

Performance of Xpert MTB/RIF for diagnosing tuberculosis among household contacts of index TB patients in South Africa

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Abstract:

Background

Screening household contacts of Tuberculosis (TB) patients is recommended as a key TB control activity, but is resource intensive and demonstrated variations in yield. Xpert MTB/RIF is a simple, more sensitive diagnostic test that has the potential to detect more TB cases than smear microscopy. We describe the performance of Xpert MTB/RIF among symptomatic household contacts of TB patients.

Methods

We enrolled household contacts of recently diagnosed (<2 weeks) smear-positive and Xpert positive TB index patients in the Bojanala District, Northwest Province, South Africa. All contacts were screened for TB symptoms (cough>24 hours, fever, weight loss or nights sweats); persons with ≥ 1 TB symptom provided one spot sputum for smear microscopy, Xpert MTB/RIF and MGIT culture. We determined Xpert MTB/RIF test performance using MGIT culture as the gold standard.

Results

From 216 index patients, 619 contacts were enrolled: 60.6% were female, median age was 22 years (inter-quartile range: 9, 40) and 126 (20.4%) self-reported/tested HIV-positive. 54.3% (336/619) of contacts had ≥ 1 TB symptom, of which 297/336 (88.4%), provided a sputum specimen; 289 (97.3%) had complete testing, of whom 18 had a contaminated MGIT culture result (five Xpert MTB/RIF-positive and 13 Xpert MTB/RIF-negative) and so 271 contributed to the diagnostic performance analyses. MGIT culture identified 33/289 (11.4%) as positive for *Mycobacterium tuberculosis* (MTB), 16/289 (5.5%) were positive by Xpert MTB/RIF and 6/289 (2.1%) were positive for acid fast bacilli on smear. Xpert MTB/RIF sensitivity was 21.2% (95% confidence interval [CI]: 9.0, 38.9), specificity 98.3% (95% CI: 95.6, 99.5), positive predictive value (PPV) 63.6% (95% CI: 30.8, 89.1), negative predictive value (NPV) 90.0 (95% CI: 85.7, 93.4). Xpert MTB/RIF sensitivity was higher for smear-positive specimens than for smear-negative specimens; 100% (3/3) for smear-positive vs. 12.9% (4/30) for smear-negatives, $p=0.06$.

Conclusion

Among symptomatic household contacts investigated for TB, Xpert MTB/RIF detected all smear-positives but very few smear-negative pulmonary TB cases. The low TB yield from Xpert MTB/RIF in this study suggests that among symptomatic household contacts, mycobacterial culture testing should supplement Xpert MTB/RIF where available especially among smear-negative patients, while the diagnostic performance of Xpert MTB/RIF Ultra is evaluated in this particular population.

Introduction

South Africa remains one of the highest TB burden countries in the world; a 2017 report by the World Health Organization (WHO) estimates the TB incidence rate at 781 per 100,000 population, suggesting that despite ongoing efforts, more directed strategies are required to curb the epidemic [1]. One potential strategy recommended by WHO is household contact tracing (HHCT), an approach which involves screening household contacts of known pulmonary index TB patients for TB. However, HHCT is rarely implemented by TB programmes due to the effort and cost required to conduct screening and variable yield for finding active TB disease among contacts [2-7]. Sputum-smear microscopy has been the mainstay of TB diagnosis [8], including for HHCT screening, however its sensitivity is lower than other TB diagnostics. The introduction of the Xpert MTB/RIF assay, an automated molecular test for *Mycobacterium tuberculosis* [9], is intended to overcome current shortcomings in TB diagnostics and has been recommended by WHO for TB diagnosis [10-11].

South Africa has adopted the use of Xpert MTB/RIF as the initial diagnostic test for investigating persons suspected of TB [12], primarily because of its shorter turnaround time when compared to mycobacterial culture and its ability to concurrently diagnose rifampicin resistant TB. However, there is evidence to suggest that when bacterial burden is not high within expectorated respiratory specimens, Xpert MTB/RIF is not as effective in diagnosing TB compared to mycobacterial culture [13]. A recent systematic review which evaluated the use of Xpert MTB/RIF for the diagnosis of pulmonary TB in children found that compared with smear microscopy, Xpert MTB/RIF offers better sensitivity, however its sensitivity remains suboptimum compared with mycobacterial culture testing [14]. Additionally, in the Gambia among symptomatic household contacts <15 years old with induced sputum samples, Xpert MTB/RIF returned a sensitivity of 42.9% (95% CI: 17.7-71.1) against a mycobacterial culture referent and 30% (95% CI: 7-65) amongst smear-negative, culture-positive cases [15]. In contrast, a very small pilot study from Tanzania evaluated the performance of Xpert MTB/RIF for identifying undiagnosed TB among five culture-positive household contacts, reported sensitivities of 60% (95% CI: 14.7-94.7) and 100% (95% CI: 47.8-100.0) for smear microscopy and Xpert MTB/RIF respectively [16].

