

## NEWS

## Manufacturer stands by Xpert tuberculosis test after India study questions its reliability

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A study in India that failed to detect drug resistant tuberculosis in over a third of samples has raised questions about the reliability of a molecular diagnostic test for the disease endorsed by the World Health Organization more than three years ago.

In the study of patients from Punjab the Xpert test, which was designed to simultaneously diagnose tuberculosis and detect resistance to rifampicin—a key first line drug for the infection—falsely classified 21 of 59 samples (35.5%) as susceptible to rifampicin.<sup>1</sup>

Doctors at the All India Institute of Medical Sciences in New Delhi, who conducted the study, said their findings showed that the test might not detect certain genetic mutations that could be associated with drug resistant tuberculosis.

Sarman Singh, professor of clinical microbiology at the institute who led the study, told *The BMJ*, “These are disturbingly high false negative results: patients with drug resistant TB [tuberculosis] could be mistakenly labelled as rifampicin susceptible and could receive inappropriate first line therapy.”

The Xpert test is marketed by Cepheid, a molecular diagnostics company based in Sunnyvale, California, and yields results within two hours—rather than the six weeks taken by the standard bacterial culture techniques used to detect resistance patterns of tuberculosis strains.

In a statement circulated last week to Indian laboratories that offer the test, Cepheid responded to the study, saying that the weight of evidence to support the use of Xpert to detect rifampicin resistance tuberculosis “remains overwhelming.” “One study based on a small, skewed population should not be exaggerated or used as evidence for any actions until further corroborative data are available,” said Martin Colla, Cepheid’s programme manager for Asia.

The test looks for a set of mutations known to be associated with resistance to rifampicin. The study, said Singh, showed that although Xpert had an excellent ability to rapidly diagnose tuberculosis, certain drug resistant strains of the disease in India might have mutations that the test could not pick up.

However, Cepheid officials and independent tuberculosis specialists have noted that the efficacy of Xpert has been validated through studies in Azerbaijan, India, Peru, the Philippines, South Africa, and Uganda.<sup>2,3</sup> And a Cochrane review published last year analysed studies from multiple sites, including Mumbai and Vellore in India, and established that Xpert could detect rifampicin resistance with a sensitivity of 95%.<sup>4</sup>

“We need to look at the totality of evidence rather than just an isolated study with its limitations,” said Madhukar Pai, associate professor of epidemiology at McGill University in Montreal, Canada, who was among the coauthors of the Cochrane review.

Pai told *The BMJ*, “I don’t think that any TB test has undergone the kind of rigorous scrutiny that Xpert has undergone, but if there is something really unusual about drug resistant strains in India, future research should resolve this issue.”

WHO endorsed Xpert in late 2010, and by September 2013 Cepheid had supplied over 2000 instruments used in the test to public sector institutions in 95 countries, at concessional prices.

The Initiative for Promoting Quality and Affordable TB Tests—a platform to promote molecular diagnostic tests for tuberculosis in India—estimated that 50 accredited laboratories in the country’s private sector and about 100 in the public sector offered diagnosis using Xpert.

WHO’s global tuberculosis report from last year estimated that India had the world’s highest burden of multi-drug resistant tuberculosis with about 64 000 patients, followed by China with 59 000 patients and Russia with 40 000.

Bobby John, president of Global Health Advocates, a non-governmental organisation that tracks tuberculosis and other public health issues, said, “Given India’s burden of multi-drug resistant TB, we need to quickly expand the use of rapid molecular diagnostic tools. And Xpert has already been used in Indian settings with good effect: it saves diagnosis time, and wherever it has been used it identifies more and more people with rifampicin resistance.”

In a statement to Indian laboratories that offer the test, Harkesh Dabas, secretary of the Initiative for Promoting Quality and Affordable TB Tests, said that as the All India Institute of Medical Sciences was a “credible research institution,” its claims should be examined for verification. His statement said, “If Indian drug resistant strains have unusual mutations of mixed infections that affect Xpert sensitivity, it is worth investigation.”

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