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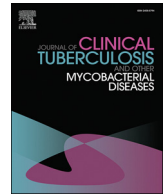
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Implementation science to improve the quality of tuberculosis diagnostic services in Uganda

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ABSTRACT

Nucleic acid amplification tests such as Xpert MTB/RIF (Xpert) have the potential to revolutionize tuberculosis (TB) diagnostics and improve case finding in resource-poor settings. However, since its introduction over a decade ago in Uganda, there remain significant gaps along the cascade of care for patients undergoing TB diagnostic evaluation at peripheral health centers. We utilized a systematic, implementation science-based approach to identify key reasons at multiple levels for attrition along the TB diagnostic evaluation cascade of care. Provider- and health system-level barriers fit into four key thematic areas: human resources, material resources, service implementation, and service coordination. Patient-level barriers included the considerable costs and time required to complete health center visits. We developed a theory-informed strategy using the PRECEDE framework to target key barriers by streamlining TB diagnostic evaluation and facilitating continuous quality improvement. The resulting SIMPLE TB strategy involve four key components: 1) Single-sample LED fluorescence microscopy; 2) Daily sputum transport to Xpert testing sites; 3) Text message communication of Xpert results to health centers and patients; and 4) Performance feedback to health centers using a quality improvement framework. This combination of interventions was feasible to implement and significantly improved the provision of high-quality care for patients undergoing TB diagnostic evaluation. We conclude that achieving high coverage of Xpert testing services is not enough. Xpert scale-up should be accompanied by health system co-interventions to facilitate effective implementation and ensure that high quality care is delivered to patients.

1. Introduction

The World Health Organization (WHO) estimates that at least one-third of tuberculosis (TB) patients worldwide are not being diagnosed or treated - the so called "Missing 3 Million" [1]. Better diagnostics are critical to improving case finding and ultimately patient and public health outcomes. Smear microscopy has been the standard of care for over 100 years but has poor sensitivity, missing at least half of all TB cases [2]. Smear microscopy also requires patients to make multiple visits to health centers, resulting in high rates of loss to follow up [3,4].

To improve case detection, there has been considerable donor and country investment in novel diagnostics. However, there has been relatively little attention paid to the quality of care provided alongside new diagnostics to patients undergoing TB diagnostic evaluation.

In 2010, Xpert MTB/RIF (Xpert) became the first nucleic acid amplification test endorsed by the WHO [5], with subsequent guidelines in 2013 endorsing Xpert as the first-line TB test for all patients [6]. Xpert is a semi-automated PCR-based test that is more sensitive than microscopy (85% vs 50–60%) [7] and provides results within two hours, including whether or not rifampin resistance is present. Since its

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endorsement by the WHO, Xpert testing capacity has been scaled-up rapidly in high burden countries [8]. By the end of 2016, a total of 6659 GeneXpert instruments (comprising 29,865 modules) and more than 23 million cartridges had been procured in the public sector in 130 of the 145 countries eligible for concessional pricing [9]. The number of modules and cartridges has continued to increase exponentially in the past few years.

Uganda has been a leader in the scale-up of Xpert on a population basis [8,10,11]. Similar to many other high burden countries, the Uganda National Tuberculosis and Leprosy Program (NTLP) and National Tuberculosis Reference Laboratory (NTRL) established a hub-and-spoke model for nationwide roll-out of Xpert in 2012 [12]. Testing sites (i.e., hubs), now present in most districts of the country, are linked with 3–5 peripheral microscopy units (i.e., spokes). Sputum samples collected at the peripheral microscopy units are transported to the testing hubs and results are returned to the microscopy centers after testing is completed. The NTRL has also installed GxAlert (SystemOne, USA) software at testing hubs to enable central monitoring of test results and device performance.