With a strong emphasis being placed on implementation of Xpert MTB/RIF for diagnosing TB in adults and children [17] coupled with reported variation in the sensitivities of Xpert MTB/RIF over mycobacterial culture testing, it seems imperative that operational research of Xpert MTB/RIF use is conducted specifically related to its performance on diagnosing TB among household contacts. We aimed to determine the performance of Xpert MTB/RIF in diagnosing TB compared to mycobacterial culture and smear microscopy among household contacts within a TB contact tracing program.

Methods

Setting

This study was nested within *The CDC-Aurum Contact Tracing Study*, a multi-country prospective cohort study (South Africa, Kenya and China) with the primary aim of comparing the yield of active TB disease among household contacts of index patients with multidrug-resistant TB (MDR-TB) with the yield of active TB among household contacts of index patients with drug-susceptible TB (DS-TB).

Study procedures

Index patients diagnosed with MDR-TB or DS-TB were identified through routine testing within the Bojanala District in the Northwest Province. According to the 2015/16 District Health Barometer, the incidence of TB in the Bojanala district was estimated at 419 per 100,000 population, with an estimated HIV co-infection rate among TB patients of 66.6% [18]. Pulmonary index TB patients were eligible if they were recently diagnosed (≤ 2 weeks); Xpert MTB/RIF or *mycobacterium tuberculosis* culture positive; and smear positive. Index TB patients and their household contacts provided written informed consent prior to study participation; an additional assent form was completed for children < 18 years old by their respective guardians. Household contacts ≥ 5 years old were screened for TB using a symptom screening questionnaire; any household contact who reported at least one of a cough lasting ≥ 24 hours, night sweats, fever or unintentional weight loss was investigated further for TB by providing one spot sputum which was sent to a single reference laboratory for quality-assured smear microscopy, Xpert MTB/RIF and MGIT testing. Sputum samples were transported in cooler boxes containing temperature loggers to maintain a 2-4°C temperature until they reached the laboratory and subsequently processed on the same day if they were of considered sufficient quality (mucoïd or purulent) and quantity (3-5ml). The

laboratory was ISO 15189 and Good Clinical Laboratory Practice (GCLP) accredited. In addition, the lab has been conducting Xpert MTB/RIF testing since 2011, and to date, have completed 7,626 tests. Household contacts <5 years old were referred to their local health facility for further TB investigation and isoniazid preventative therapy (IPT).

At the laboratory, each sputum was first decontaminated using NaOH-NALC-sodium citrate solution to a final [NaOH] of 1%. Following centrifugation, the pellet was suspended in approximately 1.5-2 ml of phosphate buffer pH 6.8. The sediment was split to perform all TB testing; an aliquot was taken first for MGIT testing as previously described [13] to prevent contamination followed by the Xpert MTB/RIF assay and then the smear microscopy. A Genotype MTBC test (HAIN Lifescience, Germany) was performed on all MGIT culture-positive samples to differentiate between MTB and nontuberculous mycobacteria. Individuals with positive TB test results were re-contacted and provided with a referral letter to their nearest clinic for treatment initiation. HIV counselling and testing was offered within the households of index TB patients to all contacts who reported an initial unknown or negative status.

Definitions and statistical analysis

For the purposes of the analysis, a culture was considered positive if MTB was detected after being identified to species level; a negative culture was defined as the absence of MTB growth after 42 days. Time to culture positivity (TTCP), defined as the number of days it takes for a positive culture result on the MGIT culture system, is used as a measure of mycobacterial burden.

Descriptive statistics were used to summarize demographic and socio-economic characteristics of household contacts included in the analysis. The yield of TB among household contacts along with 95% confidence intervals was determined for all diagnostic tests and sensitivities and specificities were calculated. Diagnostic yield was defined as the (# of positive tests/total # of tests performed) X100. All confidence intervals for proportions were exact. Comparison of proportions calculated from different samples (for example, sensitivity of Xpert MTB/RIF compared between those who were smear positive and smear negative) were done using Fisher's exact test. Comparison of proportions calculated from

the same sample (for example, sensitivity of Xpert MTB/RIF compared to sensitivity of smear microscopy) were done using McNemar's test.

