Towards ending tuberculosis: what gets measured gets done
The fight against tuberculosis faced two challenges in 2007: co-infection with HIV and the emergence of drug resistant strains made the disease more deadly. WHO and its partners have pursued a culture of measurement and innovation, leading to more effective and affordable diagnostic tests, firm policies for their appropriate use, and several new treatments in the pipeline. In May 2014, WHO launched an ambitious strategy to end TB by 2035, and is elevating the TB fight from the technical to the highest political levels.

During the first five decades of its history, WHO gave TB control widely varying degrees of priority, first swinging up, then down, then dramatically up again in line with the evolving epidemiology of this disease. In 1948, the newly established agency singled out malaria, TB and sexually transmitted diseases, especially syphilis, as epidemics requiring urgent international attention. The discovery of streptomycin in 1944, shown to have striking therapeutic efficacy, meant that it was widely available by 1948. The availability of two new TB drugs, isoniazid and pyrazinamide, in the early 1950s, followed by the discovery of rifampicin some 20 years later, transformed TB from a major killer to a disease that could be easily and cheaply cured, at least in affluent nations.

In the developing world, a series of research studies, supported by WHO and the governments of India and the United Kingdom, laid the foundation for a radical integration of TB control into general health services. Patients were treated in homes instead of segregated in specialized hospital wards. Doctors diagnosed cases based on respiratory symptoms alone. The mobile radiography units – long the symbol of TB control in poor countries – were dismantled. As treatment courses were long, TB control borrowed from the success of the leprosy programme and recommended that patients be directly observed as they took their daily medicines, thus improving adherence.

The tuberculosis epidemic was held at bay, but just barely. The incidence of new cases declined in middle-income countries, but at half the rate seen in wealthy nations.

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By the 1980s, tuberculosis had lost its status as a top international priority at WHO and elsewhere. Research dwindled. Medical journals that had been exclusively devoted to tuberculosis were rebranded as journals covering respiratory diseases. International conferences on tuberculosis diminished in frequency and then stopped altogether. At WHO, only two TB experts were kept on its headquarters staff. TB dropped to the status of a largely forgotten disease. In reality, though, its power to resurge was merely waiting in the wings. That neglect changed dramatically in 1993, when WHO took the unprecedented step of declaring the epidemic a global emergency. The agency had good reasons to do so.

Two major crises

In 2007, when Dr Margaret Chan took office, WHO estimated that 13.7 million people were living with active tuberculosis, including 9.3 million new cases. TB killed an estimated 1.8 million people that year, making it one of the world’s biggest infectious killers. Tuberculosis control faced two major crises. First, the emergence and then explosive spread of the HIV epidemic was accompanied by sharp increases in TB morbidity and mortality. As immunodeficiency spread, more of the roughly two billion people who harmlessly harbour *Mycobacterium tuberculosis* as a latent infection developed overt disease. The two epidemics converged to deliver an especially deadly blow, most notably in sub-Saharan Africa.

Second, strains of the bacterium resistant to multiple drugs emerged, making multidrug-resistant tuberculosis, or MDR-TB, a formidable new threat. Second-line drugs were toxic, difficult to administer, in short supply, and at least 100 times more costly. Whereas treatment of drug-susceptible TB took six months, the time needed to treat MDR-TB was 20 months or more. Even with the best treatment and supportive care available, fewer than 50% of patients could be cured. The threat was global. In wealthy countries, drug-resistant strains showed how quickly they could exploit populations made vulnerable by poverty, illness, social marginalization, or lack of access to basic health care. In the US, MDR-TB gained its first foothold in the homeless populations living on the streets and sidewalks of New York City.

Moreover, TB experts were still reeling from the results of an investigation of an especially severe TB outbreak at Tugela Ferry Hospital located in a rural and desperately poor district in South Africa. The results of that investigation, published in 2006, found 221 patients with MDR-TB. Of these, 53 were infected with a strain that was resistant to the two most powerful classes of first-line drugs but also to at least two of the six most powerful classes of second-line drugs. All 53 patients were co-infected with HIV. Working together, WHO and the US Centers for Disease Control and Prevention defined the newly detected form of this disease as “extensively drug-resistant TB”, or XDR-TB.

