



Source: Bull World Health Organ., 2013.

Scaling Life-Saving Interventions Faster *Case Studies Series*

Xpert[®] MTB/RIF

Tuberculosis (TB) is one of the leading causes of morbidity and mortality worldwide. Each year around 10 million people gets infected by TB and more than a million die from it. Drug-resistant TB is an increasing global health threat. One of the main reasons why this disease has been so difficult to control is the lack of a rapid diagnostic method, as well as detection of drug resistance forms in primary care settings. Conventional diagnostic methods are slow, technically demanding and not very accurate. In 2008, Xpert MTB/RIF a rapid, reliable diagnostic test for TB, entered the market and revolutionized TB control, bringing a diagnostic tool closer to the point of care. The following case study highlights key elements that determined the pace of development and uptake of Xpert MTB/RIF.

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This case study is part of a series that explores pathways and important factors that contribute to the development and uptake of global health interventions—from proof of concept to scale-up.

Xpert® MTB/RIF

The Xpert® MTB/RIF, is a fully automated molecular test to diagnose tuberculosis (TB), including its most resistant form rifampin (RIF), in less than 90 minutes and with minimal laboratory expertise.



Source: Bull World Health Organ., 2013.

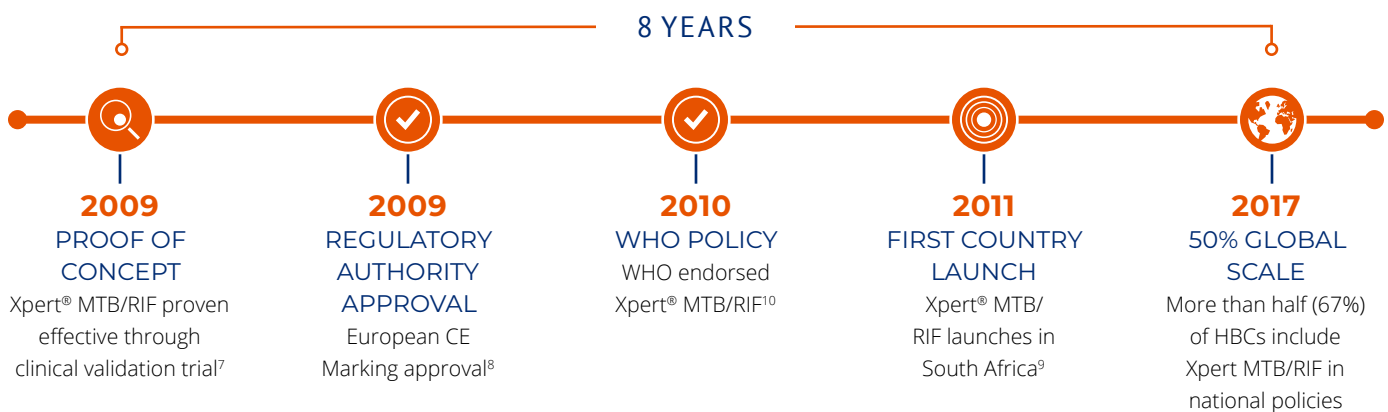
GLOBAL BURDEN OF DISEASE: APPROXIMATELY 10 MILLION NEW CASES AND 1.2 MILLION TB DEATHS IN 2018¹

PROOF OF CONCEPT TO 50% GLOBAL UPTAKE: 8 YEARS

TOTAL DISTRIBUTION:

- ▶ 34.4 MILLION XPERT® MTB/RIF CARTRIDGES PROCURED BY COUNTRIES ELIGIBLE FOR CONCESSIONAL PRICING AT THE END OF 2017²
- ▶ 67% OF HIGH BURDEN COUNTRIES (HBC) INCLUDED XPERT® MTB/RIF IN THEIR NATIONAL POLICY (2017) UP FROM 31% IN 2015^{2,4}

PRICE: \$9.98 PER CARTRIDGE, FOR THE PUBLIC SECTOR IN 145 HIGH-BURDEN AND DEVELOPING COUNTRIES⁵



Tuberculosis (TB) is among the leading causes of morbidity and mortality worldwide. In 2018, an estimated 10 million individuals contracted TB, and 1.2 million died from it.¹