Xpert MTB/RIF sensitivities, specificities, and positive and negative predictive values were calculated using MGIT culture as the reference standard. Xpert MTB/RIF assay cycle threshold values (C_T), which is the number of polymerase chain reaction cycles after which each of the five probes is considered positive was also documented; this provided a semi-quantitative measure of bacillary burden in sputum, reported as high (<16 cycles), medium (16-22 cycles), low (23-28 cycles) and very low (>28 cycles) [19]. We excluded specimens that were culture-contaminated from the diagnostic accuracy analyses. Data was analysed using Stata 13 (StataCorp, College Station, TX, USA). A final HIV status for each household contact was determined by combining the self-reported status with additional testing results obtained through testing that was conducted within the households.

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee, US Centers for Disease Control and Prevention, and the research committee of the North West Province, South Africa.

Results

Index patient characteristics

216 index TB patients were included in this study; 73 with MDR-TB and 145 with DS-TB (Table 1). The median age was 36 years (interquartile range [IQR], 33-41) for MDR-TB patients and 37 years (IQR, 35-40) for DS-TB patients. The median number of household contacts per index patient was 3 (IQR, 1-4) for both MDR- and DS-TB patients.

Household contact characteristics

There were 619 household contacts included in this study from the 216 index TB patients. Household contact characteristics are shown in Table 2. Females comprised 60.6% of contacts and the median age was 22 years (IQR, 9-40). There were 336 (54.3%) contacts who presented with at least one TB symptom; of which a cough ≥ 24 hours was the most common symptom, reported by 98.5% of symptomatic contacts. A sputum sample was collected from 297 (88.4%) symptomatic contacts representing 47.8% of all household contacts; 289 (97.3%) had complete results for all three diagnostic tests. 126 (20.4%)

contacts self-reported/tested HIV-positive. Previous history of TB was reported among 42 (6.8%) household contacts.

Comparison of diagnostic performance

MGIT Culture testing

Figure 1 and Table 3 show the results of Xpert MTB/RIF and MGIT tests for the 289 specimens. MGIT testing identified 33 (11.4%) patients as positive for MTB, 8 (2.8%) were Nontuberculous mycobacteria, 18 (6.2%) were contaminated, and 230 (79.6%) were negative for any growth. The mean TTCP among culture-positive contacts was 15.1 days (95% confidence interval [CI]: 11.8, 18.4), the median was 12 days (IQR, 9-22) and the range was 2-37 days (Figure 2). Among samples that were both MGIT culture and Xpert MTB/RIF positive, the median TTCP was 6 days (IQR, 5-10), whereas among samples that were MGIT culture-positive and Xpert MTB/RIF negative, the median TTCP was 18 days (IQR, 10-26).

Xpert MTB/RIF testing

Xpert MTB/RIF testing identified 16 (5.5%) patients as positive for MTB. The Xpert MTB/RIF quantitation results for the 16 sputa in which *M. tuberculosis* was detected were “high” for 4 (25.0%), “medium” for 1 (6.3%), “low” for 6 (37.5%) and “very low” for 5 (31.2%). The mean C_T value among Xpert-positive contacts was 24.2 (95% confidence interval [CI]: 20.8, 27.8), the median was 24.9 (IQR, 17.3-30.6) and the range was 13.5-33.1. Four (4) of the 16 Xpert MTB/RIF positive patients tested negative on MGIT culture; 2 were smear-positive (1+) and 2 were smear-negative.

The Xpert MTB/RIF performance characteristics overall, stratified by smear and HIV status, using MGIT culture as the reference standard are shown in Table 4. Overall, 271 (93.8%) sputa had an interpretable result for MGIT and Xpert MTB/RIF; we excluded 18 specimens from this analysis that were contaminated in MGIT (five Xpert-positive and 13 Xpert-negative). Xpert MTB/RIF sensitivity was 21.2% (95% CI: 9.0, 38.9), specificity 98.3% (95% CI: 95.6, 99.5), positive predictive value (PPV) 63.6% (95% CI: 30.8, 89.1), negative predictive value (NPV) 90.0 (95% CI: 85.7, 93.4). Xpert MTB/RIF sensitivity was higher for smear-positive specimens than for smear-negative specimens; 100% (3/3) for smear-positive vs. 12.9% (4/30) for smear-negatives, p=0.06.

