# Still dying in plain sight: missed and misclassified deaths due to tuberculosis in hospitals

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**The study reported by Garcia-Basterio and co-workers has used Xpert MTB/RIF Ultra in cadavers for the first time, to improve detection of TB cases that would have ordinarily been missed by histology or clinical examination.** http://bit.ly/2P9Zpyz

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Diagnostic tests for tuberculosis (TB) have undergone an era of unprecedented innovation [1]. Over the past century, the bacteriological diagnosis of TB was primarily based on sputum smear microscopy and culture (solid and subsequently liquid culture). Rapid new molecular tests have been introduced, including the automated nucleic acid amplification test Xpert MTB/RIF (Xpert) and its recent successor Xpert MTB/RIF Ultra (Ultra) [2–4]. Diagnostic algorithms have been developed that combine these new tests with established tools [5–7]; however, such algorithms are often country- or setting-specific, depending on test availability, differ in quality of implementation [2–4, 8], and are infrequently deployed in decedents.

The study by Garcia-Basterio *et al.* [9] shows that the benefits offered by new tests are yet to fully filter down to the patients who likely stand to benefit the most (*i.e.* the sickest patients, who are often inpatients at centralised hospitals). For example, Xpert has proven utility in such patients, including when done on non-sputum specimens [10–12], as does the bedside urine-based Alere lateral flow LAM assay [13], which is the only TB test with randomised clinical trial evidence of a mortality benefit [14], and the promising new urine-based FujiFilm SILVAMP assay [15]. Ultra itself has improved sensitivity for pulmonary TB compared to Xpert [16] but Ultra's utility in establishing TB as a cause of death in hospitalised decedents is hitherto undescribed.

Sensitive tests are critical for identifying missed cases and, when combined with autopsies, guiding TB mortality estimates [17, 18]. Such estimates can inform the effectiveness of TB control measures and, as exemplified by the current study, establish when pre-mortem diagnoses are incorrect. The latter can be due to non-specific symptoms and the limited availability and sensitivity of TB tests (sensitivity is worse in HIV-positive patients due to paucibacillary disease) [19–21]. Furthermore, incorrect or incomplete pre-mortem diagnoses can preclude further investigation. In other words, once an initial diagnosis is established, potential comorbid TB may not be investigated. Finding these missing cases is the major thrust of the World Health Organization (WHO) End TB initiative [22–26].

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An early systematic review and meta-analysis of 3237 autopsies in HIV-positive people found TB to be the cause of death in 39% of adult decedents [17]. In those who died of TB, 46% were undiagnosed at the time of death. Subsequent autopsy studies (table 1) continue to highlight that the status quo has essentially remained unchanged. There thus continues to be high transmission risk to health workers and other patients from undiagnosed TB cases in hospitals. As discussed in a WHO document [27], one solution to limit nosocomial TB transmission is the FAST framework (Find cases Actively, Separate safely, and Treat effectively) which could, for example, be deployed in facilities where autopsies indicate a large burden of undiagnosed TB [28].

Importantly, the aforementioned meta-analysis [17] pre-dated studies that used Xpert. TB detection was thus primarily based on clinical signs and symptoms in combination with smear microscopy and the histological staining of tissue lesions [17, 29]. These tests have suboptimal sensitivity for TB and are typically not done systematically in patients or decedents unless TB was suspected. However, hospitals in high burden settings do not have the capacity and infrastructure to adequately screen and test all inpatients. This is despite a large body of evidence that has consistently proven high burdens of undiagnosed TB in hospitals in endemic countries [14, 30], and the obvious but important fact that these patients represent an easily accessible and semi-captive population. Hence, without the systematic use of new molecular tools, irrespective of the suspected reason for admission, it is likely that diagnoses will continue to be missed in hospitals in high burden countries. Furthermore, without the use of these tools as part of autopsies (irrespective of the suspected reason for death), it is likely that the frequency of TB in decedents will continue to be poorly characterised and we will miss critical data on the performance of TB control interventions. There are also limited data on the frequency and type of comorbidities in which TB occurs amongst decedents. This might prove useful to guide further investigations once a primary diagnosis with a known high rate of comorbid TB is established.