Extensively drug-resistant TB was extreme in every sense. It was extremely lethal. Of the 53 patients with XDR-TB, all but one died, with an average survival time of only 16 days following diagnostic confirmation. While some infections had been acquired in the community, the vast majority of infections moved from person to person in the hospital setting. That made the emergence of
XDR-TB extremely alarming, as few hospitals in sub-Saharan Africa were equipped to prevent the spread of infection; many had no reliable supplies of electricity or clean running water.

The news quickly got worse. A retrospective investigation, jointly undertaken by WHO and CDC, of samples stored in an international network of specialized TB laboratories confirmed that XDR-TB had already spread well beyond the African continent. By the end of 2014, XDR-TB had been reported in 105 countries, with the highest incidence in Belarus, Georgia, Latvia and Lithuania.

### Estimated new tuberculosis cases in 2015

![Estimated new tuberculosis cases in 2015](image)

Source: WHO

### A problem-solving culture of innovation

In dealing with these dramatic new threats, WHO and its partners had much to build on. In 2006, a new Stop TB Strategy was launched by WHO following intensive exploration and discussion with the managers of TB control programmes in high-burden countries and their partners, including technical agencies and donors. At that time, broad adoption of the WHO DOTS strategy, or directly-observed treatment, short course, had produced remarkable progress in TB control for nearly a decade. The new strategy was designed to pursue DOTS expansion while adding
five new lines of action judged essential for meeting the MDG TB target. Ways to tackle TB/HIV co-infection and MDR-TB were included together with strategies for strengthening health systems, engaging all care providers in the private and public sectors, empowering people and communities, and promoting targeted research. To support the new strategy, WHO issued a fully costed Global Plan to Stop TB 2006–2015.

WHO had already established a culture of innovation. The Stop TB Partnership, hosted and housed at WHO, demonstrated a remarkable ability to solve problems through the creation of innovative new facilities and mechanisms, including the establishment of a dedicated global drug facility. By procuring drugs at competitive prices and consistently ensuring that their quality met WHO’s stringent standards, the global drug facility brought order to a market previously characterized by chaos.

To address the many problems raised by the emergence of MDR-TB, WHO established a Green Light Committee in 2000 to ensure the supply of second-line drugs, oversee the proper and rational use of drugs, and make them more affordable. Before releasing second-line drugs, the committee rigorously reviewed country proposals to ensure that their use would not further promote drug resistance. That requirement had the additional advantage of transferring high-level expertise in drug management from WHO to national control programmes. The Global Fund backed the initiative by issuing a requirement that all funds for the purchase of second-line drugs must be approved by the Green Light Committee.

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**Policy breakthroughs**

In 2008, WHO and UNAIDS introduced the “3 I’s” strategy for addressing the management of HIV/TB co-infection. Intensified case finding was the first prong of the strategy. Even in an era with widespread access to antiretroviral therapy, too many people living with HIV died because of undiagnosed TB co-infection. WHO recommended that all people living with HIV should be screened for their TB status with a clinical algorithm at each clinical encounter. In the second prong of the strategy, WHO recommended that people infected with HIV, but proven to not have TB, should be given isoniazid preventive therapy for at least six months as part of a comprehensive package of HIV care. That recommendation was strengthened by evidence that the effects of isoniazid preventive therapy augmented the effects of antiretroviral therapy in reducing the incidence of TB. As people with HIV are exceptionally vulnerable to the risk of nosocomial TB transmission, the third prong set out measures for infection control that should be strictly implemented in all facilities providing HIV care.

In July 2011, WHO issued its first-ever negative policy recommendation to tackle diagnostic practices that were both dangerous for TB control and wasting resources in the millions of dollars. WHO urged countries to ban the use of inaccurate and unapproved commercial blood tests to diagnose active tuberculosis. Before making that recommendation, WHO meticulously gathered and verified compelling evidence that these serological tests were inconsistent, imprecise, and put patients’ lives at risk. The many false-positive results delivered by these tests meant that patients took toxic medicines for months, for no reason. False-negative results meant that
people received no treatment and took no precautions to prevent infecting others, a particularly
dangerous failure for an airborne disease that readily spreads via a cough or a sneeze.

WHO estimated that more than a million of these inaccurate blood tests were carried out each
year, often at great costs to patients, who paid up to $30 per test. At that time, the marketing
of blood tests for TB was targeted at countries with weak regulatory control of diagnostics,
where perverse market incentives were allowed to override the welfare of patients. In short,
a multimillion dollar business was selling substandard tests with unreliable results.