Multidrug-resistant TB (MDR) and extensively drug-resistant TB (XDR) are an increasing global public health concern.¹ Rapid diagnosis and timely and appropriate treatment initiation are fundamental to reduce the burden of TB. Delays in diagnosis and treatment lead to higher morbidity, mortality and transmission. Conventional diagnostic methods (e.g. sputum smear microscopy, culture and drug susceptibility testing (DST)) for TB are slow (6-8 weeks for bacterial growth from samples to be detected), technically demanding, and are not very accurate – resulting in patients going undiagnosed, or diagnosed too late, and not receiving treatment or receiving inappropriate treatment.¹³

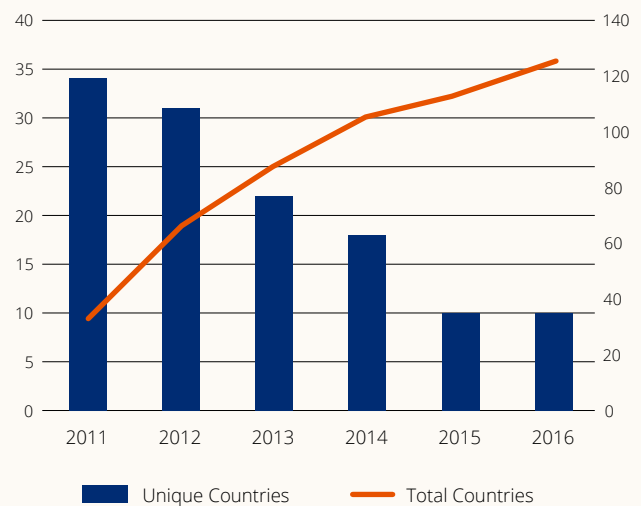
The limitations of conventional TB diagnostics and the pressing need to improve diagnostic capabilities at the point of care drove the Foundation for Innovative New Diagnostics (FIND) to facilitate a partnership between industry (Cepheid) and academia (UMDNJ/Rutgers) in 2006 to improve diagnostics for drug-resistant TB.⁸ This effort was funded by the U.S. National Institutes of Health and the Bill & Melinda Gates Foundation (BMGF). The resulting innovation from this partnership, named Xpert® MTB/RIF, is a fully automated molecular rapid test to diagnose tuberculosis and rifampin-resistant TB. The test provides a diagnosis in less than 90 minutes and with minimal laboratory expertise. It uses a cartridge with the patient’s sample (i.e. sputum, nasopharyngeal aspirate, gastric aspirate and stool (pediatric diagnosis)), and the test is automatically performed by the multi-disease diagnosing platform GeneXpert®.

The development of Xpert® MTB/RIF has been a landmark event in the fight against TB, and is used as an example of a relatively fast pathway from development to scale up. In December 2010, a dynamic policy development occurred in which WHO assessed published and unpublished data on Xpert® (shared before publication thanks to nondisclosure collaborative agreements) and endorsed Xpert® MTB/RIF.¹⁰ Subsequently in 2011, a WHO policy statement recommended the use of Xpert® MTB/RIF as the initial diagnostic test in individuals suspected of MDR-TB or HIV-associated TB.¹⁰ Following these endorsements,

the political will of several institutions (public and private) and multiple countries changed. Xpert® began to roll-out worldwide, primarily in TB-affected regions in low- and middle-income countries. In March 2011, South Africa, which then had the second largest number of cases in the world, “announced a rapid, nationwide scale up of access to Xpert, to be achieved within a 2–3 year period”, and by the end of the year 33 additional countries were providing the diagnostic (Figure 1).⁹