Garcia-Basterio *et al.* [9] report the first use of Ultra for TB detection in cadavers [9]. Using DNA-based tests, including Ultra and an in-house PCR, the authors found 14% of deaths in children and adults (excluding trauma) were caused by TB. Alarmingly, when compared to their complete diagnostic autopsy reference standard, 80% of these TB diagnoses were missed pre-mortem before routine PCR testing was implemented at the facility. Critically, many TB decedents did not report cough or fever at admission. This is indicative of the poor utility (and likely quality) of symptom screening and highlights the importance of having a screening threshold for TB as low as feasibly possible (all HIV-positive patients should be tested).

Importantly, many patients in the study were Ultra-positive for TB, but histology-negative, making use of the latter technique increasingly hard to justify in the molecular era, especially where this is a risk of drug resistance. However, in the case of previous TB that, as a result of remnant mycobacterial DNA, can cause false-positive PCR results [31, 32], histology and other diagnostic modalities may have utility when the clinical picture is not compatible with TB.

Lastly, the study suggests hospitals in high burden settings should routinely do autopsies combined with thorough investigations for TB, especially in a subset of decedents with high risk. This would, for example,

TABLE 1 Selection of recent mortality studies amongst hospitalised decedents

| Study | Key findings and conclusions |
|---|---|
| **Ford *et al.*** [35] **(2016)** | • Systematic review and meta-analysis assessing the proportion of in-hospital deaths in people living with HIV<br>• 18% of deaths were due to tuberculosis (TB) (11% of deaths in paediatric hospitalisations)<br>• Important missed opportunities to link TB detection to HIV care in hospitals, as well as ART provision, are highlighted |
| **Bates *et al.*** [36] **(2015)** | • 62% of inpatients at a tertiary hospital in Lusaka, Zambia had TB as a cause of death, a quarter of which were undiagnosed at admission<br>• 85% of TB decedents were HIV-positive<br>• Common TB comorbidities were pyogenic pneumonia (33%) and anaemia (19%)<br>• Use of a rigorous TB reference standard (including Xpert) during autopsies showed diagnoses at admission were often not accurate |
| **Saavedra *et al.*** [37] **(2016)** | • Review of medical records to identify causes of death amongst HIV-positive inpatients at a tertiary hospital in Ghana<br>• 35% of deaths were due to TB (other frequent causes were cerebral toxoplasmosis and pneumonia)<br>• TB was the only factor associated with early death<br>• Many patients were not initiated on ART at admission; early ART initiation will likely reduce TB mortality in hospitals |

serve as a useful tool to monitor if case detection at admission was sufficiently effective and a proxy of the quality of the diagnostic and treatment programme (including for latent TB infection) in the absence of or complementary to a prevalence survey [22–26]. Such a readout must be linked with interventions that strengthen health worker education and training so that lapses in TB diagnosis or nosocomial infection control can be readily addressed.

Strengths of the study include it being the first evaluation of Ultra in decedents, use of a rigorous diagnostic autopsy reference standard in a large cohort, and an underrepresented setting (Mozambique) where only one previous TB autopsy study has been done [33]. Limitations include a lack of culture, which may help clarify the nature of Ultra-positive results (especially trace results) especially in the absence of other positive results, and the use of Ultra only in a subset of decedents (Ultra's yield, and consequently the rates of TB in decedents, is hence likely underestimated).

So, what are the next steps? We know that TB diagnosed in hospitals in Africa is the tip of the iceberg, that health workers and facilities are unable to routinely identify all patients who need TB testing (such patients often do not have symptoms), there is evidence that new tools (including non-sputum tools) have utility and save lives [13–15, 34] and, perhaps most importantly, that the patients are already right under our noses in hospitals. Clearly, all patients entering hospitals in high burden, HIV endemic settings should be universally tested for TB, irrespective of symptoms. Furthermore, all decedents receiving an autopsy should undergo molecular testing for TB. The status quo in high burden settings is otherwise indefensible. Urgent implementation action from political, national programme, and activist communities is required.

Conflict of interest: B.W.P. Reeve reports in-kind donations of Xpert Ultra cartridges for an unrelated study and travel support to attend a conference from Cepheid, in-kind donations of MTBDRplus test strips for an unrelated study from Hain Lifesciences, outside the submitted work. R. Centis has nothing to disclose. G. Theron reports in-kind donations of Xpert Ultra cartridges for an unrelated study from Cepheid, and in-kind donations and financial support from Hain Lifesciences for an unrelated study.

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