Xpert MTB/RIF sensitivity was higher for patients who were HIV-positive than for HIV-negative patients, although there was no statistical evidence to support a true difference; 40.0% (4/10) for HIV-positive vs. 13.0% (3/23) for HIV-negatives, p=0.21. Similarly, there was

no statistical evidence for a difference in Xpert PPV by HIV status; 66.7% (4/6) in HIV-positives vs. 60.0% (3/5) in HIV-negatives; $p=1.0$. Xpert specificity and NPV was also not statistically different by HIV status (Specificity [98.9%] for HIV-negatives vs. [96.1%] for HIV-positives, $p=0.9$; NPV [90.2%] for HIV-negatives vs. [89.3%] for HIV-positives, $p=1.0$).

Among the specimens with MTB diagnosed on Xpert MTB/RIF, rifampicin resistance was detected in 2/16 (12.5%). The two specimens that were rifampicin resistant on Xpert MTB/RIF were contaminated on MGIT culture, therefore phenotypic susceptibility testing could not be performed.

The overall yield of TB, that is, the proportion of TB cases diagnosed as positive on MGIT culture or Xpert MTB/RIF or smear microscopy was 6.8% (95%CI: 4.9, 9.1) of all household contacts; MGIT culture diagnosed a yield of 5.3% (95% CI: 3.7, 7.4), Xpert MTB/RIF of 2.6% (95% CI: 1.5, 4.2) and smear microscopy of 1.0% (95% CI: 0.4, 2.0). When comparing the sensitivity of each test with the “all TB cases” referent ($n=42$), MGIT culture sensitivity was 78.6% (95% CI: 63.2, 89.7), Xpert MTB/RIF was 38.1% (95% CI: 23.6, 54.4) and smear microscopy was 14.3% (95% CI: 5.4, 28.5). If MGIT culture and smear microscopy testing are combined, the sensitivity is 85.7% (95% CI: 71.4, 94.6) compared to 100 % (95% CI: 91.6, 100.0) when MGIT culture and Xpert MTB/RIF testing are combined.

Among the 42 TB cases identified through MGIT culture, Xpert MTB/RIF and smear microscopy, 81% (34/42) were started on TB treatment; reported through patient record review at the referring health facility. Among TB cases diagnosed on Xpert MTB/RIF ($n=16$), 12 (75%) were successfully started on TB treatment.

Discussion

In this study, we evaluated the performance of Xpert MTB/RIF for diagnosing TB amongst household contacts of index TB patients and found that it performed poorly in comparison to mycobacterial culture, diagnosing only 21.2% of all culture-confirmed cases. The sensitivity of Xpert MTB/RIF varies in different settings, ranging from 58% to 100% [20], however there are few estimates of its sensitivity for household contact tracing; one paper from Tanzania reported a sensitivity of 100% among five culture-positive contacts, while another from the Gambia among 14 culture-positive children <15 years reported a sensitivity of 42.9% [15 16]. We found no difference in sensitivity and specificity of Xpert MTB/RIF by HIV status and a higher sensitivity among smear-positive pulmonary TB.

The poor sensitivity of Xpert MTB/RIF from our study and previous studies [15 16] may be explained by the lower sputum bacillary burden usually present during early development of TB disease, such as among household contacts or in children [21]; one study from South Africa which looked at TB diagnosed in children <15 years within a primary health care setting, reported a 43.3% sensitivity of Xpert MTB/RIF when compared to culture [22]. Further evidence as to the link to bacillary burden is that TTCP is a strong correlate of Xpert MTB/RIF positivity in pulmonary specimens, thus where there is a low sputum bacillary burden, TTCP is usually longer, which correlates with poorer sensitivity of Xpert MTB/RIF [19 23]. Our results show a similar trend, among culture-positive TB patients, the median TTCP was shorter in Xpert MTB/RIF positive patients compared to Xpert MTB/RIF negative patients (6 days versus 17 days) and thus lends credibility to the poor sensitivity of Xpert MTB/RIF due to a lower bacillary burden. In essence, screening household contacts of pulmonary index TB patients through HHCT identifies their TB disease development earlier, thus increasing the likelihood of a lower bacillary sputum sample; this is in contrast to patients who self-present to health facilities with advanced TB disease.

