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# **Xpert MTB/RIF — why the lack of morbidity and mortality impact in intervention trials?**

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## **Abstract**

Compared with smear microscopy, the Xpert MTB/RIF assay (Xpert), with superior accuracy and capacity to diagnose rifampicin resistance, has advanced tuberculosis (TB) diagnostic capability. However, recent trials of Xpert impact have not demonstrated reductions in patient morbidity and mortality. We conducted a narrative review of Xpert impact trials to summarize which patient-relevant outcomes Xpert has improved and explore reasons for no observed morbidity or mortality reductions. We searched PubMed, Google Scholar, Cochrane library, and Embase and identified eight trials meeting inclusion criteria: three individually randomized, three cluster-randomized, and two pre-post trials. In six trials Xpert increased diagnostic yield of bacteriologically-confirmed TB from sputa and in four trials Xpert shortened time to TB treatment. However, all-cause mortality was similar between arms in all six trials reporting this outcome, and the only trial to assess Xpert impact on morbidity reported no impact. Trial characteristics that might explain lack of observed impact on morbidity and mortality include: higher rates of empiric TB treatment in microscopy compared with Xpert arms, enrollment of study populations not comprised exclusively of populations most likely to benefit from Xpert, and health system weaknesses. So far as equipoise exists, future trials that address past limitations are needed to inform Xpert use in resource-limited settings.

**Key Words:** Xpert MTB/RIF, clinical trials, impact, study design, limitations, health system weaknesses.

## Introduction

In 2009, the commercial release of the Xpert MTB/RIF assay for the GeneXpert platform (Xpert) represented an important breakthrough in the fight against tuberculosis (TB). With features including sensitivity to diagnose culture-positive TB from sputum samples among persons living with HIV (PLHIV) of about 79%,<sup>1</sup> significantly superior to smear microscopy (45%),<sup>2</sup> ability to detect rifampicin resistance-conferring mutations, capacity to provide results from sputum within 100 minutes, robustness under varying temperature and humidity conditions, and minimal training requirements, Xpert has advanced TB diagnostic capability for clinicians managing presumptive TB patients in resource-limited settings, especially those with suspected HIV-associated TB and persons with suspected drug-resistant TB.<sup>3</sup>

With ample evidence that undiagnosed TB or TB diagnosed late in the course of disease is an important cause of death among persons with HIV,<sup>4,5</sup> there was optimism that rapid scale-up of Xpert in settings with high HIV prevalence, as recommended by the World Health Organization (WHO),<sup>6</sup> would significantly impact key patient outcomes like morbidity and all-cause mortality.<sup>7</sup> For example, modelling studies predicted that, compared with status quo (smear-microscopy), Xpert would avert >100,000 deaths in five sub-Saharan African countries over 10 years.<sup>7</sup> In line with WHO recommendations and published expert opinion,<sup>6,8</sup> several trials set out to evaluate Xpert impact on patient outcomes, including morbidity and mortality.<sup>9-16</sup> Despite optimism, however, published trials of Xpert impact have not yet observed morbidity and mortality reductions. We conducted a narrative review of published Xpert impact trials to answer two questions: (1) what impact has Xpert had on patient-relevant outcomes, and (2) why have Xpert impact trials not demonstrated morbidity and mortality reductions?

## **Materials and Methods**

### **Search strategy**

We conducted a narrative literature review according to published guidelines.<sup>17</sup> We searched PubMed, Google Scholar, the Cochrane Library, and Embase over the time period January 1, 2005, to December 31, 2015 for reports published in English with the terms “Xpert MTB/RIF assay” or “GeneXpert” or “Xpert” and “impact” or “trial” or “clinical trial”.

### **Study selection**

Studies that met the following criteria were included: (1) the study was a clinical trial, as defined by the International Committee of Medical Journals (ICMJ) (i.e., “any research study that prospectively assigned human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes”),<sup>18</sup> (2) the study included Xpert in one of the intervention arms or phases, and (3) a stated primary or secondary aim of the study was to assess Xpert impact on at least one patient-related outcome.

