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EDITORIAL

Evaluating the impact of Xpert® MTB/RIF on mortality from TB: are we asking the right questions?

K. Chani,[1,2] M. P. Sekadde,[3] R. A. Dlodlo,[4] S. M. Graham[2,5]

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In this issue of the Journal, Walusimbi et al. share findings of a study that used programmatic data to evaluate the impact of on-site access to Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) on case notifications and deaths among people treated for TB in Uganda.[1] Since 2012, the National Tuberculosis and Leprosy Program (NTLP) of Uganda has expanded the implementation of Xpert. During the 3-year period of this evaluation (from 2016 to 2019), 80,976 people with TB were notified to the NTLP, and the number of health facilities with on-site Xpert increased from 96 to 184. The annual TB caseload increased by 27% from 24,287 TB case notifications in the first year to 30,739 in the third year, as did the numbers and proportions that were diagnosed at Xpert "on-site" facilities: from 15,070 (or 62% of case notifications) in the first year of analysis to 24,829 (or 81%) in the third year. However, the proportion of people who were treated for TB but whose treatment outcome was 'died' did not change over time, remaining at 8% in both periods. Death was more common among those detected at on-site Xpert facilities (8.6% of 59,475 notifications) compared to those detected at "off-site" facilities that relied on specimen referral for Xpert testing (7.6% of 21,501). Furthermore, mortality was not lower over time or by site among TB-HIV co-infected patients.

The increase in case detection observed was not limited to an increase in bacteriologically confirmed TB at on-site Xpert facilities and there was a proportionate increase in clinically diagnosed cases.[1] Such findings are consistent with previous studies that found that the introduction of Xpert is consistently associated with an increase in TB case detection and treatment, but not with a reduction in mortality.[2–4] Possible reasons attributed to the lack of impact on mortality have included health system weaknesses that result in delays in treatment initiation, pre-treatment loss to follow-up, high levels of empiric treatment, high levels of unknown treatment outcomes including loss to follow-up, study design issues and the exclusion of high-risk populations most likely to benefit from treatment. Such populations include people with multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) and those co-infected with HIV.[3,5]

The study by Walusimbi et al.[1] evaluated mortality in people diagnosed with and treated for TB. However, does such analyses ask the right questions when trying to determine the full benefits associated with TB diagnosis among people with presumed disease using Xpert rather than sputum smear microscopy? Mortality analyses among those diagnosed and treated for TB – as was also done in previous studies[6] – do not evaluate the impact of Xpert on overall community TB mortality. Left untreated, it is estimated that around half of the patients with TB will eventually die.[7] If a diagnostic can increase case detection, and thereby case notification rate in the population, additional people who would otherwise not have been treated are offered treatment. Therefore, by reducing the pool of undiagnosed and untreated, Xpert may substantially reduce overall TB-related mortality in that population, as well as impact ongoing transmission and incidence of new infections. An important limitation of programmatic data, such as reported by Walusimbi et al., and similar analyses, is that they do not include all people with TB in the community. People who remain undetected and excluded from care cascades are not included in these studies. Xpert has advantages over sputum smear microscopy in that it is more sensitive and therefore detects more people with bacteriologically confirmed TB. However, it is not surprising that among people with TB who are diagnosed and treated, the type of diagnostic employed does not have a significant impact on end-of-treatment outcomes. Xpert has potential impact on outcomes for sub-groups, such as people with MDR/RR-TB, because early detection and initiation of effective treatment is likely to be beneficial. Furthermore, early detection with appropriate treatment for TB may also improve post-TB outcomes of mortality and chronic morbidity.[8] A systematic review and meta-analysis conducted by Romanowski et al. reported that TB survivors had nearly three times higher risk of dying than the general population.[9] An acknowledged limitation of this Ugandan study was that data were unavailable for analysis of people with MDR/RR-TB or of those with TB-HIV by level of immunosuppression.

Finally, an "unintended consequence" of the Xpert roll-out documented in some high TB burden countries, and of the policy recommendation of Xpert as the preferred diagnostic, is that smear microscopy is no longer being used to diagnose TB in settings when Xpert is not available.[10] Stock-outs of Xpert cartridges and other challenges, such as non-functional Xpert modules and inefficient sample transportation, have been reported across TB programmes in low- and middle-income countries.[10] These may lead to delays in diagnosis and treatment initiation or loss to follow-up.

AFFILIATIONS
1 Australian National University, Canberra ACT,
2 Burnet Institute, Melbourne, VIC, Australia;
3 National Tuberculosis and Leprosy Programme, Kampala, Uganda;
4 International Union Against Tuberculosis and Lung Disease (The Union), Bulawayo, Zimbabwe;
5 University of Melbourne Department of Paediatrics, Royal Children's Hospital, Melbourne, VIC, Australia

CORRESPONDENCE
Correspondence to: Kudakwashe Chani, National Centre for Epidemiology and Population Health, Australian National University, Canberra ACT, Australia. Email: Kudakwashe.Chani@anu.edu.au

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It would be important to assess to what extent these issues contribute to lack of mortality benefits among patients treated for TB.

Xpert has transformed the TB diagnostic landscape and an increase in case detection and treatment coverage provides benefits for individuals with TB – and their community – that may not be identified by an analysis limited to programmatic treatment outcome data alone. The full impact on mortality and long-term health outcomes requires analysis within a wider context beyond case notifications, including for specific sub-groups such as people with MDR/RR-TB.

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