No formal impact studies of this massive scale-up of Xpert testing have been carried out. Review of national case reporting data indicates a nearly four-fold increase in confirmed MDR TB patients from 2009 to 2017, small increases in TB case notification from 40 to 42,000 cases before 2010 to 57,756 cases in 2017, and an increase in the proportion of bacteriologically-confirmed cases from 60% to 65% to 87% in the same period [13]. However, while some of these increases are potentially attributable to Xpert scale-up, there remain unresolved questions critical to understanding the effectiveness of Xpert scale-up and to identifying opportunities to further improve case finding. These include: How rapidly and efficiently are Xpert referral networks functioning from both the health system and patient perspectives?; What is the variability in quality of TB diagnostic care within Xpert referral networks?; and What policy changes and co-interventions could further enhance Xpert implementation?

Over the past 3–4 years, we have tried to address some of these questions in a collaborative partnership with the Uganda NTLP and NTRL. Our objectives have been to:

- 1) Quantify gaps in the process of TB diagnostic evaluation at peripheral health centers linked to Xpert testing sites.
- 2) Identify modifiable barriers to high quality TB diagnostic evaluation; and
- 3) Develop and test theory-driven interventions to improve the quality of TB diagnostic evaluation.

All summarized studies underwent review by Institutional Review Boards (IRBs) at both the University of California, San Francisco (UCSF) and Makerere University, and participants were appropriately consented except when IRBs granted an explicit waiver of informed consent.

2. Defining the quality gap

To define the quality gap, we assessed adherence to national and international guidelines [12,14,15] for evaluation of patients with presumed TB at 24 peripheral health centers (hubs) linked to 16 Xpert MTB/RIF testing sites (spokes; Fig. 1) [16]. We included health centers that: (1) used sputum smear microscopy as the primary method of TB diagnosis; (2) participated in NTLP-sponsored external quality assurance for sputum smear microscopy; and (3) referred sputum samples to a district or regional health facility for Xpert testing. We excluded health centers that (1) performed sputum smear microscopy on less than 150 patients per year and (2) diagnosed less than 15 smear-positive TB cases per year using data from 2015. 24 health centers meeting these criteria and located outside of, but within 150 km of the capital region of Kampala were selected in consultation with the Uganda NTLP. We prospectively extracted individual patient data from routine TB

registers on all adults evaluated for pulmonary TB at these health centers. We excluded data on patients who (1) had sputum collected for monitoring of response to anti-TB therapy; (2) had sputum collected as part of active, community-based case finding (e.g., contact tracing, community outreach campaign); (3) had a documented prior history of TB treatment (e.g., reason for Xpert testing or TB treatment marked as treatment failure, relapse, or treatment after loss to follow-up); (4) were referred to a study health center for TB treatment after a diagnosis was established elsewhere; (5) were started on treatment for presumptive extra-pulmonary TB only; or (6) were less than 18 years old. Data from TB registers were used to capture their outcomes at each step of the TB diagnostic evaluation cascade of care, including whether they underwent sputum-based TB testing, TB testing dates and results, and treatment initiation dates. We used these data to assess quality indicators derived from national and international guidelines for TB care [12,14,15]: 1) the proportion of patients with presumed TB referred for sputum-based TB testing; 2) the proportion completing TB testing if referred (defined based on national guidelines as a single valid Xpert result or examination of at least two sputum smears (if HIV-negative); and 3) the proportion rapidly (i.e., within 14 days) initiated on TB treatment if smear- or Xpert-positive.

Over a 12-month period from January to December 2017, 6744 adults underwent evaluation for pulmonary TB at the 24 study sites [16]. We found that 79% were referred for sputum-based TB testing, 56% completed TB testing if referred, and 75% were treated within 14 days if smear or Xpert results were positive. The gaps at each step indicate that the cumulative probability of a patient with sputum smear- or Xpert-positive TB being diagnosed and treated upon presenting to these health centers was only a 43%. In addition, with respect to Xpert utilization, only 20% of patients with presumed TB (33% of people living with HIV infection (PLHIV) and 7% of people living without HIV infection) were referred for Xpert testing, and only 53% of patients with positive Xpert results were initiated on treatment within 14 days. The low uptake of Xpert testing for PLHIV is particularly concerning as rates of smear-negative disease are higher and thus continued reliance on smear microscopy can lead to unacceptably high rates of false-negative results [17].