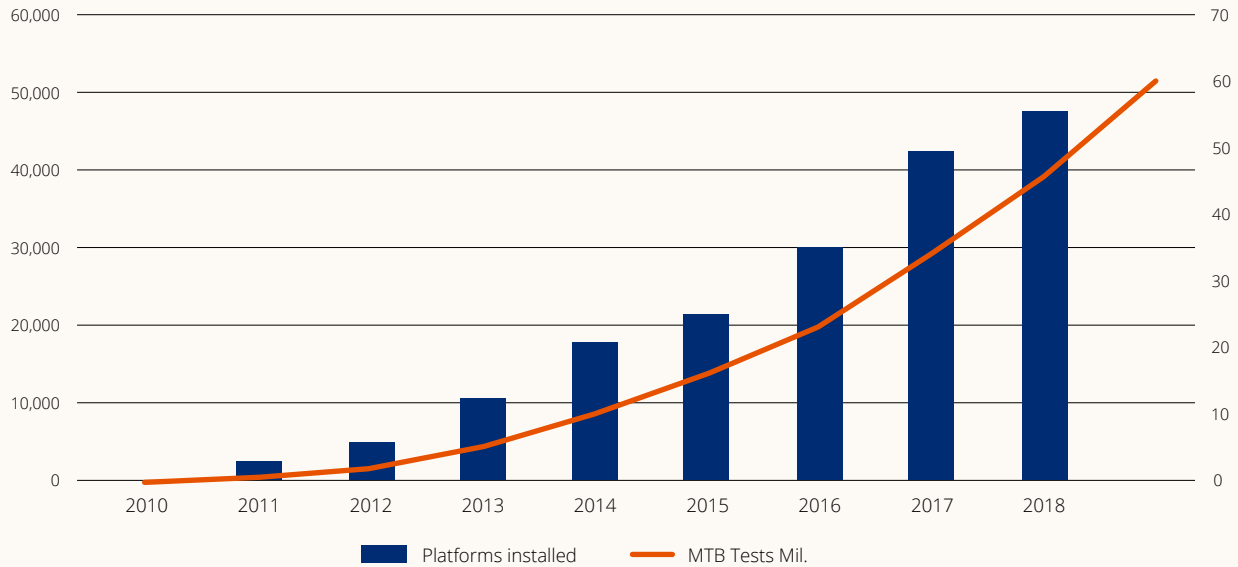
Other key events sped the scale up of Xpert® MTB/RIF worldwide. Prior to launching Xpert, FIND also negotiated prices with the industry to significantly reduce the upfront cost of both the GeneXpert platform and the Xpert MTB/RIF cartridges for LMICs.¹⁴ In August 2012, a public-private partnership made up of PEPFAR, USAID, UNITAID, and the Bill & Melinda Gates Foundation negotiated a buy-down arrangement that resulted in an additional 40% price reduction of Xpert® MTB/RIF cartridges from USD\$16.86 to \$9.98 for 145 high-burden and developing countries, guaranteed until 2022.⁵ Less than a year later, in 2013, after reviewing new scientific evidence, WHO updated its policy and recommended the use of Xpert® MTB/RIF as the initial diagnostic test for all individuals (adults and children) presumed to have

Figure 1. **Country Provision of Xpert MTB/RIF**



Data provided by GDF of public data from Cepheid 2010-2017.

Figure 2. **MTB Tests Delivery Trend vs GeneXpert Platforms Installed**



By Cepheid on an email communication in 2019

TB, thus increasing the potential market size for the intervention.¹¹ These events had a strong impact on the rollout and scale up of Xpert® MTB/RIF worldwide, with the majority of countries providing the diagnostic by 2014 (see Figure 1). Also by 2017, 32 out of the 48 (67%) countries listed as a high TB-burdened country (HBC) included Xpert® MTB/RIF in their national policy as the initial diagnostic test for all people suspected of having pulmonary TB, a 113% increase from 2015.^{2,4} Countries eligible for concessional prices procured 6.2 million cartridges in 2015, up from 550,000 in 2011.^{2,4} By the end of 2018, 46 million cartridges had been delivered to high TB-burdened countries (HBC) (see Figure 2).³

Xpert® MTB/RIF has advanced point-of-care diagnosis, however, its drawbacks include a relatively high cost, reliance on sophisticated hardware to perform the diagnosis (GeneXpert® platform), a stable connection to an electrical power grid, air-conditioned temperatures to operate effectively, a reliable cold chain for storing the cartridges (2-28°C), and trained laboratory staff. These drawbacks all pose critical challenges in remote locations, especially in those with hot climates.¹³ The shelf-life of the Xpert® MTB/RIF cartridge is only 16 months, which necessitates efficient procurement and distribution to assure a

reliable supply of cartridges. Additionally, the lack of uniformity in country procurement processes pose another barrier to scale up. To address this, the Stop TB Partnership’s Global Drug Facility (GDF) provides technical assistance to countries to improve their procurement mechanisms and has a pooled procurement mechanism that allows countries to get better prices for TB drugs and diagnostics.¹⁸

In order to overcome some of these obstacles as well as to improve its diagnostic capabilities, this innovation continues to evolve. In 2015, a plan to bring this diagnostic tool even closer to the most remote point-of-care settings (primary health posts and centers)—the GeneXpert® Omni—was unveiled. This platform consists of a mini-portable, battery operated GeneXpert® system that will not require an air-conditioned environment and a computer, just a mobile device to transmit data that enables its use in the most remote healthcare settings. However, several technical challenges have delayed the Omni’s launch. In response to this delay, in 2018 Cepheid launched the GeneXpert Edge as an interim solution. The Edge is a portable, battery operated platform, but still relies on air-conditioned temperatures and computer, which prevent it from being used as real point-of-care diagnostic.¹⁷

