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## Making Publicly Funded Medical Technologies Accessible in Developing Countries

# Tuberculosis

## High Price of Publicly Funded GeneXpert TB Diagnostic Impedes Public Health Impact

**Global TB Problem:** Tuberculosis (TB) is estimated to infect about 8.6 million people each year with around 1.3 million dying annually from the disease. 96% of these deaths occur in lower- and middle-income countries. Tuberculosis comes in two major forms, pulmonary (within lungs) and extra-pulmonary (outside lungs)<sup>1</sup>. Both are caused by mycobacterium that, in a stage called latency, can live in an infected person for years without causing symptoms. TB is normally treatable with a set of antibiotics using a method called directly observed treatment short-course (DOTS)<sup>2</sup>. DOTS is effective in most cases, but resistance to antibiotics is a major problem. Drug-resistant forms of TB are estimated to cause about 500,000 deaths annually. A major barrier to effective treatment for drug resistant forms is a lack of accurate and efficient diagnostics<sup>3</sup>.

**Inefficient Diagnostics:** The traditional diagnostic for active pulmonary TB is sputum smear microscopy. This test detects 98% of active pulmonary cases and can detect 91% of resistant cases<sup>4</sup>. It only costs around \$2.50<sup>5</sup>. However, the diagnostic takes between 5 and 10 days for results and is ineffective in detecting pulmonary cases in young children as well as extrapulmonary cases<sup>6</sup>. In addition, the test must be performed in a laboratory by skilled research staff, which makes it difficult or impossible to practice in many settings where it is most needed. Current treatment guidelines suggest immediate treatment with standard drug therapy when presented with clinical signs or a smear positive test. In cases of drug resistance, effective treatment is delayed until further sputum smear and eventually culture tests conclude resistance is present<sup>7</sup>. This delay to treat resistant forms of TB means clinics incur more costs from two courses of treatment and increases the spread of resistant TB.

**New Xpert:** Cepheid released the Xpert MTB/RIF TB diagnostic device in 2010, a result of projects funded by a partnership with the Foundation for Innovative New Diagnostics (FIND) and grants from the National Institute of Allergy and Infectious Diseases (NIAID). It can detect around 50% more cases of TB than sputum smear tests, due to its enhanced ability to detect extra-pulmonary or “smear negative” cases.<sup>8</sup> Xpert is 98% accurate for resistant samples and 94% accurate for diagnosing potential resistance. Rather than requiring 5 to 10 days to deliver results and up to 4 weeks for effective treatment, Xpert provides results in only 2 hours<sup>9</sup> and can allow treatment within 4 hours<sup>10</sup>. Unfortunately, Cepheid’s pricing is prohibitively high for the device to be utilized everywhere it is needed:

- The current price of the GeneXpert machine is \$17,000 or \$17,500 for lower- and middle-income countries, as negotiated by FIND diagnostics and UNITAID<sup>11</sup>.
- The concessional price of the Xpert MTB/RIF cartridge used for TB diagnosis (one test per cartridge) is now \$9.98 per unit, at least until 2022<sup>12</sup> – approximately four-times the cost of the sputum-smear test.
- The machine has a fail rate of around 7%, with a median time around 297 days. In order to be protected from full replacement fees, Cepheid offers a warranty of \$2,900 per year, or a discount of \$6,850 for 5 years.
- Calibration costs \$1,800 per unit when necessary<sup>13</sup>.

While there are other access barriers for the Xpert MTB/RIF diagnostic (such as need for a reliable electricity source), the cost barrier is extreme. Each unit with a five-year warranty would cost a country at least \$23,850 without calibration or Xpert MTB/RIF cartridges for diagnosis. For comparison, the up-front costs of the machine are equal to 9,540 sputum-smear microscopy tests. Even at half the efficacy of Xpert MTB/RIF, this cost difference could pay for nearly 5,000 diagnoses. This number still does not include the cost of the one-time-use cartridge, which is an additional \$9.98 per test.

The cartridges were created with at least four U.S. grants from NIAID – one of the 27 institutes and centers of the National Institutes of Health – and grants from FIND, which is funded by multiple national governments, including three agencies primarily funded by the U.S. government<sup>14</sup>. While the concessional costs of \$17,000 for GeneXpert and \$9.98 for XpertMTB/RIF are significantly lower than the non-negotiated costs of around \$180,000 and \$60, respectively<sup>15</sup>, they still leave the diagnostic out of reach for many.

**WHO Recommendations:** In 2011, the World Health Organization released official recommendations for use of Xpert MTB/RIF in the field. The WHO strongly recommends Xpert as an initial diagnostic for patients with HIV/TB co-infection or presumed to have MDR-TB. There are also conditional recommendations “recognizing major resource implications,” which include using Xpert as a follow-on test to microscopy for those not presumed to have MDR-TB or HIV co-infection<sup>16</sup>. In 2013, the WHO also recommended Xpert for testing of cerebrospinal fluid specimens from patients presumed to have TB meningitis and other specimen from presumed extrapulmonary cases<sup>17</sup>.

**Unreliable Concessions:** According to a letter from Treatment Action Group and the Global TB Community Advisory Board, Cepheid’s concessional pricing has been ignored and misreported in both Russia and China. The letter claims that Russia’s public sector ordered at least 50 units more than the number of concessional units reported by Cepheid. Cartridges were reportedly sold in Russia by a third party at full price. In China, sales reps are quoted giving prices higher than \$180,000 for GeneXpert IV, even with concessional pricing in place<sup>18</sup>.

