globally. AIDS patients are 30 times more likely to get TB, and TB causes HIV patients to get rapidly sicker, making it the leading infectious cause of death for people who have HIV.

TB is especially difficult to manage in HIV co-infected patients, and DOTS was never really able to address this. TB is harder to diagnose in AIDS patients; and these patients have higher treatment failure rates, higher relapse rates and frequently suffer from complications due to interactions between their TB and AIDS drugs.

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**Fifteen of the 22 high-burden TB countries have not reached the Stop TB targets and half are not on track to do so.**

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**FIGURE 2: TB in South Africa (1990-2011)**

Multidrug-resistant TB: a public health crisis

MDR-TB is resistance to two of the most important TB drugs – meaning it cannot be treated with standard DOTS. XDR-TB is resistance to even more drugs; and totally drug-resistant TB (TDR-TB) is now being reported in some countries.

The WHO has called MDR-TB a public health crisis.3 As of 2012, nearly 4% of new TB cases, and 20% of cases that had previously been treated with standard drugs, were found to be drug-resistant.12 The WHO estimates that there were 450,000 new cases and 170,000 deaths from MDR-TB globally in 2012, with deaths rising rapidly in countries like India.12

If management of TB is difficult in poor countries, management of MDR-TB is far more so. It is not uncommon for a patient to wait two months for an MDR-TB test result; and due to the difficulties involved with diagnosis, the main indication of MDR-TB is often failure of a patient’s first course of standard TB treatment.13

Treatment for drug-resistant TB (DR-TB) can take more than two years and requires hospitalisation in a TB isolation ward for two months, with daily injections for the first six months of treatment. Not only is the treatment much longer for MDR-TB, but MDR-TB drugs are less effective and more toxic. Side effects include psychosis, deafness and nausea,14 and many patients die before the treatment with these weakly-bactericidal drugs can take effect.

A key problem is that most patients and health systems cannot afford to treat MDR-TB. The drugs alone can cost 300 times more than standard TB drugs (around $2000 per patient), and the full cost of treating each patient is prohibitively expensive at an average of $5,000 per patient.2

As a result, fewer than 25% of the world’s known MDR-TB patients receive proper treatment12 and less than half (48%) of those who received treatment in 2010 were successfully cured.1

In the Philippines, for example, just over 5% of MDR-TB cases are detected and notified, and only 42% of these are cured15 – this means that only two out of every 100 MDR-TB patients will be treated and cured.

The Post-2015 TB Strategy sets a goal to diagnose and treat all MDR-TB patients.4 But the reality is that, without the introduction of new MDR-TB treatments that are simple to use and affordable in developing countries, it will not realistically be possible to reach these targets.16

TB patient, Brazil (Credit: WHO/Jean Chung)
THE FUTURE OF TB
Funding TB research & development

In 2014, the WHO made a decisive statement that R&D is the key to controlling and eventually eliminating TB: without discovery, development and uptake of new drugs, diagnostics and vaccines the world will never be free of the threat of TB.

But TB R&D funding is not keeping up with these goals. In 2012, TB received the third highest amount of neglected disease R&D funding globally (behind HIV/AIDS and malaria) – just over half a billion dollars ($502m). However, this funding has been dropping steadily in recent years, with a $73m decrease between 2010 and 2012. TB had the largest absolute decrease in funding out of all the neglected diseases in 2012.

A key issue is that so few countries or organisations provide significant funding for TB R&D. For two decades, most governments have focused their investment on supporting DOTS, with little or no interest in funding the new tools that are now urgently needed to manage TB. In 2012, apart from the United States (US), which gave $169m, only three governments gave more than $10m to TB R&D – the United Kingdom ($18m), the European Commission ($11m), and India ($11m).

Indeed, in 2012, a staggering half of all global TB funding ($249m, 50%) came from just two organisations – the US National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation (who also made up 84% of all philanthropic funding for TB).

Industry also makes a significant contribution, but – unless they work with public partners or Product Development Partnerships (PDPs) – they may be unwilling to take their products through to commercialisation in developing countries, or their commercial products may be poorly suited or too expensive for developing country use.

The TB product pipeline

The investment of this handful of major funders has kept the TB research pipeline alive, and the entry of new PDP funders such as Germany (in 2011) and Australia (2012) is adding to the momentum.