That negative policy recommendation had a rapid and welcome impact. In June 2012, India’s
Ministry of Health and Family Welfare banned the manufacture, sale, distribution and use of
the tests throughout the country. The government decree directly attributed that decision to
a “negative policy statement issued by WHO that commercial serodiagnostic tests provide
inconsistent and imprecise findings.”

A breakthrough in testing technology

When the emergence and spread of HIV brought TB roaring back, the tools for coping with the
surge in cases were antiquated. Sputum microscopy, quick and cheap but tedious and prone
to human error, had been the principal diagnostic test for more than a century. Growing the
bacterium in culture was the highly accurate diagnostic “gold standard” but could take up to
two months to get results. Drugs for treating drug-susceptible TB dated back to the 1950s and
1970s, with nothing new since. Needless to say, no ready-made diagnostic tools were on hand
to manage the formidable new challenges of MDR-TB and XDR-TB.

In 2009, case-finding and testing were still missing nearly 40% of suspected TB cases. The
prevalence of MDR-TB had increased to an estimated half a million cases, of whom fewer
than 7% were diagnosed and, of those diagnosed, only one in five received treatment. Nearly
two million people were still dying of TB each year, mainly from drug-susceptible forms of the
disease that could have been easily and cheaply cured.

In the autumn of 2010, a breakthrough looked eminent. The Foundation for Innovative New
Diagnostics, or FIND, in partnership with the Cepheid corporation and the University of Medicine
and Dentistry of New Jersey, had developed a new molecular platform for the diagnosis of TB
using the Xpert MTB-RIF machine, or Xpert. Many – though not all – hailed the new technology
as having the potential to revolutionize TB testing.

With its compact and sleek table-top design that looked like an espresso machine, the Xpert
machine had much to offer. Fully automated, it was easy to use and posed no biosafety hazards
for staff. Large-scale testing and demonstration projects in India and South Africa showed high
sensitivity and specificity in the detection of both drug-susceptible TB and MDR-TB. As a major
advantage, the test produced results in less than two hours instead of weeks or months.
That speed greatly increased the prospects of successful case management: patients waiting
for test results could be immediately started on the right treatment.
However, as sceptical critics noted, operation of the machine required a steady and reliable supply of electricity. The machine needed yearly maintenance and calibration and performed best under controlled conditions of temperature and humidity – luxuries in most facilities providing care in high-burden countries. Moreover, with all its advantages, Xpert came on the market at a prohibitively steep price. The initial market price of different testing machines ranged from $17,000 to $62,000. The cost of the disposable test cartridges, with their short shelf lives and huge demands for storage space and waste disposal, ranged from $17 to $120 – equivalent to the entire annual per capita health expenditure in most high-burden countries.

In September 2010, FIND submitted its dossier of trial results to WHO for evaluation. In December 2010, WHO formally endorsed the use of the new molecular assay. WHO recommended Xpert as the first-choice test for presumptive TB in people living with HIV or suffering from severe disease, and in individuals with presumptive MDR-TB. That endorsement by WHO was the seal of approval needed to change the situation dramatically. What followed demonstrated the power of WHO to get multiple partners working in concert to take an innovation forward in a massive, structured, phase-wise campaign, precisely targeted at hot spots in greatest need and gathering further evidence along the way.

FIND leveraged its investment by directly negotiating price reductions with the manufacturer; reduced prices were offered to nearly 150 purchasers in low- and middle-income countries. The US government, UNITAID, and the Bill and Melinda Gates Foundation provided upfront payment of $11 million to the manufacturer to reduce unit prices further. The price of cartridges dropped from $17 to under $10.

In 2013, UNITAID and WHO started the largest rollout of Xpert ever, with UNITAID investing nearly $26 million to purchase more than 220 Xpert machines and 1.4 million cartridges for 21 countries in Africa, Eastern Europe, and Asia. Through the concerted and determined efforts of multiple partners, high-burden countries were indeed being equipped with a revolutionary new tool for detecting difficult forms of TB.

Other new diagnostic options were also gaining recognition. As part of its programme for the testing of new technologies, WHO evaluated molecular line probe assays for the rapid screening of patients at risk of MDR-TB and issued policy recommendations on their use. WHO also evaluated the use of loop-mediated isothermal amplification (TB-LAMP), a manual assay that required less than one hour to perform and could be read with the naked eye under ultraviolet light. Nonetheless, the ideal of an inexpensive point-of-care diagnostic test that matched the simplicity and accuracy of HIV antibody tests and required no electricity remained elusive.