Studies were excluded if there was no direct comparison between patients receiving standard of care (sputum microscopy) and patients receiving an intervention including Xpert; therefore, so-called “hypothetical trials”, where patients received both microscopy and Xpert and investigators hypothesized the impact of Xpert in a scenario where only microscopy was available, were excluded. In addition, studies in which outcomes of patients receiving Xpert were compared with historical national average outcomes when microscopy was standard of care, were excluded.<sup>8</sup> Pre-post trials at the same health

facilities, which compared patient outcomes between pre-Xpert microscopy phases and post-Xpert rollout phases, were included in the review, as these trials meet the ICMJ definition of a clinical trial.<sup>18,19</sup>

The titles and abstracts of studies identified in the search were retrieved and assessed by one reviewer who excluded those that were clearly not relevant. The full texts of remaining studies were assessed for inclusion by four reviewers, using the inclusion and exclusion criteria described above.

### **Data extraction**

Data were extracted directly into a spreadsheet that included the following variables: first and second authors, publication year, abbreviated study name, setting, design, randomization level, sample size, study population inclusion criteria, standard of care, intervention and role of Xpert MTB/RIF in the intervention, key questions related to Xpert MTB/RIF impact on patient outcomes, and key results including diagnostic yield, time to TB diagnosis, time to TB treatment, TB treatment initiation rates, empiric TB treatment initiation rates, loss to follow-up (LTFU) before TB treatment, TB treatment outcomes, overall treatment outcomes among all patients enrolled, and predictors of mortality. In addition, trial limitations as they relate to trial design, conduct, or health system weaknesses were either abstracted or postulated based on published data.

## **Results**

### **Characteristics of studies included**

Eight clinical trials, reported in 11 publications, were included (Table 1). Of the eight trials, six were from sub-Saharan Africa, one from Brazil, and one from Indonesia. All eight trials were considered pragmatic (i.e., conducted in routine healthcare settings, with the potential for existing programmatic

weaknesses to impact trial outcomes). Six of the eight trials included a randomization component, while two were pre-post trials.<sup>13,16</sup> Of the six randomized trials, all had two arms or phases, three were individually randomized,<sup>9,14,15</sup> and three were cluster-randomized.<sup>10-12</sup> Of the three cluster-randomized trials (CRT), one was a parallel group trial,<sup>10</sup> one a stepped-wedge trial,<sup>11</sup> and one a time-randomized trial at a single clinic,<sup>12</sup> where patients were randomized to receive microscopy or Xpert depending on which week they attended the clinic. For the three individually randomized trials, sample sizes were 242, 424, and 1,502 patients. For the three CRTs, the number of clusters were: 51 in the time-randomized trial with 1,985 patients enrolled, 14 in the stepped-wedge CRT with 24,227 patients enrolled, and 20 in the parallel group CRT with 4,656 patients enrolled.

Study populations varied across the eight trials; six enrolled persons being evaluated for TB,<sup>9-13,15</sup> referred to as presumptive TB patients in this review, one enrolled HIV-positive patients starting ART regardless of TB symptoms,<sup>14</sup> and one enrolled presumptive TB patients considered to be at risk for multi-drug resistant (MDR) TB.<sup>16</sup> Six of eight trials were focused on assessing Xpert impact among adults ( $\geq 18$  years at enrollment),<sup>9,10,12-15</sup> while two included both adults and children.<sup>11,16</sup> In the control arms, sputum smear microscopy was used in six trials,<sup>9-12,14,16</sup> tracheal aspirate smear microscopy in one trial,<sup>15</sup> and sputum fluorescent smear microscopy in one trial.<sup>13</sup>

### **Xpert Impact on TB Diagnostic Cascade**

All eight trials reported diagnostic yield of bacteriologically-confirmed TB (i.e., the percentage of study enrollees providing sputum samples who tested positive for TB via either microscopy or Xpert). In six of eight trials, Xpert achieved higher diagnostic yield than microscopy (Table 2); in these six trials, compared with microscopy, Xpert increased TB diagnostic yield by a factor of about 1.6,<sup>9</sup> 1.2,<sup>10</sup> 1.5,<sup>11</sup> 1.5,<sup>12</sup> 3.0,<sup>15</sup> and 1.2,<sup>16</sup> respectively.