Data from quality indicators at 24 peripheral health centers in Uganda demonstrated that despite rapid scale-up of Xpert testing using a hub-and-spoke model, the overall quality of TB diagnostic evaluation remains poor and that there are considerable opportunities to enhance Xpert implementation. In particular, few patients received Xpert testing (including those recommended to have Xpert as a first-line test) and nearly half with positive Xpert results were not being rapidly linked to treatment. In addition, we also showed that it is possible to use routine data sources to monitor and improve the quality of TB services at the facility-level, a capacity that is an important pre-requisite for establishing any mechanism for continuous quality improvement.

3. Understanding the quality gap

We conducted a series of mixed methods studies using the Theory of Planned Behavior as our conceptual model. This is a well-known behavioral theory proposed by Ajzen in 1985 to understand factors that affect an individual's intention to carry out a certain behavior [18]. According to this theory, clinicians' knowledge and attitudes, perceived social pressure, and perceived behavior control will impact their intention to follow TB diagnostic evaluation guidelines. In addition, we hypothesized that certain patient- and health system-level factors might make it easier or harder to take up or consistently adhere to guidelines (Fig. 2). We collected data on these factors using qualitative and quantitative approaches.

From interviews ($N = 22$ staff at 6 health centers) and field observation of health center staff (one 2–3 day field visit at each of 6 health centers), we identified key barriers across four thematic areas: human resources, material resources, service implementation, and