### New drugs push WHO into a novel role

For the first time in more than 40 years, a novel class of TB drugs with a novel mechanism of action, bedaquiline, was granted accelerated approval by the US Food and Drug Administration in December 2012. That approval, which was based on late phase II clinical data, created a unique dilemma for WHO. As the new drug was so desperately needed for the treatment of MDR-TB, the risk was great that countries would start using it in ways that would contribute to the rapid
development of resistance – causing the world to lose its first new TB chemotherapeutic drug in more than four decades. The lack of phase III trial data on safety and efficacy created another worry: would early use of the drug actually do more harm to patients than good?

These concerns pushed WHO into the novel role of translating available data into guidelines and advice aimed at protecting both patient welfare and the lifetime of the drug. The following year, WHO issued its interim guidance for the inclusion of bedaquiline in the combination therapy of MDR-TB in accordance with existing WHO guidelines for the programmatic management of drug-resistant TB. The guidance set out requirements for patient selection, informed consent, drug administration, monitoring of efficacy, and pharmacovigilance to detect and manage adverse drug reactions and potential interactions with other drugs.

In 2014, WHO performed a similar evaluation of a second novel class of drugs with a novel mechanism of action, delamanid, still in phase III trials but granted conditional approval by the European Medicines Agency in April 2014. WHO interim guidance, published the same year, stipulated the specific conditions and safeguards that must be in place before programmes use delamanid to treat adults with MDR-TB.

In 2015, five anti-TB drugs, including bedaquiline and delamanid, were added to the WHO Model List of Essential Medicines. Four of the newly listed drugs were recommended by WHO for use in the treatment of MDR-TB and XDR-TB. The fifth drug, rifapentine, was indicated for the preventive treatment of latent TB in people living with HIV. The inclusion of these TB drugs in the Model List is expected to stimulate the interest of drug manufacturers to invest more in the development of new anti-TB medicines.

Also in 2016, WHO announced good news for the control of MDR-TB. A new DNA-based test was available that could identify genetic mutations in MDR-TB in just 24 to 48 hours, down from the three months previously required. In addition, WHO announced a new and shorter treatment regimen that allowed MDR patients to complete treatment in half the time and at nearly half the cost. Such innovative steps forward supported the feasibility of new goals.

**The ultimate ambition: end TB**

In May 2014, the World Health Assembly approved WHO’s ambitious new strategy to end the tuberculosis epidemic by 2035. The strategy, with its three indicators and milestones at five-year intervals, had a visionary goal: zero TB deaths, zero TB disease, and zero TB suffering. Three pillars provided the foundation for this visionary goal: integrated patient-centred TB care and prevention, bold policies and supportive systems, and intensified research and innovation. Though ambitious even for an optimistic organization like WHO, the wisdom of aiming high for TB was being firmly endorsed by external economic evaluations.

In January 2015, *The Economist* news magazine published a report on “The economics of optimism”, which ranked the benefit per dollar invested in various development initiatives. Reducing tuberculosis ranked first among health development initiatives, showing a return of $43 on every investment dollar. As *The Economist* noted, the prominence given to TB was a “no-
brainer”. The ranking drew on the work of the Copenhagen Consensus Center, an initiative which commissioned some 60 teams of economists, plus representatives from the UN, civil society, and business communities, to rank the sustainable development targets that would produce the most “phenomenal” value for money. The TB target was one. As the Copenhagen Center noted, “The economic case, put simply, is that TB treatment is low cost and highly effective, and on average may give an individual around 20 years of additional life.”

As a further endorsement, the related Nobel laureates guide to the smartest targets for the world 2016–2030, issued in 2015, pared the 169 targets in the 2030 Agenda for Sustainable Development down to just 19. The nine people-related targets included the reduction in tuberculosis deaths by 90%. As the guide noted, concentrating on this select list of 19 targets could triple the benefits for the world’s poorest.

The new End TB Strategy has another solid reason for its hope. In 2016, WHO estimated that, since the start of the century, efforts to stop TB had saved some 49 million lives. To secure high-level commitment to do even more, WHO will be holding its First ministerial conference on ending tuberculosis in the sustainable development era in November 2017 in Moscow, Russian Federation. As requested in a resolution of the UN General Assembly, a high-level meeting on the fight against tuberculosis will be held in 2018. The momentum to end TB is already building at the highest political level.