In the four trials that reported time from sample collection to result availability among drug-sensitive TB positive cases, Xpert reduced this time in three trials<sup>9,13,15</sup> (Table 2). In these three trials,<sup>9,13,15</sup> Xpert and microscopy tests were performed on-site (i.e., at the point-of-care), whereas in the trial that showed no difference in time to result availability, both Xpert and microscopy tests were performed off-site at a separate laboratory.<sup>14</sup>

Six of eight trials reported median time from enrollment or sputum collection to standard TB treatment initiation among all patients who started TB treatment, regardless of reason for starting TB treatment; in four of six trials there was either strong evidence the median time to treatment was shorter<sup>9,11,12</sup> or weak evidence it was shorter<sup>13</sup> in the Xpert than microscopy arms (Table 2). In these four trials, Xpert reduced median time to TB treatment by about 1 day,<sup>9</sup> 3.3 days,<sup>11</sup> 4 days,<sup>12</sup> and 1 day,<sup>13</sup> respectively.

In the one trial comparing time to diagnosis of rifampicin resistant (RR) TB and time to second-line TB treatment between Xpert and culture arms, Xpert reduced time to diagnosis from 75 days to 1 day, and time to second-line TB treatment from 88 days to 16 days (Table 2).<sup>16</sup> Xpert was located on-site in the post-Xpert phase, whereas in the pre-Xpert phase, all culture and drug susceptibility testing occurred at an off-site laboratory.

In the seven trials reporting percentages of enrollees initiating drug-sensitive TB treatment by study end,<sup>9-15</sup> TB treatment initiation rates were only significantly higher in the Xpert arm in one trial.<sup>12</sup> Across the seven trials, among presumptive TB patients, TB treatment initiation rates ranged from 12.5% to 81% in the microscopy arms and from 10.8% to 85% in the Xpert arms (Table 2).

In the one trial reporting the percentage of enrollees initiating second-line TB treatment among presumptive MDR TB patients, the percentage starting second line increased from 39.3% in the microscopy and culture phase to 58.5% in the Xpert phase (Table 2).<sup>16</sup>

Among seven trials reporting the percentage of enrollees receiving empiric TB treatment (i.e., TB treatment based on clinical picture or chest x-ray) by study end, five reported higher percentages of enrollees receiving empiric TB treatment in the microscopy than the Xpert arms; in these five trials, Xpert reduced the percentage of enrollees receiving empiric TB treatment by about 35%,<sup>9</sup> 48%,<sup>10</sup> 47%,<sup>12</sup> 53%,<sup>13</sup> and 54%,<sup>15</sup> respectively (Table 2).

### **Xpert Impact on Patient Outcomes**

In the two trials reporting the percentage of bacteriologically-confirmed TB patients LTFU before TB treatment start,<sup>9,10</sup> one trial reported lower LTFU in the Xpert arm (15% vs. 8%,  $p=0.03$ )<sup>9</sup> (Table 3). In the one trial reporting the percentage of RR TB patients LTFU before second-line TB treatment, the percentage LTFU before second-line treatment initiation declined from 52.4% to 31.0% after Xpert rollout ( $p<0.001$ ).<sup>16</sup>

Only one trial compared TB treatment morbidity outcomes, as measured by TB scores and Karnofsky Performance Scores after TB treatment initiation;<sup>9</sup> in this trial morbidity scores were similar between arms (Table 3).