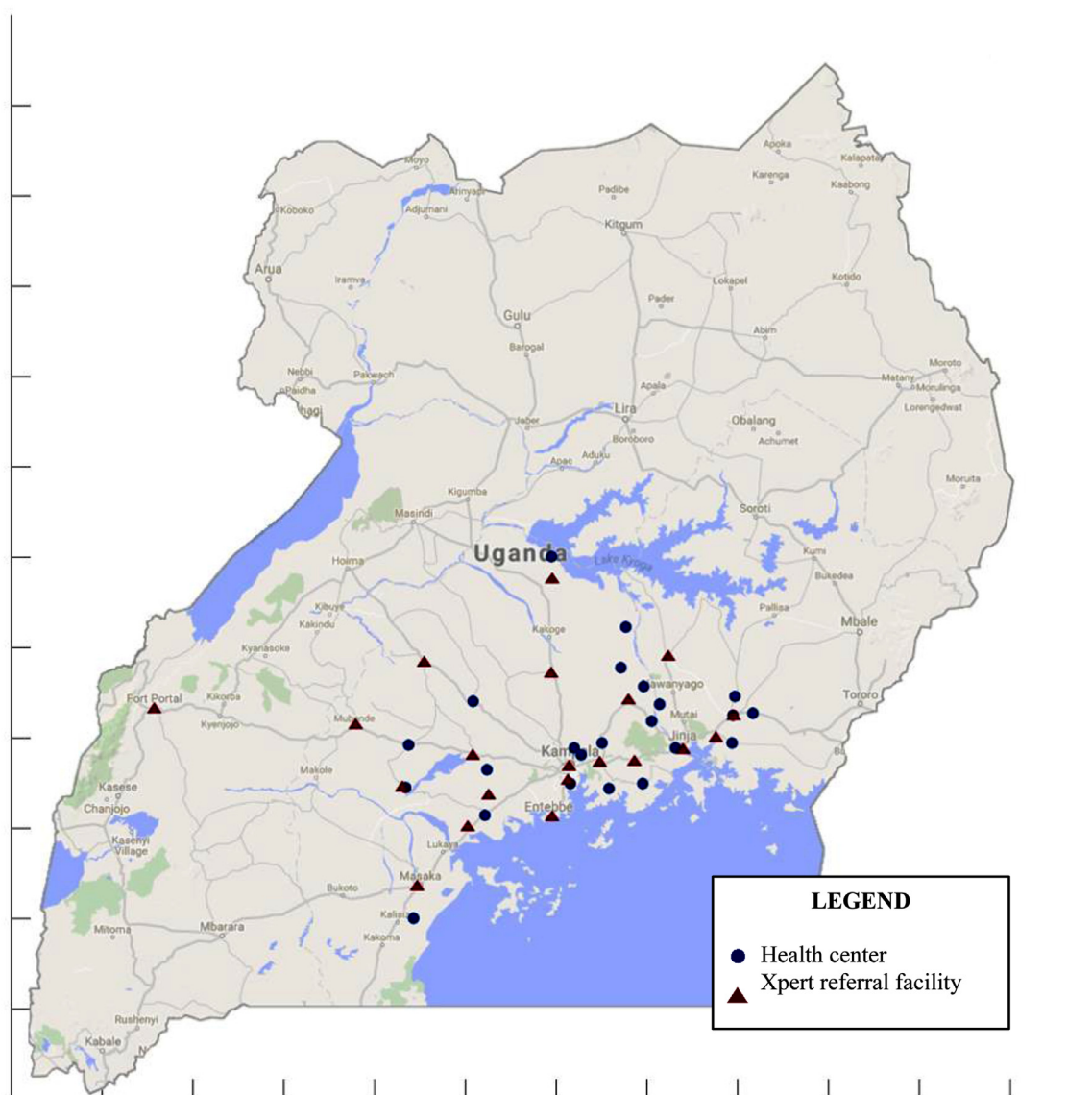


Fig. 1. Location of study sites. The map shows the location of study sites, including 24 peripheral health centers with TB microscopy units (circles) and the 17 Xpert testing sites (triangles) to which they refer sputum samples.

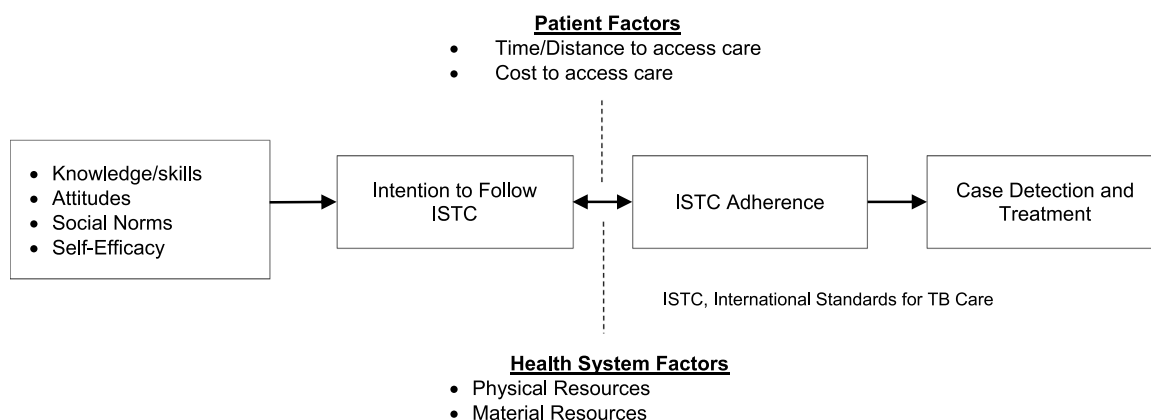


Fig. 2. Conceptual model for understanding reasons for gaps in TB diagnostic evaluation. We used the Theory of Planned Behavior to identify factors associated with provider's intention to follow guidelines for TB diagnostic evaluation. We also collected data on patient and health system factors that might influence sustained guideline adherence.

ISTC International Standards of Tuberculosis Care [29].

service coordination [19]. Human resource barriers to guideline adherence included lack of knowledge about current guidelines; a lack of skills (microscopy); belief that TB evaluation is not urgent; and low self-efficacy due to heavy workloads in the laboratory and low confidence that patients will return regardless of their efforts. Providers at local facilities also cited issues with the material resources required to conduct their work, including stock outs of sputum cups, reagents, and medicines; limited space for assessing and counseling patients; and poorly ventilated laboratory facilities. Barriers to service implementation included high staff turnover, inconsistent and delayed specimen transport to Xpert testing sites, and the inability to track and follow-up with patients with positive TB test results. Finally, health center staff noted several examples of poor service coordination that contributed to their inability to provide high quality care. These included a lack of regular communication among health center staff and insufficient oversight from NTLP supervisors.