Our finding has important implications for the use of Xpert MTB/RIF in the context of household contact tracing as it would mean that in the absence of mycobacterial culture, substantial TB cases would be missed, therefore limiting the impact of contact tracing for TB control. The argument for an improved diagnostic test among household contacts is further compounded by high resources required for contact tracing; one report suggesting a median cost per additional case of TB identified through such active case finding activities ranging

from USD58 – 1390 [3]; use of Xpert MTB/RIF only for diagnosing TB cases in this setting would therefore be a substantial loss and inefficiency of resources since only one-fifth of cases are being identified. In our study, Xpert MTB/RIF was also positive on an additional nine patients; four were culture-negative and included in this analysis, and five which were culture-contaminated and not included in the diagnostic accuracy analyses. Among the four culture-negative Xpert MTB/RIF positive patients, two were smear-negative and two were smear positive; the smear-negative TB patients also reported previous TB which might explain the Xpert MTB/RIF positive result and more likely a false positive, however the two smear-positive patients might be indicative of a false-negative culture result. Two-thirds of Xpert MTB/RIF positive contacts were treated for TB according to the South African tuberculosis management guidelines [12]. These TB cases would have been missed by mycobacterial culture if it were being used alone, thus, it would seem an ideal testing strategy would be to use Xpert MTB/RIF and mycobacterial culture when testing for TB in a household contact tracing context. In addition, Xpert MTB/RIF also allows for a shorter time to diagnosis compared to mycobacterial culture as well as detection of rifampicin resistant TB but on its own might not be as effective [9]. Perhaps, the next generation Xpert MTB/RIF Ultra cartridge, which is slowly gaining market penetration, with its lower limit of detection may offer far better sensitivity for detecting TB in household contacts compared to the current Xpert MTB/RIF assay, however this too will require further evaluation in this setting, particularly among smear-negative persons suspected of TB.

The Xpert MTB/RIF yield in our study was higher than smear microscopy (2.6% versus 1.0% respectively), a trend which is consistent with other studies in the literature [9 15 21 24], and more importantly it did identify all smear-positive cases. Smear microscopy remains the most used and widely available tuberculosis diagnostic method in low-income and middle-income countries, particularly in peripheral settings that do not have access to higher-level laboratories [21], however this finding emphasizes the need to replace smear microscopy with an alternate testing method. The extensive roll-out of Xpert MTB/RIF globally, means that Xpert MTB/RIF will likely replace smear microscopy as the initial test for TB, however, we believe that in the context of household contact tracing, a more suitable testing approach which would improve the yield from such an intervention, would be a simultaneous use of mycobacterial culture with Xpert MTB/RIF; the combination of which

has shown an improved yield [15]. In addition, our results have shown that when culture is combined with Xpert MTB/RIF testing, the overall sensitivity is also improved to 100% in this population. Although we acknowledge the introduction of Xpert MTB/RIF Ultra to overcome some of the shortfalls in the first generation cartridge, preliminary evidence suggests that it might not be as effective, with one study reporting a 17% increase in sensitivity over Xpert MTB/RIF [25].

We found no difference in the sensitivity and specificity of Xpert MTB/RIF by HIV status, albeit with very low statistical power, and this is consistent with a study from Tanzania which reported that the performance of Xpert MTB/RIF was not affected by HIV status [26]. Other reports have suggested that the impact of HIV status on Xpert MTB/RIF sensitivity decreased when adjusting for percentage smear-positive, suggesting differences could be attributed to differences in smear status [20-27]. The assumption is that smear-negative TB is more likely among HIV-positive patients, a smear status which negatively affects the TB diagnostic performance of Xpert MTB/RIF. Thus, in the context of household contact tracing, it would seem the broader question should rather be whether a trade-off exists when opting for the exclusive use Xpert MTB/RIF for TB detection; recent evidence evaluating the use of Xpert MTB/RIF Ultra among HIV-positive patients suggests that some of these trade-offs might be overcome, however this may still be problematic as the reported study was not done among a household contact population [25]. In such a population, not including mycobacterial culture as part of the testing strategy would certainly miss a proportion of TB cases and therefore minimize its impact as an intervention irrespective of HIV status.