Of eight trials, five reported incidence of unfavorable outcomes following TB treatment initiation (i.e., LTFU, death, TB-attributable death, or some combination of these outcomes).<sup>9,12,13,20,21</sup> Across the five trials the percentage with unfavorable TB treatment outcomes was similar between microscopy and

Xpert arms (Table 3). In the one trial that compared incidence of TB-attributable death following TB treatment initiation between microscopy and Xpert arms, TB-attributable deaths were reported to be significantly lower in the Xpert than microscopy phase (2.3% vs. 3.8%),<sup>21</sup> but there was considerable LTFU (15.9% in Xpert phase and 16.2% in microscopy phase), limiting ability to interpret this finding (Table 3).

In all six trials that compared all-cause mortality between microscopy and Xpert arms,<sup>9,10,12-15</sup> no difference in all-cause mortality was observed at any time point after enrollment (Table 3). Two trials compared risk of LTFU between Xpert and microscopy arms<sup>13,14</sup> and in one trial LTFU incidence was higher in the microscopy (10%) than Xpert (2%) arms ( $p < 0.001$ ),<sup>13</sup> but sensitivity analysis suggested this did not affect the conclusion of no mortality difference between arms (Table 3).

### **Predictors of Outcomes**

Five trials reported multivariable models describing predictors of mortality among trial enrollees. In the four trials that enrolled presumptive TB patients, being HIV-positive vs. HIV-negative (two trials), being HIV-positive and not on ART vs. HIV-negative (1 trial), being HIV-positive with ART status unknown vs. being HIV-positive and not on ART (1 trial), and not knowing HIV status vs. being HIV-negative (2 trials), were factors predictive of mortality. In the fourth trial reporting a multivariable model, which enrolled only HIV-positive patients starting ART, CD4 count  $< 100$  cells/ $\mu$ L vs.  $\geq 100$  cells/ $\mu$ L was predictive of mortality.

### **Discussion**

Across the eight trials reviewed, Xpert generally had a beneficial impact early in the TB diagnosis and treatment cascade: six of eight trials reported improvements in yield of bacteriologically-confirmed

drug-sensitive TB among patients who provided sputa, three of four trials reported reduced time to drug-sensitive TB-diagnosis, four of six trials reported reduced time to drug-sensitive TB treatment, and five of seven trials reported reduced rates of empiric drug-sensitive TB treatment in the Xpert compared with the microscopy phase or arm. In addition, in the one trial examining impact of Xpert on drug-resistant TB treatment outcomes, compared to culture, Xpert achieved remarkable reductions in time from sputum collection to RR TB detection, reductions in time to second-line TB treatment, and reductions in apparent LTFU before second-line TB treatment. However, Xpert had less impact in later stages of the TB diagnosis and treatment cascade; rates of TB treatment initiation were similar between microscopy and Xpert arms in six of seven trials, TB treatment outcomes were similar between arms in all five trials reporting this outcome, and mortality was similar between arms in all six trials reporting this outcome. There are several possible reasons related to trial design, trial conduct, and prevalent health system weaknesses that might help explain why improvements in outcomes early in the diagnostic cascade did not translate into observed improvement in final patient outcomes (Table 4).

## **Trial Design**

### *Higher Rates of Empiric TB Treatment in the Microscopy Arms*

Despite improvements in diagnostic yield of bacteriologically-confirmed TB in Xpert arms in most trials, higher incidence of empiric TB treatment in the microscopy arms meant that likelihood of TB treatment by study end was similar between microscopy and Xpert arms in most trials, with empiric TB treatment of culture-positive smear-negative TB patients in the microscopy arms largely removing any potential for observed Xpert impact (Table 4).<sup>22,23</sup> For example, in the TB-NEAT study,<sup>9</sup> of the 68% of patients with smear-negative tuberculosis in the microscopy arm, that were later correctly detected by Xpert, 93% were treated empirically anyway (Table 4). In these trials, an important driver of empiric TB treatment in the microscopy compared with the Xpert arms may have been that clinicians

administering the study were not blinded to the diagnostic used and were aware of the study hypothesis. Therefore, in all study settings, clinicians would have known firstly that there was a relatively high pre-test probability of true TB among all patients enrolled, and secondly that the predictive value of a negative test was lower in the microscopy arm than the Xpert arm, resulting in higher empiric TB treatment in the microscopy arm.<sup>22</sup>

