Impact of scaling up Xpert MTB/RIF testing on the detection of Rifampicin resistant TB cases in Karachi, Pakistan

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Abstract:

Setting: Pakistan ranks fourth among high multi-drug resistance tuberculosis burden countries with only 19.2% of the 15,000 estimated incident cases being notified. Increasing treatment coverage for multi-drug resistance tuberculosis is a key priority for National Tuberculosis Program in Pakistan. World Health Organization recommends the use of Xpert MTB/RIF® assay as the first-line diagnostic test for individuals with presumed tuberculosis.

Objective: To describe a multi-faceted case-finding intervention targetting the public and private sectors that utilized Xpert MTB/RIF as a frontline diagnostic test for individuals with presumptive tuberculosis, in Karachi, Pakistan, and its impact on case-notifications of multi-drug resistance tuberculosis.

Design: Cross sectional study

Results: A total of 51,168 were tested on Xpert MTB/RIF®, of which 7,581 and 1,534 people were diagnosed with TB in the public sector (Reverse-Public private mix) and private sector (Social business model) arms, respectively, 574 (6.3% of all TB cases) were identified with Rifampicin resistance. A total of 517 (90.1%) people with rifampicin resistant tuberculosis, identified through the project were initiated on second-line treatment. The intervention resulted in 194 additional cases of rifampicin resistant tuberculosis, an increase of 43% over the baseline.

Conclusion: This project, one of the largest Xpert MTB/RIF® testing programs conducted at a city level, resulted in significantly increased detection and treatment of multi-drug resistance tuberculosis.

Introduction:

Multi-drug resistant tuberculosis (MDR-TB) represents a significant threat to the ambitious global targets for ending TB [1,2]. In 2016, out of the estimated 490,000 people developing MDR-TB, only 153,119 (31.2%) were diagnosed and 129,689 (26.4%) were enrolled on second line treatment, and reported (Global report 2017) [2]. For many years, inadequate diagnostic capacity, particularly the limited availability of sensitive rapid diagnostic tests has been a key constraint [3]. The World Health Organization (WHO) currently recommends the use of Xpert MTB/RIF®(Xpert) assay as the first-line diagnostic test for individuals with presumed TB [Meeting Report 4]. While South Africa witnessed large increases in the numbers of people detected with drug resistance by using Xpert as the initial diagnostic test [5], many countries have used restrictive algorithms primarily due to high costs, relative to conventional smear microscopy [6] where limiting testing to previously treated patients and those with other risk factors misses out on MDR-TB among the large numbers of incident TB cases [7].

Pakistan has the fourth highest burden of MDR-TB globally [2]. Increasing treatment coverage for MDR-TB forms an integral part of the National Strategic Plan for TB in Pakistan [8]. However, of an estimated of 15,000 incident MDR-TB cases, only 2,881 (19.2%)(country profile) were enrolled for treatment in 2016, highlighting a significant treatment coverage gap [2]. Up to 90% of the MDR-TB burden is among people without known history of previous anti-TB treatment and are not currently covered through routine drug susceptibility testing (DST) [3]. While the absolute number of MDR-TB cases is high, the prevalence of MDR-TB among both new (4.2%) and retreatment cases (16%) in Pakistan is low, relative to other high MDR-TB burden countries in Eastern Europe and Central Asia [2].(Pakistan's only drug resistance survey was conducted in 2012-2013). To find additional cases of MDR-TB, testing on a large pool of people is required which may be resource intensive [9]. Additionally, in Pakistan, three-quarters of the population accesses healthcare through the private-sector [10]. However, the Public Private Mix (PPM) contribution to TB case notification was 28% in 2016 , (global report 2017), previous efforts to form linkages with private-providers for drug-susceptible TB have not focused on detection of MDR-TB. Xpert testing in the private sector without donor or government subsidies is prohibitively expensive for most patients [11].

The Xpert assay was introduced in Pakistan in 2011[3]. However, further experience in scaled implementation of Xpert testing is required to inform its utilization across the different levels of the health system. This study describes a multi-faceted case-finding intervention targetting the public and private sectors that utilized Xpert as a frontline diagnostic test in Karachi, Pakistan, and its impact on case-notifications of drug resistant tuberculosis (DR-TB). We aim to fill the gaps in published literature on potential constraints in implementation of Xpert testing in high MDR burden, programmatic settings.

Study Population and Methods:

Study setting

Karachi is the country's largest city and economic hub, with a population estimated of 23 million [12] with over 60% of the population residing in high-density slums [10]. Approximately 15 private-sector facilities are registered as Basic Management Units (BMUs) with the NTP where TB diagnostic and treatment services are available. A total of 3 programmatic management for drug-resistant TB (PMDT) sites (two in the public-sector, one private-sector), are present in the city where patients can receive MDR-TB treatment, offered free-of-cost.