Through surveys of patients ($N = 64$) and community members ($N = 114$) [20], we learned that pathways for patients seeking care for chronic cough were complex and costly. Most ($> 80\%$) patients made repeated health facility visits (median 3 visits), and most visits (88%) were to health facilities that did not provide TB diagnostic services. The most common health facilities visited were pharmacies, community health posts and private clinics, and many patients made repeated visits to the same facility. The costs of seeking care for TB symptoms were high, accounting for on average 29% of monthly household income. Visiting a Level IV health center where TB microscopy and Xpert referral are possible alone accounted for 11% of monthly household income and took upwards of 9 h to complete. The substantial time and cost inherent in seeking care for TB symptoms impacts patient behavior – 40% of patients surveyed indicated they were unlikely to complete additional visits, even when recommended, to obtain additional testing or receive results.

Last, we conducted additional interviews and observations at 23 peripheral health centers and the 15 sites to which they referred sputum samples for Xpert testing. [21] The results identified barriers at each step of the process for referring samples for Xpert testing. Challenges with sputum collection for Xpert testing included a shortage of sputum containers (8/23 health centers) and lack of refrigerators for sputum storage prior to transport (10/23 health centers). The latter resulted in health centers only collecting specimens for Xpert testing on days when transport was expected to happen. Sputum transportation to Xpert testing facilities (hubs) was irregular and varied in frequency from 1 to 3 times/week. Xpert testing at hubs was limited by non-functioning modules (5/15 testing sites), lack of back-up electricity (2/15 testing sites) and failure to implement daily device maintenance (7/15 testing sites) resulting in unacceptably high ($> 5\%$) error/invalid rates (10/15 testing sites). Notification of results to referring health centers was often delayed, typically taking up to 2 weeks.

In consultation with multiple key local stakeholders involved in the provision of TB care, including NTLP officials and clinicians involved in front-line TB care, we prioritized and selected barriers to target for intervention using the PRECEDE framework, a well-validated framework for designing behavior change interventions [22]. The framework classifies barriers as predisposing, enabling, or reinforcing factors (Table 1). Interventions that target barriers within all three of these categories are more likely to result in successful behavior change [22]. The barriers selected to target for intervention included: 1) predisposing factors: low self-efficacy due to time and resource constraints, and the belief that TB evaluation is not urgent; 2) enabling factors: failure of patients to return after their initial health center visit (due to time and costs), inconsistent and delayed transport to Xpert testing sites, and inability to track and follow-up patients; and 3) reinforcing factors: a lack of communication and coordination among staff and insufficient oversight from NTLP supervisors (Table 1).

4. Improving the quality gap

We sought to design an intervention to improve the quality of TB diagnostic services within the hub-and-spoke model for Xpert testing that targeted the key barriers that we had identified through our formative research. To do so, we reviewed the literature and consulted with stakeholders (health workers, health center directors, district health officers, NTLP officials) regarding the feasibility and acceptability of each of the potential intervention options. The resulting “Single-sAMPLE (SIMPLE) TB evaluation strategy included four key components:

- 1) Single-sample LED fluorescence microscopy was selected because of its ability to provide a TB diagnosis and initiate treatment at the initial visit for the majority of patients with TB. The patient barriers targeted included the high-cost of clinic visits. The health-system barriers targeted include the high laboratory workload and the prevailing belief among clinicians that TB evaluation is not urgent. The intervention involved on-demand preparation/examination of two smears from a single sputum sample, an approach we have previously shown is as accurate as examining smears from different samples [23].
- 2) Daily sputum transport to Xpert testing hubs was selected to facilitate same-day (or next-day) Xpert testing for all smear-negative patients. The barriers targeted included the failure of patients to return after their initial health center visit and inconsistent or delayed specimen transport to Xpert testing sites. This intervention involved identifying a primary and alternate boda boda (motorcycle) rider for each peripheral health center, linking the riders to laboratory staff, and tracking sample pick-up and delivery using a paper logbook.
- 3) Short Message Service (SMS)-based communication of Xpert results to health centers and patients was selected to reduce delays in reporting results and improve linkage to treatment. The barriers targeted included the failure of patients to return after their initial health center visit and inability of health center staff to track and follow-up such patients. This intervention involved installing GxAlert software (System One, Northampton, USA) and a USB modem at all Xpert testing hubs, establishing an automated SMS platform linked to a central GxAlert server at the Uganda National TB Reference Laboratory and training staff at Xpert testing hubs to use GxAlert software.
- 4) Performance feedback was selected to facilitate continuous quality improvement. The barriers targeted included lack of communication and coordination between health center staff and insufficient oversight from NTLP supervisors. It involved providing health centers with a monthly report card with quality indicators reflecting adherence to each step of TB diagnostic evaluation and training health center staff to review and discuss report cards amongst themselves at monthly staff meetings using a Plan-Do-Study-Act (PDSA) framework [24,25].