### *Study Populations not Exclusively Focused on Priority Populations*

Of the eight trials, six enrolled presumptive TB patients, one HIV-positive adults starting ART, and one patients with presumptive drug-resistant TB. In the six trials enrolling presumptive TB patients, HIV prevalence ranged from 8% to 76% (Table 4). The main advantage of Xpert over smear-microscopy in diagnosing drug-sensitive TB is ability to diagnose culture-positive smear-negative TB, which is more common among PLHIV, especially PLHIV who are significantly immune-compromised,<sup>24,25</sup> since waning immunity is associated with reduced pulmonary immunopathology<sup>25</sup> with liberation of lower concentrations of bacilli into the airways. Therefore, with smear microscopy sensitivity higher among HIV-negative persons ( $\pm 69\%$ ) than among PLHIV ( $\pm 45\%$ ),<sup>2</sup> one would expect Xpert impact on TB diagnostic yield and therefore morbidity and mortality to be higher among exclusively HIV-positive study populations than study populations including HIV-negative persons.<sup>23</sup>

The only study to assess Xpert impact among exclusively HIV-positive persons was by Mupfumi *et al* in Zimbabwe. In this study, other limitations (e.g., very high rates of empiric TB treatment in both arms and small sample size (N=424)), might explain lack of observed impact. The high rates of empiric TB treatment observed in the Zimbabwe trial raise the issue that, although Xpert should increase diagnostic yield of bacteriologically confirmed TB to a greater extent in HIV-positive than HIV-negative populations, rates of empiric TB treatment are also likely to be higher in HIV-positive than HIV-

negative populations.<sup>23</sup> Consequently, restriction of Xpert impact trials to exclusively HIV-positive outpatient populations might not, by default, increase probability of observing Xpert impact on mortality.<sup>23</sup>

Only one pre-post trial from Indonesia enrolled patients considered at high risk of MDR TB.<sup>16</sup> This trial showed remarkable impact of Xpert in reducing median time to RR TB diagnosis (from 75 to 1 day) and in median time to second-line TB treatment (from 88 to 16 days). In addition, there was a reduction in LTFU of RR TB patients before second-line TB treatment initiation. Although there are limited data on Xpert impact among patients at risk for MDR TB,<sup>26</sup> the reduction in time to diagnosis and appropriate treatment of RR and MDR TB has potential to reduce transmission and mortality from MDR TB and prevent emergence of extensively drug-resistant (XDR) TB.<sup>7,26,27</sup> However, patterns of empiric initiation of second-line TB treatment among patients at risk of MDR TB also need to be considered when evaluating Xpert impact.<sup>23</sup> It is perhaps surprising that only two of the eight trials examined Xpert impact among exclusive priority populations for Xpert rollout (i.e., HIV-positive patients at high risk for TB and presumptive MDR TB patients).<sup>6</sup>

#### *Most Trials Evaluated Xpert Impact among Outpatients*

A recent meta-analysis of autopsy studies in resource-limited settings showed that the majority of deaths among HIV-infected inpatients that were due to TB (37%), involved disseminated TB (>85%).<sup>4</sup> Although the autopsy meta-analysis among hospitalized patients is not representative of all deaths among PLHIV, this finding suggests that disseminated TB is a common precursor to death among patients who die from TB.<sup>4</sup> Therefore, restricting trial enrollees to healthier outpatients, who are unlikely to have disseminated TB, in six of eight trials (Table 4), through study exclusion criteria,<sup>9</sup> enrollment at outpatient primary healthcare clinics (PHCs),<sup>10-12</sup> or because study enrollment required

sputum production,<sup>9-14</sup> might have excluded many patients likely to benefit from early accurate TB diagnosis with Xpert. In these outpatient study populations, the improvements in time to diagnosis and time to TB treatment through earlier confirmation of bacteriologically-confirmed TB with Xpert, might not have resulted in significant improvements in patient morbidity or mortality outcomes.<sup>23</sup>