The last decade has seen the development of several new products to diagnose and treat TB. Pharmaceutical companies launched two new TB drugs in 2013 for use in developed world markets, and one of these is now being developed in a fixed-dose combination.
suitable for use in developing countries. MDR-TB diagnosis has also been revolutionised by the Xpert MTB/RIF test, which can diagnose DR-TB in 90 minutes instead of six weeks.

Dozens of new TB leads are in the pipeline. While many of these will fail, particularly in the early discovery and testing stages of development, the chances of success increase rapidly as products move into final-stage clinical testing in humans.

**New TB diagnostics** are needed, including tests for ‘latent TB’ (where the patient’s infection has not yet become active), low-cost accurate screening tests, and point-of-care tests that can be used by health workers to diagnose TB and drug resistance on the spot. Of the approximately 40 diagnostic tests in development, five are already in clinical trials in humans.

**New TB drugs** are urgently needed to meet the Post-2015 TB Strategy goals and to allow scale-up of TB treatment globally, including for AIDS and MDR-TB patients, and children. Of the 66 drug candidates in the TB pipeline, 11 are already in clinical trials – and four new regimens (all from the TB Alliance) are in final-stage clinical trials. Multiple new drugs are needed because TB must be treated with combined multidrug regimens, rather than one medicine alone. Once registered, these will be the first new TB drug regimens developed for and suited to developing countries in over 50 years (see PaMZ case study below).

**New TB vaccines** have been highlighted by the WHO as the single biggest potential contributor to overcoming TB. New vaccines that are needed include more effective and long-lasting childhood vaccines and an adolescent/adult booster vaccine. Of the 28 preventive TB vaccine candidates in the pipeline, 19 are in clinical trials.ii

PDPs are developing 74% of TB vaccines and 73% of TB drugs now in clinical trials; and 23% of TB diagnostics.

While academic and public research groups conduct the majority of early-stage work (basic research, discovery, and laboratory testing), PDPs are the lead organisations in converting these discoveries into new TB products for the developing world.

Of the TB product candidates in clinical trials in 2014, PDPs are responsible for 74% of vaccines and 73% of drugs; as well as 23% of diagnostics in clinical and pre-clinical stages.

PDPs are non-profit organisations that collaborate with private, public and philanthropic partners to identify and fast-track promising R&D opportunities. They help to accelerate the research, development and approval of new and repurposed neglected disease products by pooling resources and filling gaps that exist between the academic and commercial sectors.

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ii Two therapeutic TB vaccines are also in development with the aim of boosting response to TB treatment
Diagnosis of MDR-TB has been revolutionised with the advent of Xpert MTB/RIF, a new test that detects TB and MDR-TB on the spot, reducing TB deaths from delayed diagnosis and mistreatment. Xpert MTB/RIF uses modern methods to provide quicker and more reliable TB detection, confirming drug resistant (DR) strains in 90 minutes instead of six weeks; and can also be used to diagnose TB in children and in patients with AIDS – two groups where diagnosis with the current tools is very difficult. Xpert MTB/RIF was endorsed by the WHO for diagnosis of both drug sensitive (DS) and DR-TB in 2013.

Studies based on five Southern African countries show that Xpert MTB/RIF has the potential to detect approximately 132,000 more TB cases over 10 years – reducing TB prevalence by 28% and preventing 182,000 TB deaths. Other studies estimate that Xpert MTB/RIF could increase TB case detection by up to 13% in some high burden countries. These gains are enabled by wider and more rapid diagnosis and treatment of infected patients, which also reduces TB transmission to others.

Although Xpert MTB/RIF is too expensive for universal use in developing countries (it was originally designed for wealthy markets) it can nevertheless make a difference to millions of TB patients while simpler and more affordable tests are being developed – and is less than the cost of unnecessary or inappropriate treatment. Xpert MTB-RIF was developed by the Foundation for Innovative New Diagnostics, a PDP, in conjunction with Cepheid and the University of Medicine and Dentistry New Jersey; with funding from the US NIH and the Bill & Melinda Gates Foundation.

CASE STUDY

DIAGNOSING DRUG-RESISTANT TB (Xpert MTB/RIF)

PaMZ is the first new multidrug treatment for TB in 50 years. It could revolutionise treatment for TB patients (especially those with DR-TB), and has the potential to deliver huge health systems savings. PaMZ will be a 3-in-1 pill that treats DS-TB, and is also effective in one-third to one-half of DR-TB cases.