We had previously shown that performance feedback was feasible as an informal quality improvement (QI) strategy and led to a 15% (from 52% to 67%) increase in the proportion of patients receiving guideline-adherent care at 6 peripheral health centers [26]. To assess the feasibility and potential impact of the remaining three components, we conducted a single-arm interventional study at 5 peripheral microscopy units linked to an Xpert testing hub [27]. Using data from all adults ($N = 1212$) undergoing TB evaluation over a 14-month period from February 2015 to April 2016, we showed that 99% were referred for sputum-based TB testing, 99.6% completed testing if referred and 86% of patients with confirmed TB were treated rapidly (within 14 days). The probability of a patient with sputum smear- or Xpert-positive TB being diagnosed and treated was 85%, nearly double what was observed under the routine hub-and-spoke model. With respect to Xpert

Table 1

Barriers targeted for intervention development. We used the PRECEDE framework to prioritize and select barriers to target in order to improve the quality of TB diagnostic services.

PRECEDE framework	Recurring themes
Predisposing factors (Knowledge, attitudes, beliefs, intention)	<ul style="list-style-type: none"> • Time and resource constraints (i.e., high workload) → low self-efficacy • Beliefs that TB evaluation is not urgent
Enabling factors (Factors that if addressed make it easier to initiate the desired behavior)	<ul style="list-style-type: none"> • Failure of patients to return after initial visit (due to time and costs) • Inconsistent/delayed specimen transport to Xpert testing sites • Inability to track and follow-up patients <p><i>“When they have a cough for more than 2 weeks they are sent to the lab. But the problem is they get the first sample and sometimes, actually most times they don't bring the second sample.”</i></p>
Reinforcing Factors (Factors that if addressed make it easier to continue the desired behavior)	<ul style="list-style-type: none"> • Lack of communication and coordination among staff • Insufficient oversight from NTLP supervisors <p><i>“...Actually at times we have met but we don't meet [regularly], only when we realize there is a problem that's when we communicate and say why is this happening, then we try to rectify.”</i></p>

utilization, 83% of smear-negative patients were referred for Xpert testing within one day and 76% of Xpert-positive patients initiated treatment within 14 days, both considerable improvements relative to routine care. In addition, automated notification of Xpert results reached referring health centers 95% of the time and patients 49% of the time [28]. These data demonstrate that the theory-informed SIMPLE TB strategy is feasible and effective at improving the quality of TB diagnostic evaluation. However, there remain further opportunities for improving linkage to care, particularly for patients with smear-negative but Xpert-positive TB.

5. Conclusion

To make progress towards elimination, donor and country funding for scaling-up novel diagnostics is essential. However, there needs to be greater investment focused on improving the quality of TB care that accompanies funding to achieve maximal impact of novel diagnostics such as Xpert. This investment should include specific funds for co-interventions such as training, process re-design, performance feedback and ancillary infrastructure (specimen transport, results notification, etc.) relevant to the local context and barriers to high-quality service delivery. Proper implementation supports are essential for new diagnostics to fully realize their promising potential. Implementation science-based approaches can facilitate a systematic assessment of key barriers and enablers and guide selection of the most appropriate and feasible implementation supports for a given context.

Declaration of Competing Interest

None for all authors.

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Ethical statement

All summarized studies underwent review by Institutional Review Boards (IRBs) at both the University of California, San Francisco (UCSF) and Makerere University, and participants were appropriately consented

except when an explicit waiver of informed consent was granted by the IRBs.

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