In the two trials that did enroll presumptive TB patients admitted to hospital (i.e., very ill patients),<sup>13,15</sup> other study limitations restrict ability to detect Xpert impact on patient outcomes. For example, in the Uganda pre-post trial,<sup>13</sup> sample size was small (N=477), empiric TB treatment was higher in the microscopy phase, a higher proportion of enrollees in the Xpert phase had  $\geq 1$  danger sign, Xpert sensitivity was surprisingly low among smear-negative TB patients (42%), and patients who died within three days of admission were excluded from analysis. In the South African study enrolling Intensive Care Unit presumptive TB patients,<sup>15</sup> only 30% of enrollees were HIV-positive, and there were higher rates of empiric TB treatment in the microscopy than Xpert arms.

It should also be noted that, compared with healthier outpatients, sicker patients admitted to hospital with TB symptoms have higher rates of empiric TB treatment.<sup>23,28</sup> Therefore, among sicker, hospitalized patients, empiric TB treatment might again replace any benefit associated with Xpert's improved diagnostic sensitivity.<sup>23</sup> If future trials were to evaluate Xpert impact on mortality among hospitalized HIV-positive patients, recent data suggest that rapid Xpert testing for disseminated TB, especially Xpert testing of urine, in the intervention arm would be important in addition to Xpert testing of sputum, which has become standard of care in many settings.<sup>4,28,29</sup>

*Either not Powered to Detect a Morbidity or Mortality Outcome or Under-powered to Detect these Outcomes*

Of the eight trials reviewed, only three had primary study aims of assessing Xpert impact on morbidity or mortality outcomes (Table 4).<sup>9,10,14</sup> TB-NEAT aimed to assess Xpert impact on 2- and 6-month morbidity scores among culture-positive patients who started TB treatment.<sup>9</sup> As described above, the higher incidence of empiric TB treatment in the microcopy arm probably explains lack of observed impact of Xpert on morbidity.<sup>23</sup> However, another possible explanation is that, among relatively healthy outpatients with presumptive TB, a very large sample size would be needed to detect differences in morbidity scores at 2 and 6 months of TB treatment, raising the possibility, in retrospect, that the study may have been under-powered.

The XTEND trial aimed to detect a 50% reduction in 6-month mortality in the Xpert compared with the microscopy arms, based on preliminary data from a pilot study at two PHCs showing a potential 74% reduction in mortality.<sup>10</sup> However, a recent meta-analysis of autopsy-confirmed causes of death among PLHIV suggests that among hospitalized PLHIV, about two-fifths (37%) of deaths were due to TB, and in nearly half of TB deaths (one-fifth of all deaths), TB was undiagnosed *antemortem*. Although the study population in the autopsy meta-analysis is different to the XTEND study population, the autopsy meta-analysis suggests that a more accurate and rapid TB diagnostic like Xpert, through early, accurate TB diagnosis and subsequent treatment *antemortem*, might avert about one-fifth (20%) of deaths among persons with advanced HIV. Among mixed HIV-positive and negative populations Xpert impact might be lower. More recent trials of TB diagnostics have assumed 20% reductions in mortality for power calculations.<sup>30</sup> Therefore, XTEND may have over-estimated Xpert impact mortality in the study population.