The contamination rate was 6.2% (18/289) amongst specimens tested on mycobacterial culture. This contamination rate is within the 8-10% upper limit which is considered acceptable and is slightly lower than a meta-analysis which reported a contamination rate of 8.6% when using liquid systems such as the BACTEC MGIT 960 for culturing [28]. We did not report any failed Xpert MTB/RIF tests in our study, however, a meta-analysis by Steingart *et al* reported a very low pooled proportion of uninterpretable Xpert MTB/RIF results at 1.0% (95% CI: 0.05%, 2.0%) [20]. The absence of any failed Xpert MTB/RIF tests should be viewed as one of its strengths and lends support to the concurrent use of Xpert MTB/RIF and mycobacterial culture in a setting such as household contact tracing as the cost associated

with visiting households would not favour a repeat visits for a more sputa as a consequence of a contaminated culture result.

The study has important strengths in that all household contacts suspected of TB were tested with smear microscopy, culture and Xpert MTB/RIF making it appropriate to compare the yield and sensitivities. The laboratory testing was also conducted by one laboratory to clinical trial standards. There are several limitations to our study which relate mainly to our small numbers of contacts and culture-confirmed TB cases and hence the precision of our estimates; this study was nested within a larger study which aimed to compare the yield of TB amongst household contacts of DR-TB and DS-TB and thus not designed to address this specific question of comparing diagnostic performance. We also only requested a single spot sputum and possibly the quantity and quality of sample may have affected the yield of TB. The use of a single spot sputum for culture may have resulted in a lower Xpert MTB/RIF PPV estimate as 5 samples that were positive on Xpert MTB/RIF, were contaminated on culture and subsequently excluded from the analysis. We also evaluated the household contacts very soon (<2 weeks) after the index TB patient was diagnosed which is much sooner than most contact tracing studies; this could explain the high proportion of smear-negative results as a consequence of a lower bacillary burden despite being culture-positive.

Among symptomatic household contacts investigated for TB, Xpert detected all smear-positives but only 13.3% of the smear-negative culture-positive TB cases. The low TB yield from Xpert MTB/RIF in this study suggests that among symptomatic household contacts, mycobacterial culture testing should supplement Xpert MTB/RIF where available especially among smear-negative patients, while the diagnostic performance of Xpert MTB/RIF Ultra is evaluated in this particular population.

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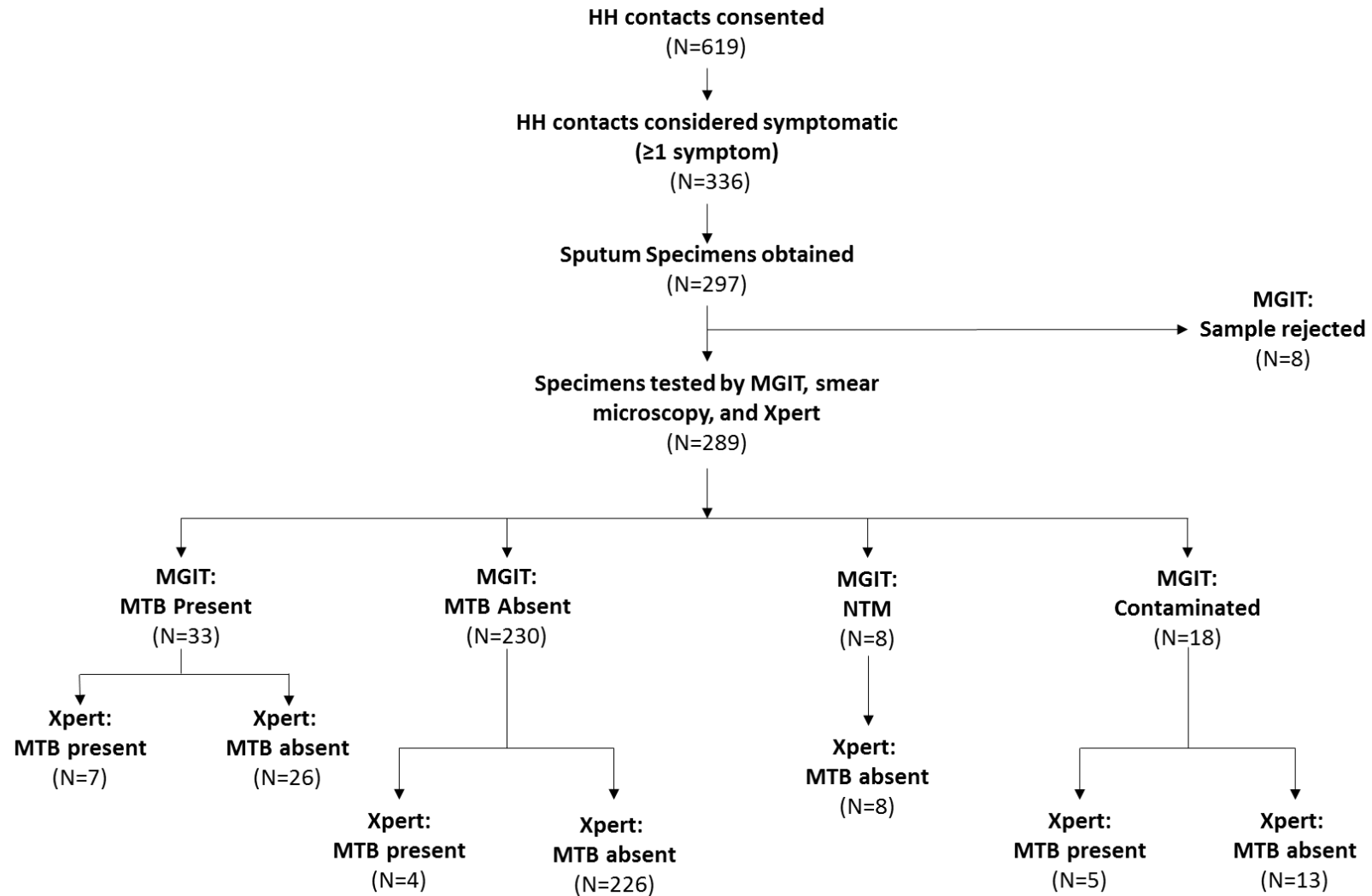