Project Interventions

This project was part of the *TBXpert Project* that aimed to increase case-notification for TB through scale-up of Xpert testing. The intervention in Karachi consisted of two distinct arms: 1) a Reverse - Public Private Mix (R-PPM) arm, targeting public-sector hospitals and Programmatic Management of Drug Resistant Tuberculosis (PMDT) sites; and 2) a Social Business Model (SBM) targeting the private-sector. A new case was defined as not having been treated for TB previously.

Reverse Public-Private Mix (R-PPM) Model:

Under this approach, TB diagnostics and treatment capacity was strengthened at exiting public-sector facilities. Xpert machines were installed at the TB laboratories of 6 public-sector hospitals and 1 private-sector PMDT site. The hospitals were provided additional staff including an Xpert technician and health workers who screened individuals in waiting areas of outpatient clinics and other wards of the hospitals for TB symptoms, as per the WHO symptom screen (ref) including cough of any duration, fever, hemoptysis, night-sweats and unexplained weight-loss. The health workers also supported the TB clinic through collection of sputum samples from other wards, assisting patients in sputum expectoration, data collection, registering and counseling of people with TB. Sputum was collected for Xpert testing from all presumptives who were able to expectorate sputum and gave consent for the test. The intervention sites were set targets for TB case-identification and compensation for staff was performance-based, with incentives provided for TB case-identification and ensuring high treatment initiation rates. Supervisory visits by managers were carried out to ensure maintenance of equipment, quality assurance of data, trouble-shooting and ensuring supply-chain of Xpert cartridges was appropriately maintained.

Social Business Model (SBM)

TB testing was carried out at three purpose-built TB centers called "*Sehatmand Zindagi"* (Healthy Life). This model utilized community-based screeners, placed at 180 private health providers' clinics (including both formal and informal) in the vicinity of the TB centers where they carried out verbal symptomatic screening (as per the WHO symptom screen) of patients and referred them for testing that is a Chest X-ray (US$3-5) and free-of-cost Xpert at the centers after a positive symptom screen and clinical evaluation by the health providers. Those individuals who could not pay for the chest Xray, were cascaded directly to Xpert while those who were unable to expectorate sputum for testing were further evaluated by a clinical officer based on clinical symptoms and chest Xray findings. The SBM intervention evolved towards developing a medical detailing team, that engaged a network of approximately 600 private-providers and encouraged referrals for TB testing. People identified with drug-susceptible TB in the SBM intervention were provided free treatment from the centers, registered as BMUs with the Provincial Tuberculosis Program (PTP). People at R-PPM sites were registered for treatment at the testing site or at the facility of referral. Individuals identified with rifampicin resistance(Rif-resistance) were referred to the one of the three PMDT sites in the city and initiated on second-line drugs, after repeat Xpert testing. Sputum samples were also obtained for culture from all patients registered for treatment for confirmation of Rif resistance.

Data Analysis:

The study utilized de-identified data collected for patient screening and testing indicators including Xpert log files and summary of laboratory reports from each intervention site, for a total time-period of 8 quarters of the intervention from Q3-2013 – Q2 2015. Aggregate summary reports for quarterly patient enrollment and treatment initiation at PMDT sites was obtained to identify the total number of Rif resistant TB cases registered in Karachi.

Summary statistics describing Xpert testing and *Mycobacterium TB* (MTB) yield at each intervention site and intervention (SBM and R-PPM) were determined. The TB REACH methodology for additionality calculations was adapted for DR-TB notifications [13]. This approach allows for a more accurate estimation of impact directly attributable to project activities. Briefly, the methodology involves determining the quarterly historical case-notifications in the intervention area of the previous 12 quarters prior to the start of the activities. A regression line is fitted to the historical notifications and extrapolated to forecast notifications that would have taken place in the absence of any intervention. These are compared with the number of actual notifications that took place during the intervention period to determine the overall additionality of cases. In order to control any bias resulting from the setup of new PMDT sites outside of Karachi, cases were known to have residential addresses outside of the city, were excluded from the analysis. All data analysis was carried out on Microsoft Excel.

Ethical Approval:

This study was approved by the Institutional Review Board (IRB) at Interactive Research and Development (IRD). The IRB is registered with the U.S. Department of Health and Human Services (DHHS), Office for Human Research Protections (IRB#00005148).

Verbal consent was obtained from participants before conducting Xpert tests.