**Cost is a barrier:** The current pricing scheme for Xpert MTB/RIF still leaves many countries and community health centers unable to provide patients access to the diagnostic, despite the public investment in its development. A WHO expert group policy paper includes several recommendations for use of Xpert MTB/RIF that cite “resource considerations”<sup>19</sup> – i.e. WHO experts recognize that cost is a barrier to expanded use of the diagnostic that would promote optimal health outcomes. For China and Russia, the lack of follow-through on the concessional prices brings into question the implementation of the scheme more broadly. Even with the \$25.9 million TBXpert Program initiated and coordinated by the WHO, there are only 21 countries guaranteed a handful of machines each (225 in total) in the rollout<sup>20</sup>. The full public health benefit of the Xpert MTB/RIF diagnostic tool will not be seen unless the price of the cartridge and unit drop significantly.

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<sup>1</sup>Institute for Health Metrics and Evaluation. *Global Burden of Disease Study*. 2010. <http://www.healthdata.org/gbd>

<sup>2</sup>Knechel NA. Tuberculosis: pathophysiology, clinical features, and diagnosis. *Crit Care Nurse*. 2009; 29(2): 34-43.

<sup>3</sup>World Health Organization. *Tuberculosis Fact Sheet N°104*. 2014. <http://www.who.int/mediacentre/factsheets/fs104/en/>

<sup>4</sup>Steingart KR, Ng V, Henry M, Hopewell PC, Ramsay A, Cunningham J, Urbanczik R, Perkins MD, Aziz MA, and Pai M. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Inf Dis*. 2006; 6(10): 664-74.

<sup>5</sup>REACH Policy Initiative. What is the cost of diagnosing a new sputum smear positive TB case in children in low income settings? *SURE Rapid Response*. 2011. <http://uchpsr.org/Rapid%20response%20taxonomy/Financial%20arrangements/RR22%20Paed%20sputum%20positive%20TB.pdf>

<sup>6</sup>Kwanjana IH1, Harries AD, Hargreaves NJ, Van Gorkom J, Ringdal T, and Salaniponi FM. Sputum-smear examination in patients with extrapulmonary tuberculosis in Malawi. *Trans R Soc Trop Med Hyg*. 2000;94(4):395-8.

<sup>7</sup>Treatment of Tuberculosis Guidelines: 4<sup>th</sup> Edition. World Health Organization: [http://whqlibdoc.who.int/publications/2010/9789241547833\\_eng.pdf?ua=1](http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf?ua=1)

<sup>8</sup>Chemhuru M, Duka M, Nanan-n’zeth KJB, Simons S, Van Den Broucke S, Farajardo E, Bygrave H. Implementation of Xpert MTB/Rif assay in Buhera district, Zimbabwe: lessons learned. *Mediciens San Frontieres*. 2012.

[http://www.msf.org/za/sites/default/files/publication/documents/GeneXpert\\_report\\_Lessons\\_learned\\_with\\_paralel\\_testing.pdf](http://www.msf.org/za/sites/default/files/publication/documents/GeneXpert_report_Lessons_learned_with_paralel_testing.pdf)

<sup>9</sup>Vadwai V, Boehme C, Nabeta P, Shetty A, Alland D, and Rodrigues C. Xpert MTB/RIF: a New Pillar in Diagnosis of Extrapulmonary Tuberculosis? *J Clin Microbiology*. 2014; 52(16): 2540-5.

<sup>10</sup>Cepheid: Xpert MTB/RIF: <http://www.cepheid.com/us/cepheid-solutions/clinical-ivd-tests/critical-infectious-diseases/xpert-mtb-rif>

<sup>11</sup>Foundation for Innovative New Diagnostics. Price for Xpert @MTB/RIF and FIND country List. 2014.

[http://www.finddiagnostics.org/about/what\\_we\\_do/successes/find-negotiated-prices/xpert\\_mtb\\_rif.html](http://www.finddiagnostics.org/about/what_we_do/successes/find-negotiated-prices/xpert_mtb_rif.html)

<sup>12</sup>UNITAID. TB Xpert project – rolling out innovative MDR-TB Diagnostics. 2011. <http://www.unitaid.eu/en/mdr-tb-diagnostics>

<sup>13</sup>FIND 2014.

<sup>14</sup>Cepheid cares about Tuberculosis. Supporting Access to Xpert MTB/RIF in high burden developing countries. 2011.

<http://www.cepheidcares.com/tb/cepheid-vision.html>

<sup>15</sup>Treatment Action Group and Global TB Community Advisory Board. Open letter re: cartridge prices, extended warranties and business in Russia and the People’s Republic of China. 2014. [http://www.tbonline.info/media/uploads/documents/tb\\_cab\\_open\\_letter\\_to\\_cepheid\\_pricing\\_06january2014.pdf](http://www.tbonline.info/media/uploads/documents/tb_cab_open_letter_to_cepheid_pricing_06january2014.pdf)

<sup>16</sup>Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and Rifampicin resistance: Xpert MTB/RIF system. World Health Organization Policy Statement. 2011: [http://whqlibdoc.who.int/publications/2011/9789241501545\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf)

<sup>17</sup>Tuberculosis Diagnostics Xpert MTB/RIF Test Recommendations. World Health Organization. 2013.

[http://www.who.int/tb/publications/Xpert\\_factsheet.pdf](http://www.who.int/tb/publications/Xpert_factsheet.pdf)

<sup>18</sup>TAG and TBCAB. Open Letter. 2014.

<sup>19</sup>WHO Policy Update. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. 2013. Section 5.1:

[http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf?ua=1)

<sup>20</sup>World Health Organization. WHO monitoring of Xpert MTB/RIF roll-out. 2014. <http://who.int/tb/laboratory/mtbrifrollout/en/>