PaMZ has the potential for huge health system savings. MDR-TB treatment will be cut from two years to six months and standard TB treatment will be cut by a third, from six to four months. The cost of a full course of PaMZ will be $50-$90, with minimal health system costs – a massive reduction on the current developing country price tag of $5000 to cover the cost of DR-TB drugs and their two years of administration in the hospital and subsequently in the clinic.

PaMZ is also a major improvement for patients. It will reduce the number of pills a patient with DR-TB must take over the full treatment period by 97% – down from 1400 tablets to less than 360. Patients using PaMZ will not need to be hospitalised and isolated for months, as tablets will replace the previous daily injections. PaMZ has the potential to be safer, have fewer side effects, and AIDS patients could be treated with PaMZ without fear of interactions with their AIDS drugs.

PaMZ was developed by the TB Alliance, a PDP. It is now entering final clinical trials, and could be available to patients in developing countries as early as 2018.

Credit: iStockphoto
In the fight against TB, children are the ‘neglected of the neglected’.20 Despite TB being a top 10 cause of child deaths globally, and representing 20-40% of TB cases in some regions,21 children have been excluded more than most in the fight for appropriate TB products. The WHO estimates that in 2012, 530,000 children under 15 were living with TB and 74,000 died from the disease.1 Others estimate that almost one million children are living with TB, including nearly 32,000 with MDR-TB.22

Child friendly treatments do not exist for DS-TB. Doctors or parents must crush or cut up adult tablets in order to get a ‘close enough’ treatment for the child. There are almost no treatments for MDR-TB and, when they do exist, they require lengthy hospitalisation, many pills daily for up to two and a half years, and months of daily injections.

Fortunately, the future looks brighter, with the first new paediatric medicines expected as soon as 2016. The TB Alliance, the PDP developing PaMZ, is working on a child-friendly fixed-dose combination of TB drugs, due in 2016. The TB Alliance is also collaborating with leading paediatric TB experts to understand the magnitude of the childhood TB burden; to encourage more commercialisation of child-friendly drugs; and to clear TB drug regulatory pathways to encourage greater investment. These efforts are aimed at cutting the current lengthy time lag – up to seven years – between a new adult formulation being developed and when it becomes available in a child-friendly formulation.

In 2012, 530,000 children under 15 lived with TB and 74,000 died from the disease.

**CASE STUDY**

**TB IN CHILDREN**

As with every major infectious disease throughout human history, prevention through vaccination is the most cost-effective tool for eradication.23 Without new vaccines, studies have predicted 163 million new TB cases in developing countries between 2024 and 2050.24

Experts suggest that a new TB vaccine, even one that is not very strong and only covers a limited geographic area, would still result in vast health improvements and cost savings. For example, a vaccine that offers 60% efficacy and has 60% coverage in only eight of the high burden TB countries, could still avert over 100 million cases of TB in infants, adults and adolescents in 30 years.24 Other studies in low-income countries, where the majority of TB cases occur, show that a vaccine with 80% efficacy that offered lifelong protection would be even more effective, preventing a remarkable 70% of TB cases over 25 years.24

However, it is not plain sailing. TB vaccines face difficult scientific and technical challenges. Scientists still do not fully understand how TB can remain latent in the body for decades, why it activates in some people but not others, or what mechanisms the bacterium uses to protect itself. And, in the absence of animal models or chemical markers to predict their likely effectiveness, TB vaccine development remains expensive: trials in humans are still the only way of knowing if a vaccine will really work.

**CASE STUDY**

**TB VACCINES**

A vaccine with even 80% efficacy would prevent 70% of TB cases.
The diagnostics, drugs and vaccines we have used for the past 50-100 years are no longer sufficient to defeat TB. Tools that developed countries used to beat TB last century are not suited to managing TB today. They cannot deal effectively with MDR-TB or TB-HIV co-infection, which did not exist when they were invented, and the effort to manage TB with these old tools places a huge strain on developing countries and those who live in them.

As the Post-2015 TB Strategy highlights, intensified research and innovation are crucial to reaching the global TB targets and eliminating TB. For the first time in 50 years, new diagnostics, new drugs and new vaccines are on the way, and could soon be available to those who need them most.

It is troubling then – just as the WHO has called for a re-energised approach to TB and when the new products to deliver on this approach are entering clinical trials – that the funding for R&D of these new products is now falling at a rate harder and faster than that of any other neglected disease.

We applaud existing funders of TB R&D for their efforts and encourage new funders to join them, responding to the WHO call to fund new tools for the fight against TB.

We can do better.
REFERENCES