Results:

TB Screening and Xpert MTB/RIF testing:

Between July 2013 and June 2015, 115,360 people with presumptive TB were identified, 80.4% through the R-PPM intervention and 19.6% through the SBM (Figure 1). Of these 39 301clients at the R-PPM sites and 11 867 clients at the SBM sites had Xpert tests performed (Figure 1). A total of 9,115 MTB+ cases were detected through the two interventions; 7,581 (83.2%) and 1 534 (16.8%) MTB+ cases were identified in the R-PPM and SBM arms, respectively. Yield of bacteriologically positive cases was 19.3% at R-PPM sites and 12.9% at the SBM sites. Table 1 shows the difference in Xpert testing, cases detected and started on treatment, between the two intervention arms.

DR-TB treatment coverage:

Of all MTB+ individuals, 8,541(93.7%) were drug susceptible, of whom 7,576 started on first line treatment (88.7% of the total). Among those with a MTB+ result, 574 (6.3%), were also identified with Rif-resistance (Rif+/DR-TB), of whom 524 (91.3%) were detected at the R-PPM sites and 50 (8.7%) at the SBM sites. The yield of Rif-resistance was 6.9% and 3.3% for R-PPM and SBM interventions, respectively (Figure 1). Within the Rif+ (presumed and confirmed Rif-resistance) identified through the project, a total of 517 were initiated on second-line treatment (90.1% of the total yield). A total of 46 (8.5%) individuals were pre-treatment loss to follow-up, whereas 11 (2.1%) deaths were recorded.

Impact on notified DR-TB cases in the intervention population (Karachi district)

At the Karachi district level, a total of 642 DR-TB cases were detected during the intervention period of which 149 were new diagnoses. This constituted a 43% increase in identification of DR-TB cases over the baseline trend (Figure 2). The proportion of newly diagnosed cases among all reported DR-TB cases increased from 7% in Q2 2013 to 22% in Q2 2015 during the intervention period (Figure 3)

Discussion:

This is the first study to investigate the impact of scaling Xpert implementation on additional DR-TB case-notifications from a programmatic setting in Pakistan. Our intervention targeted both the public, and the private sector through an innovative social business approach, distinguishing it from other studies reported from high MDR-TB burden countries.

An increase in number of DR-TB cases notifications in Karachi was observed relative to the years prior to the intervention. This study therefore supports existing evidence from other programmatic settings that have reported up to eight-fold increase in Rif resistant-TB case-detection through upfront Xpert testing [14-18]. Xpert testing has increased access to DST in countries such as South Africa, where up to 65% of new cases and 71% of previously treated cases have been tested for Rif-resistance [2], exceeding previous prevalence estimates for the disease in the country [2].

This study provides a number of lessons that can inform scale-up of Xpert in Pakistan and elsewhere. Our study highlights the significance of employing both, active case finding approaches and expanded diagnostic algorithms for Xpert testing to bridge the case-detection gap for DR-TB. Since new cases comprise up to 97% of the total TB cases notified, the burden of DR-TB is overwhelmingly within this group that does not receive routine access to DST [2]. In our study, the proportion of newly diagnosed cases among DR-TB cases increased from 7% at baseline to 22%. However, the estimates for MDR-TB among new cases are much higher, and further scale-up of Xpert testing is expected to achieve greater yields.

Operationally, treatment initiation of patients diagnosed with Rif-resistance may be challenging [19-21]. Figure 4 summarizes factors that have contributed to low enrollment of patients in MDR-TB treatment program in Pakistan. The additional human resource provided at the TB centers in the private and public-sector hospitals that worked to support linkages to PMDT sites, complimented by close collaboration with PTP, resulted in a high proportion Rif-resistance cases to be initiated on treatment, with only 8.5% pre-treatment loss to follow-up in the project. It is important that future scale-ups invest in data systems, human resource training and strengthening linkages to DR-TB treatment sites, to ensure treatment initiation and better outcomes for individuals with DR-TB.

