Point-of-care diagnostics for tuberculosis elimination?

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In recent years the development of diagnostics for tuberculosis has progressed rapidly.[1] The major advance has been the GeneXpert MTB/RIF automated molecular assay for rapid diagnosis of tuberculosis and detection of rifampicin resistance, which has been endorsed by WHO.[2] This has led to new optimism, particularly with respect to the use of this assay in low-resource settings with high tuberculosis burden, where diagnostic facilities are often limited to sputum smear microscopy and chest radiograph. Feasibility tests have shown promising results,[3] but concerns have been raised that the assay might not be appropriate for use at scale in peripheral health-care facilities.[4] So studies that assess the clinical effect of this assay have been greatly needed.

In *The Lancet*, Grant Theron and colleagues[5] report the outcome of a randomised trial comparing point-of-care Xpert MTB/RIF with smear microscopy in the management of tuberculosis. This study assesses the new molecular tuberculosis diagnostics from a public health perspective by measuring the clinical effect in several real-life situations, comparing nurse-managed Xpert MTB/RIF with a standard set-up of diagnostics with smear microscopy and radiography in well managed settings in four countries.

The findings are not unexpected: Xpert MTB/RIF improved same-day treatment initiation (23% in the Xpert group *vs* 15% in the microscopy group). Furthermore, fewer culture-positive patients in the Xpert MTB/RIF group who had a positive MTB/RIF test result did not receive treatment (8% *vs* 15%), halving drop-out, and by day 56 fewer patients in the Xpert MTB/RIF group without a positive test had been given treatment on the basis of empirical evidence (17% *vs* 26%). However, surprisingly, the proportion of patients given treatment was not higher in the Xpert MTB/RIF group: 43% of people with suspected tuberculosis were given treatment by day 56 in the Xpert MTB/RIF group compared with 42% in the microscopy group. Yet significantly more culture-positive patients in the Xpert MTB/RIF group were given treatment by day 56 (91% *vs* 84%)—so a higher number of patients with true positive tests were treated—and more culture-positive patients in the Xpert MTB/RIF group were diagnosed on the day of presentation (81% *vs* 43%). Importantly, despite a longer delay to treatment in the microscopy group, there was no effect on the primary outcome, which was difference in morbidity according to the TBscore[6] and Karnofsky performance score in culture-positive patients who had begun treatment; 2 months and 6 months after randomisation the scores were the same in the two groups. Likewise, mortality was 8% in both groups of the study; the study was not powered to detect mortality differences.

These findings will be of major interest to policy makers, because the costs of rolling out Xpert MTB/RIF are very high. Cost-effectiveness studies in low incidence areas have been promising for Xpert MTB/RIF,[7] and mathematical modelling has suggested that implementation of Xpert MTB/RIF could substantially reduce tuberculosis morbidity and mortality in southern Africa.[8] But considering the findings of Theron and colleagues,[5] the substantial financial burden of Xpert MTB/RIF rollout needs to be reassessed to see if it provides value for the cost. Placing very expensive equipment in health-care facilities in rural Africa that might have no electricity and poorly trained, underpaid staff is going to be a difficult undertaking. Are the incremental gains in same-day diagnosis and treatment initiation, as well as reduced loss to follow-up, enough to justify this investment?

Theron and colleagues[5] report from the context of a well managed tuberculosis programme in which sputum smear fluorescence microscopy and good quality radiography were available, and from a high-HIV-prevalence setting where one in four people with

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suspected tuberculosis were culture-positive and nearly every second patient was given treatment according to WHO criteria. In many other high-burden areas the number needed to test would be much higher, and in some studies from areas with high HIV prevalence only one in six people with suspected tuberculosis ended up receiving tuberculosis treatment.[9,10]

In Guinea Bissau, an algorithm based on WHO definitions and TBscore has been used, and only one in ten people received treatment according to WHO guidelines (Rudolf F, Bandim Health Project, personal communication). At a cassette cost of US$10 (reduced price for low-resource settings), testing large numbers of people with suspected tuberculosis will put substantial pressure on already resource-limited tuberculosis programmes in which the drugs for treatment might not always be available. Hence, the provocative question raised by this study is whether tuberculosis elimination is most likely to be advanced by distributing GeneXpert machines to all peripheral health facilities in the world, or by investing the same amount in ensuring that health facilities have the set-up available in this study—ie, well trained and paid staff, electricity, and reagents. I would support the latter, because that approach is likely to promote the necessary shift towards building health care in general—what has been called the diagonal approach to global health[11]—instead of the vertical approach that large-scale implementation of Xpert MTB/RIF entails.

Xpert MTB/RIF is highly appreciated, but, considering the knowledge now available, the benefit of large rollout might be highly context specific. An important use of Xpert MTB/RIF might be mainly in regional facilities in areas where multidrug-resistant tuberculosis is highly prevalent, rather than for large-scale diagnosis of drug-susceptible tuberculosis. Xpert MTB/RIF could have a role in the clinic in better-resourced countries such as South Africa, with high prevalence of multidrug-resistant tuberculosis and drop-out. Until less costly and user-friendly follow-on technologies become available, Xpert MTB/RIF might have a role in tuberculosis hotspots in such settings.

Yet caution is needed, because many patients are wrongly identified as having rifampicin-resistant tuberculosis, and might risk being sent to isolated facilities far from home for unnecessary multidrug-resistant tuberculosis treatment.[12] As the investigators state, the projected epidemiological effect of Xpert MTB/RIF might be overestimated, so this fascinating and promising new tool is unlikely to be the magic bullet that paves the way towards tuberculosis elimination. To reach that goal, better methods for case identification are needed, but the overwhelming number of latently infected individuals should also be targeted.

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I declare that I have no conflicts of interest.

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