Figure 1. Flow diagram of Xpert MTB/RIF and MGIT culture testing results

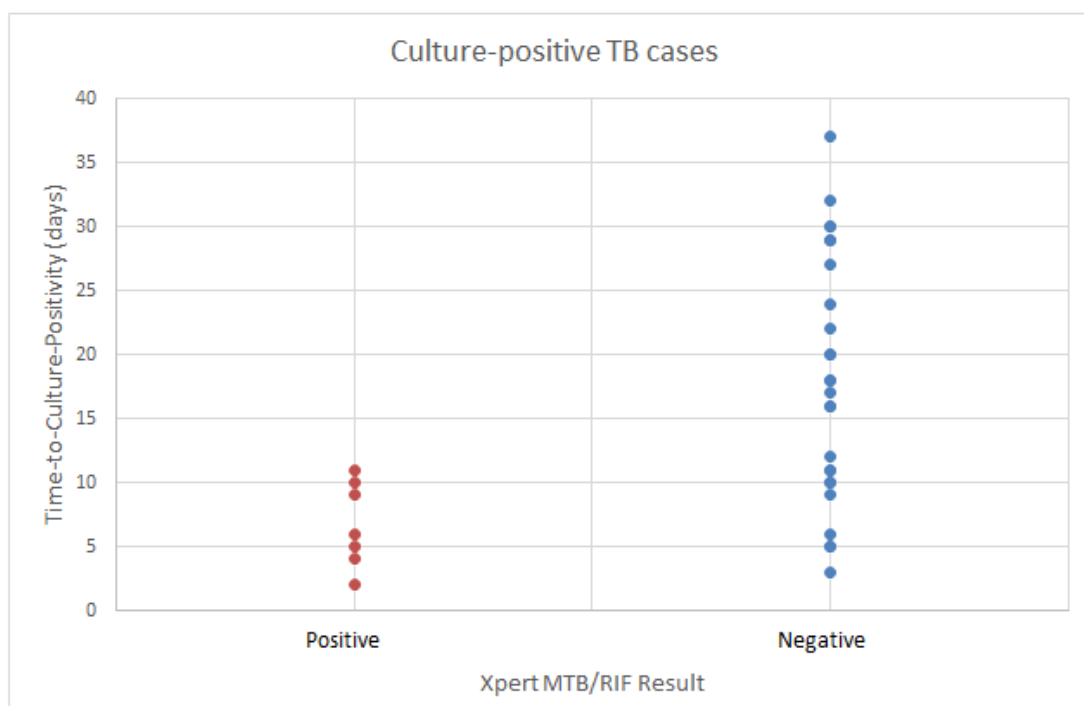


Figure 2: Distribution of TTCP for each of the 33 culture-positive TB cases

Table 1. Characteristics of Index MDR-TB and DST-TB patients

Characteristic	MDR-TB (n=73)	DS-TB (n=145)
Gender, n (%)		
Male	39 (53.4)	78 (53.8)
Female	34 (46.6)	67 (46.2)
Age, n (%)		
18-29	17 (23.3)	30 (20.7)
30-39	26 (35.6)	52 (35.9)
40-49	21 (28.8)	47 (32.4)
≥50	9 (12.3)	16 (11.0)
Median (IQR)	36 (30-45)	37 (30-45)
Number of household contacts, n (%)		
1	21 (28.8)	38 (26.2)
2	15 (20.6)	26 (17.9)
3	9 (12.3)	28 (19.3)
4	13 (17.8)	20 (13.8)
≥5	15 (20.5)	33 (22.8)
HIV status, n (%)		
Positive	62 (84.9)	100 (69.9)
Negative	11 (15.1)	43 (30.1)

Table 2. Characteristics of household contacts and culture-positive TB cases

Characteristic	All household contacts (N=619)	Culture-positive TB cases (N=33)
Gender, n (%)		
<i>Male</i>	244 (39.4)	16 (48.5)
<i>Female</i>	375 (60.6)	17 (51.5)
Age, n (%)		
<i><18</i>	263 (42.5)	12 (36.4)
<i>18-29</i>	123 (19.9)	7 (21.1)
<i>30-39</i>	74 (12.0)	4 (12.1)
<i>40-49</i>	59 (9.5)	6 (18.2)
<i>≥50</i>	100 (16.1)	4 (12.2)
<i>Median (Inter-quartile range)</i>	22 (9-40)	27 (14-42)
TB symptoms, n (%)		
<i>Cough ≥24 hours</i>	331 (53.5)	33 (100.0)
<i>Fever</i>	20 (3.2)	3 (9.1)
<i>Night sweats</i>	18 (2.9)	2 (6.1)
<i>Unintentional weight loss</i>	30 (4.9)	5 (15.2)
<i>≥1 TB symptoms</i>	336 (54.3)	33 (100.0)
