

GeneXpert: A New Tool for Diagnosis of Tuberculosis

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In Bangladesh, tuberculosis (TB) is one of the major public health problems. In 2016 World Health Organization (WHO) rank Bangladesh as 7th among the world's 22 high-burden TB countries¹. With an estimated population of 161 million, these estimates correspond with an annual incidence of about 362,000 all forms of TB cases and about 73,000 deaths annually². Sputum microscopy still remains the primary tool for the laboratory diagnosis of TB. In 2016 Damien Foundation registered 10787 smear negative pulmonary TB clinically diagnosed and extra pulmonary TB². Smear positive TB is responsible for spreading the diseases in the community. Delay in the diagnosis worsens disease process; causes risk of death and enhance TB transmission. In many countries, good quality microscopy of sputum specimens identifies the vast majority (95-98%) of smear positive TB patients³.

The GeneXpert is a new test for TB. It can find out if a person is infected with TB, and also if the TB bacterium of the person has resistance to one of the common TB drugs, rifampicin. Contrary to the tests that exist at the moment, it works on a molecular level to identify 'Mycobacterium Tuberculosis' (MTB). This means that it does not use microscopy but a kind of chemical test to look for the TB bacterium. The GeneXpert is a small machine, about the size of a microwave oven, which can fit easily on a small table. It has been developed in the United States by a company called Cepheid and an organization called the Foundation for Innovative New Diagnostics (FIND), supported by the American National Institutes of Health (NIH). The test is also called the Xpert MTB/RIF (for mycobacterium tuberculosis and rifampicin).

The GeneXpert is a machine that can detect MTB in a sample of sputum. A person suspected of having TB needs to give a sputum sample, which the health care worker then places in a small tube. From the tube, the sample is fed into the machine, and then biochemical reactions are started to see if the sample contains the TB bacterium. The machine looks for the DNA specific to the TB bacterium. If there are TB bacteria in the sample, the machine will detect their DNA and automatically multiply it. This technique is called PCR (polymerase chain reaction)

and allows the machine to also look at the structure of the genes. This is important to detect if a TB bacterium has developed resistance to drugs. The DNA of the TB bacterium is, in a way, like a long string of different colours. If one or more of the colours change (if there is a mutation in the DNA), then the bacterium can become resistant to certain TB drugs. The GeneXpert can test for resistance to one of the most common TB drugs, rifampicin. This means that it can tell us two things: first, whether or not a person has TB, and second, whether or not the TB that the person has can be treated with rifampicin. The test is very quick and only takes about two hours— much faster than the other TB tests, which usually take at least a few days.

In December 2010, WHO endorsed the GeneXpert for use in TB endemic countries and declared it a major milestone for global TB diagnosis. This followed 18 months assessment of its field effectiveness in TB, MDR-TB and TB/HIV co-infection⁴. This test and others that are likely to follow could have the potential to improve the diagnosis of TB in those that are likely to be missed by traditional test⁵. WHO recommended that the test should be used as the initial diagnostic test in individuals suspected of having MDR TB or HIV associated TB. They also suggested that it could be used as a follow on test to microscopy in settings where MDR TB and/or HIV is of lesser concern, especially in smear negative specimen because of lack of accuracy of smear microscopy. WHO did also emphasize that the test does not eliminate the need for conventional microscopy, culture and drug sensitivity testing as these are still required to monitor treatment progress and to detect other types of drug resistance. The GeneXpert can't be used for treatment monitoring as it detects both live and dead bacteria⁶.

In September 2013 UNAID and WHO started the largest rollout of GeneXpert with UNAID investing US \$25.9 million to purchase over 220 GeneXpert machine and 1.4 million test cartridges for 21 countries in Africa, Eastern Europe and Asia. By 2014, the use of GeneExpert had expanded significantly and total 4.8 million cartridges were bought by 116 low and middle income countries at concessional prices. By 2015, 69% of the countries recommended using GeneXpert as the initial

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diagnostic test for people at risk of developing drug resistant TB and 60% recommended it as initial diagnostic test for people living with HIV. Between 2011 and 2016 more than 16 million tests had been carried out in 122 countries⁷.

In 2014, Dr Md Zeaur Rahim, consultant of ICDDRB's bacteriology laboratory, also assessed the effectiveness of GeneXpert in different public health facilities in Bangladesh. By using this automated diagnostic test, additional 13% of patients were identified who initially went undetected in the conventional test⁸ and the study recommended that the National TB Control Program (NTP) should include GeneXpert test for rapid diagnosis of smear negative pulmonary TB and extra-pulmonary TB cases. Hence, from 2014, it has been introduced widely in Bangladesh.

This issue of JAFMC has included a study relating to the GeneXpert test in a population of suspected TB patients which were conducted in Surya Kanto Hospital, Mymensingh from September 2014 to September 2017. The authors found that out of 300 cases, 162 (54%) cases were smear positive and 138 (46%) were negative for MTB. Among the smear negative cases 18 (13.1%) were positive for MTB by GeneXpert test.

The NTP follow the Directly Observed Treatment Short-course (DOTS) Strategy to improve the quality of the TB services. Free of charge diagnostic and treatment services of TB are offered under NTP in various government hospitals in collaboration with non-governmental organizations (NGOs). They have also incorporated the GeneXpert test in smear negative but suspected TB cases in many centres like ICDDR, IDCH, IEDCR, AFIP, Infectious Disease Hospital and other Medical College Hospitals etc. The results of these centers are encouraging in detecting significant number of TB in traditional smear negative cases.

A review⁹ to assess the diagnostic accuracy of Xpert TB found that when used as an initial test to replace smear microscopy it had pooled sensitivity of 89% and specificity of 99%. However, when Xpert TB was used as an add-on for cases of smear negative microscopy the sensitivity was only 67% and specificity 99%.

The main advantages of the test are diagnostic reliability in compare to sputum microscopy and the speedy result in compare to the culture test. For diagnosis of TB, although sputum microscopy is both quick and cheap, it is often unreliable.

It is particularly unreliable when people are HIV positive. Although culture gives a definitive diagnosis, to get result usually takes 2-6 weeks rather than few hours¹⁰.

However the test also has some disadvantages which include the shelf life of cartridge is only 18 months. A very stable electricity supply is required. The instrument needs to be recalibrated annually. The cost of the test is quite high. The temperature ceiling is critical. Therefore it cannot be made available in peripheral and remote centers. The test may be false positive in treated case of TB by detecting the dead mycobacterial DNA¹¹. In future, ultra-sensitive GeneXpert tests will be required to overcome these limitations.

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