In power calculations for the randomized trial from Zimbabwe,<sup>14</sup> investigators assumed a 67% reduction in mortality and a 58% reduction in TB incidence giving an overall 61% reduction in mortality or TB in



the first six months of ART. Again, the autopsy meta-analysis suggests the study may have over-estimated Xpert impact on all-cause mortality in power calculations.<sup>4</sup>

### **Trial Conduct**

All trials were conducted in a programmatic setting where LTFU of enrollees is a problem; however, in five of eight trials LTFU restricted ability to fully interpret key outcomes (Table 4). LTFU among study enrollees can result in non-differential or differential outcome ascertainment error between arms. Non-differential error in outcome ascertainment between arms can result in reduced power to detect true differences in morbidity and mortality, while differential outcome misclassification between arms can bias study outcomes. It is possible, as was done for the XTEND trial, to monitor and report LTFU in both arms, and then through subsequent tracing activities ascertain final vital status. Such tracing activities help to reduce impact of LTFU on ability to interpret study outcomes.<sup>31</sup>

### **Health System Weaknesses**

In all the trials reviewed, certain health system weaknesses probably blunted ability to detect Xpert impact on patient outcomes (Table 4). Common health system weaknesses included high prevalence of unknown HIV status at enrollment in four of five trials reporting this variable ( $\geq 15\%$ ),<sup>10-12,15</sup> and low ART coverage among known HIV-positive persons in all three trials reporting this variable (26%–31%).<sup>9,10,15</sup> Notably, sub-optimal HIV management (i.e., unknown HIV status, HIV-positive and not on ART, or HIV-positive with unknown ART status) was predictive of poor final outcomes in four trials.<sup>9,10,15,21</sup> Recent data show that all PLHIV regardless of CD4 count or disease stage should start ART to reduce mortality risk.<sup>32</sup> Therefore, in an HIV-positive person not on ART, earlier TB diagnosis and TB treatment through Xpert rather than microscopy may carry lower health benefit.<sup>23</sup>

Another health system-related weakness was high LTFU before TB treatment in three trials<sup>9,10,16</sup> and high LTFU following TB treatment initiation in four trials.<sup>9,12,13,21</sup> LTFU of patients before they can fully benefit from TB treatment indicated by an accurate TB diagnosis diminishes Xpert impact. In XTEND, secondary analysis of trial data showed low compliance with clinical care algorithms following a negative Xpert or microscopy test (i.e., low adherence to a care plan including chest x-ray, sputum culture, or hospital referral within 2 weeks of a negative test).<sup>33</sup> Improving compliance with the algorithm following a negative Xpert test might increase impact of the whole Xpert algorithm on mortality.<sup>33</sup> Operational research to identify health system strengthening interventions that should be implemented in conjunction with Xpert rollout to maximize Xpert impact could inform best practices for Xpert scale-up.<sup>10</sup>

## **Conclusion**

In conclusion, despite improvements in diagnostic yield among patients who can produce sputa, reductions in time to diagnosis, and reductions in time to TB treatment in Xpert compared with microscopy arms in most trials, Xpert was not shown to impact the all-important patient outcomes of interest (patient morbidity or mortality). Trial characteristics related to trial design, trial conduct, and health system weaknesses might explain lack of observed impact. The higher rates of empiric TB treatment in microscopy compared with Xpert arms was a key feature in most trials that contributed to lack of observed Xpert impact on mortality. This suggests empiric TB treatment remains an important strategy for clinicians, especially where Xpert is not available. So far as equipoise exists, future trials of Xpert impact, that take into account past trial limitations, would be helpful to inform Xpert use in resource-limited settings.

## Authors Statements

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**Authors' contributions:** SDL and AFA conceived the study. AFA led development of the search criteria, abstraction tools, abstraction exercise, and prepared the first draft of the manuscript. All authors contributed to the literature review, data abstraction, writing the manuscript, and critically revising the manuscript for intellectual content. All authors have read and approved the final manuscript. AFA is the guarantor of the paper and submitted the paper for publication after receiving approvals from all authors.

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