Editorial

The Good, the Bad and the Ugly of the Next-Generation Xpert Mtb/Rif® Ultra Test for Tuberculosis Diagnosis

Pros y contras de la prueba xpert MTB/RIF® ultra de nueva generación para diagnosticar la tuberculosis

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Tuberculosis (TB) remains a global health concern in the 21st century. It has been estimated that in the year 2015, there were around 10.4 million new cases and 1.8 million deaths attributable to TB.[1] The ambitious global End TB strategy led by the World Health Organization, aims to achieve 90% reduction in TB incidence and 95% reduction in TB mortality by 2035.[2] This will not be possible without more effective vaccines, shorter and safer treatment regimens for both latent TB infection and TB disease (including drug-resistant TB), and improved diagnostic tests. Diagnostic improvement is of paramount importance, given that only two thirds of the estimated number of cases are actually diagnosed or reported to the health authorities. In addition, the high prevalence of drug resistance in many countries urgently requires improved tools for the timely detection of drug-resistant TB.

After many years of limited progress in the TB diagnostic field, several assays have become available for diagnosing TB in the last decade, many of them endorsed by the World Health Organization: Xpert MTB/RIF®, Line Probe Assays, urine lateral flow lipoarabinomannan (LF-LAM) and loop-mediated isothermal amplification (TB-LAMP).[3,4] Among them, Xpert® MTB/RIF (Cepheid, Sunnyvale, USA; hereinafter Xpert) has proved to be the major game changer for TB diagnosis around the world, especially in low-resource highly endemic settings. It is a cartridge-based automated nucleic acid amplification test, which provides results in around two hours. The high sensitivity and specificity for TB diagnosis (around 89% and 99% respectively against liquid culture as reference tests[5]) and the ability to detect mutations in the *rpoB* gene (that confer resistance to rifampicin, proxy of multidrug resistance) are key features that have changed the diagnostic algorithms in most countries of the world. The introduction of this technology has been so impactful that in many settings, Xpert is now the initial test for a TB presumptive patient rather than smear microscopy, which had been the frontline test for TB diagnosis for over 100 years.

At the end of March 2017, the World Health Organization recommended the replacement of Xpert by a next-generation assay, called Xpert® MTB/RIF Ultra (hereinafter Xpert Ultra), based on its increased sensitivity compared to Xpert which could improve the diagnosis of paucibacillary forms of TB disease, such as childhood TB, HIV-associated TB, or extrapulmonary TB.[6] The limit of detection of the new cartridge has gone down from 131 bacilli per ml of sputum for traditional Xpert to 16 for Xpert Ultra. However, the initial head-to-head studies comparing Xpert and Xpert Ultra show that this improved sensitivity comes at a cost of reduced specificity in some patients.[7] The introduction of this new tool, eagerly awaited by the TB community, needs to be welcomed since the results of the first studies conclude that it is at least as good as the traditional Xpert (the good). However, several considerations (here referred as the bad and the ugly or unknown) need to be taken into account in its implementation.

The Good: One of the major limitations of current tests for TB diagnosis is their insufficient sensitivity among vulnerable groups (children, HIV positive patients), whose sputum is often paucibacillary. The new test has so far shown a 17% (95% CI: 10–25) and 12% (95% CI: 5–21) increased sensitivity among smear-negative culture-positive patients and HIV-infected patients in a sample of 1520 persons.[6] This will probably allow TB confirmation in a higher proportion of cases starting treatment. In theory, a proportion of smear-negative or Xpert-negative patients, who would otherwise need further diagnostic work up or antibiotic treatment to exclude other infectious causes of their symptoms, will be able to start treatment right away.

Added good news is that the Xpert Ultra cartridges will run on the same GeneXpert platform used by traditional Xpert cartridges and the concessional price per cartridge will be kept the same (around US$ 10) for low-resourced countries.[8]

The Bad: Available data shows that specificity is lower than for the traditional Xpert, and this specificity cost is higher for

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previously treated patients.[6] This means that this new tests will be yielding a higher proportion of false positive results. This is thought to be due to the detection of non-viable bacilli, which are detected despite successful completion of treatment of a previous TB episode. This decreased specificity means that laboratory results, especially among retreated patients, need to be accompanied by a good clinical history and physical exam. Specificity needs to be further evaluated in the context of active case finding strategies.

The Ugly (unknown): At this point, it remains unclear how a higher Xpert Ultra's sensitivity will impact critical public health indicators such as the number of people starting treatment or even mortality. Despite the considerable increase in sensitivity of Xpert compared to microscopy, its public health gains in studies attempting to measure its impact on mortality were somewhat diluted.[9,10] Likewise, the gains in terms of total number of patients put under treatment after its introduction were modest.[11,12] Both disappointing outcomes are likely to be explained by high rates of empirical treatment and under use/misuse of the test within the TB diagnostic algorithms in certain settings. Xpert Ultra on its own is not likely to greatly modify these indicators, unless TB diagnostic algorithms and clinical practices undergo important changes.

Interpretation of results will be particularly challenging in the context of active case finding programs, such as contact screening or prevalence surveys. Although Xpert Ultra has not been tested yet in these scenarios (this will soon be happening), the interpretation and clinical management of a positive result in asymptomatic patients with or without *rpoB* mutation (especially in the case of a "trace call" result, a new category corresponding to the lowest bacillary burden that can be detected, potentially reflecting incipient/subclinical TB) needs to be elucidated.

The first batches of the new generation test will come with shorter shelf life than traditional Xpert (8 months from manufacturing as of February 2017). It is expected than this shelf life will be increased when more evidence of its durability is available.[7] However, this means that countries will need to be more careful in their procurement and utilization plans, in order to avoid the waste of expired cartridges.

In conclusion, the mass implementation of the new generation test carries the promise of diagnosing more TB patients, but it needs to be embedded in thoroughly designed TB diagnostic algorithms. It is the time to accelerate research efforts in order to fill the existing knowledge gaps about its best use within the TB diagnostic algorithms and obtain the highest gains for TB control.

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