In 2017, Cepheid launched a new updated version of the Xpert® MTB/RIF cartridge, the Xpert® MTB/RIF ULTRA which has a better TB detection capability (increased sensitivity) and a more definitive identification of RIF susceptibility and resistance. In March of that year, the WHO recommended Xpert® MTB/RIF ULTRA as a replacement for the current Xpert® MTB/RIF cartridge.¹⁴

In recent developments, in June 2020, the WHO consolidated guidelines on tuberculosis and recommended that Xpert® MTB/RIF and Xpert® ULTRA should replace the traditional smear microscopy/culture and drug susceptibility testing (DST) as the initial diagnostic test for TB and rifampicin-resistance detection.¹² In July 2020, FIND and Cepheid launched their new Xpert® MTB/XDR test that is able to detect TB that is extensively drug-resistant, the most complicated form of TB (resistant to multiple first-and second-line TB drugs), in anticipation of a review and recommendation by WHO by the end of 2020.¹⁶ At the same time, market competition in LMICs is increasing for Xpert® MTB/RIF, with new diagnostic tests, TruenatTMMTB and Truenat MTB Plus, developed by FIND, Molbio Diagnostics, and the Indian Council of Medical Research (ICMR), endorsed by WHO in July 2020.²⁰

Xpert® MTB/RIF has revolutionized TB control by bringing a rapid, reliable diagnostic nearly to the point-of-care. But in countries where weak and dysfunctional health systems and inadequate infrastructure are highly prevalent, having this tool available does not solve the problem of poor-quality TB services. In order to effectively address the disease burden of TB, a more comprehensive approach is needed. An approach that not only involves expanding the coverage of screening, diagnostics, and treatment services, but also improves the quality and timeliness of those TB services through health system strengthening.¹⁹

KEY INSIGHTS TO LAUNCH AND SCALE

Global public and private sector partners were involved at every stage of the development and scale up of Xpert MTB/RIF catalyzing the speed of uptake and coverage. These collaborative partnerships were key for research, development, and funding which contributed to the generation of the scientific evidence that resulted in WHO's endorsement. Numerous implementation partners

worked with the governments (national and sub-national levels) assisting with the integration of Xpert® MTB/RIF into national TB programs, providing comprehensive training programs, building laboratory capacity, and offering technical support.

Initial price negotiations by FIND and the buy-down arrangements, that reduced the price to less than USD \$10 a test, had a strong impact on making this technology available in the countries most impacted by TB. However, this pricing is only available to the public sector and anyone seeking care in the private sector continues to pay significantly higher prices, estimated to average US\$68.73 per test, for their diagnosis.²¹ Going forward, including high quality private sector providers in lower pricing negotiations could be considered, especially in urban environments where they provide care for significant proportions of the population.

Although product features limited scalability in certain environments, continuous innovation and improvement played an important role in expanding scale and ultimate uptake. Such innovation is necessary to ensure access closer to the point-of-care and to reach remote locations. Limited shelf-life required faster procurement, delivery and distribution processes; cold chain transportation and storage made it more challenging in hot climates and remote locations. Relatively high cost, reliance on sophisticated and expensive hardware, a stable supply of electricity, and skilled laboratory staff, are all factors which pose ongoing challenges to scaling, and are being addressed through ongoing improvements in the product.

A comprehensive approach to TB care is needed. Integrating TB care – screening, diagnosis, and treatment – within primary health care would be an important step forward. Xpert® MTB/RIF is a critical diagnostic tool which will only reach its full potential when it can be used across the health system, including the most distal points of primary care. As Dr Tedros Adhanom Ghebreyesus, WHO Director-General, said during the launch of WHO's latest Global TB Report: "Sustained progress on TB will require strong health systems and better access to services. That means a renewed investment in primary health care and a commitment to universal health coverage."²²

COVID INSIGHT

The COVID-19 pandemic has brought some opportunities and challenges to the scaling of the GeneXpert platform and the Xpert® MTB/RIF cartridges. Cepheid launched a rapid molecular test for COVID, the Xpert Xpress SARS-CoV-2 cartridge, which uses the same GeneXpert machines used for TB diagnosis. This opens the opportunity to scale the deployment of more GeneXpert platforms and likewise the possibility to scale the Xpert MTB/RIF cartridge. This has also triggered some concern among the TB scientific community because of the potential disruption of TB diagnoses due to the re-purposing of testing systems like GeneXpert platforms for COVID.²³

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