The R-PPM intervention involved fewer human and infrastructural investments in comparison to the private-sector intervention. The public sector sites carrying out the project interventions were high volume tertiary care hospitals, providing a large population base to screen from. Four-fifths of all Xpert tests were carried out through the R-PPM intervention. A higher MTB+ rate (MTB+ve out of all those tested) of 19.3% was also observed compared to SBM (12.9%) and it detected over 90% of all Rif-resistant cases in the project. We hypothesize that sicker individuals are found at tertiary care hospitals compared to GP clinics leading to higher MTB+ and Rif+ yields at these sites. Our experience, therefore, supports targeted approaches such as R-PPM that leverage existing infrastructure and carryout structural enhancements and process improvements to increase access to DST. The private-sector intervention utilized a novel approach to PPM by establishment of new health centers and a referral network of private-providers through a sustainable social business model. While the SBM approach only detected 16.8% of all MTB+ cases and 50 Rif-resistant in the project cases, the number of referrals and Rif-resistant cases identified in the private sector increased over the course of the project and were less likely to be detected in the public sector. Comparable trends are experienced in the establishment of any new business, where generating "foot-fall" often takes significant time before reaching maturity [22]. Similar strategies may be considered in countries with a rampant private health sector, particularly in South-Asia and Africa. While about three-quarters of all health services are availed in the private sector in Pakistan [10,11], only 28% of all TB cases were notified through private facilities [2]. During the study period the PPM contribution to TB case notifications was 15-20% in Pakistan and varied between 13-17% in India and about 55% in China (global report 2017). Increased engagement with the private-sector is therefore necessary despite lower yields and higher costs to identify additional cases that would likely have otherwise remained undiagnosed [1,2].

The potential options for diagnostic algorithms and case finding strategies need to be carefully appraised and measured against cost implications for each setting. Of the 48 high burden countries, at least 15 have adopted national guidelines based on testing of all presumptive TB cases on Xpert [2]. This may not be feasible in resource-constrained settings, including for countries with donor support for TB programs. However, testing algorithms focused on drug resistance presumptives only, may limit case-detection as a significant number of MDR-TB cases are among new TB cases. Pakistan's first national anti-tuberculosis drug resistance survey reported Rif-resistance in 4.4% (95% CI: 2.4–4.9) of new cases [23]. Application of novel screening tools such as digital chest x-rays with computer-aided detection (CAD) has the potential to save Xpert cartridges and consequentially save costs [24, 25].

In our study, Xpert testing could only be performed on less than half of people identified as needing testing. Support was provided for expectoration through nebulizers and mucolytic agents, incurred additional costs and patient counseling efforts. Similar challenges may be encountered in other active case finding programs. Our experience with technical issues and equipment malfunctions is consistent with those reported by early Xpert implementers elsewhere [11,26-27]. The costs of equipment maintenance, biomedical support, module re-calibrations and backup power supplies need to be incorporated within program budgets. Ensuring appropriate supply chains of cartridges and transport of patient sputum samples to Xpert testing sites are also probable challenges for large-scale implementers.

An important limitation of the study was that we were unable to determine as to what fraction of the additionality in DR-TB cases is attributable to the implementation of Xpert testing relative to the active case finding efforts in the project. As laboratory-level data was unavailable, it was not possible to ascertain the additional increase in testing for Xpert through active case-finding or to analyze the differences in yield of Rif-resistance in new versus retreatment cases. The study was conducted in a major urban center and may not be generalizable to rural settings where yield may be lower due to lower patient volumes and underdeveloped laboratory facilities.

Conclusion:

This study describes a multi-faceted scale-up of Xpert testing in public and private sectors in Karachi, Pakistan. An increase in the case-notifications for DR-TB were observed, relative to the historical trends supporting existing evidence from other programmatic settings in high DR-TB burden countries. A high proportion of those identified with Rif-resistance were initiated on second line treatment under the project. Further scale up of Xpert testing needs to take into account the most appropriate diagnostic algorithms weighed against cost implications, and ensure appropriate technical and operational support for effective program delivery.

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Authors contributions: WA, SMAZ and SK were involved in conception of the study and finalizing the study design. WA, AM and UK were involved in conducting data collection. SSH and SMAZ were involved in conducting the literature review, data analysis, data interpretation and drafting the manuscript. RF, JC and AK reviewed the drafts critically and finalized the manuscript. All authors reviewed and approved the final version to be published.

Conflict of Interest: The authors declare they have no competing interests.

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Figures:

Figure 1: TB screening and Xpert MTB/RIF testing results

Overview of Xpert MTB/RIF testing and TB case detection as part of the TBXpert initiative, from July 2013 to June 2015, in Karachi, Pakistan

Figure 2: DR-TB case notifications (pre-and post-intervention)

DR-TB case notifications trend during intervention period and forecasted baseline trend (in the absence of any intervention), from July 2013 to June 2015, in Karachi, Pakistan

Figure 3: Proportion of newly diagnosed cases among all DR-TB cases

Proportion of newly diagnosed cases among all DR-TB cases, from July 2013 to June 2015, Karachi, Pakistan

7: Factors contributing to low enrollment of MDR-TB patients in treatment programs

Illustration of factors that have historically contributed to low enrollment of MDR-TB patients in treatment programs in Pakistan