<i>≥2 TB symptoms</i>	41 (6.6)	5 (15.2)
<i>≥3 TB symptoms</i>	13 (2.1)	2 (6.1)
HIV status, n (%)		
<i>Positive</i>	126 (20.4)	10 (30.3)
<i>Negative</i>	493 (79.6)	23 (69.7)
Previous history of TB, n (%)		
<i>Yes</i>	42 (6.8)	6 (18.2)
<i>No</i>	577 (93.2)	27 (81.8)

Table 3. Results for MGIT culture Xpert MTB/RIF for 289 specimens

		MGIT Culture				
		MTB	Negative	NTM	Contaminated	Total
Xpert MTB/RIF	MTB	7	4	0	5	16
	Negative	26	226	8	13	273
	Total	33	230	8	18 ^a	289

Table 4. Performance characteristics of the Xpert MTB/RIF test overall, and stratified by smear microscopy status and HIV status, using MGIT culture as the reference standard

		Overall (N=271) ^a	Smear status		HIV status	
			Positive (N=5) ^b	Negative (N=266)	Positive (N=62)	Negative (N=209)
Xpert MTB/RIF sensitivity	N/N	7/33	3/3	4/30	4/10	3/23
	% (95% CI)	21.2 (9.0, 38.9)	100.0	13.3 (3.8, 30.7)	40.0 (7.5, 70.1)	13.0 (2.8, 33.6)
Xpert MTB/RIF specificity	N/N	234/238	0/2	234/236	50/52	184/186
	% (95% CI)	98.3 (95.8, 99.5)	0.0	99.1 (97.0, 99.9)	96.1 (86.7, 99.5)	98.9 (96.2, 99.9)
Xpert MTB/RIF PPV	N/N	7/11	3/5	4/6	4/6	3/5
	% (95% CI)	63.6 (30.8, 89.1)	60.0 (14.7, 94.7)	66.7 (22.2, 95.7)	66.7 (22.3, 95.7)	60.0 (14.7, 94.7)
Xpert MTB/RIF NPV	N/N	234/260	0/0	234/260	50/56	184/204
	% (95% CI)	90.0 (85.7, 93.4)	0.0	90.0 (85.7, 93.4)	89.3 (78.1, 96.0)	90.2 (85.3, 94.0)

^a Excluded from the analysis were 18 specimens that were contaminated in MGIT culture

^b Sensitivity of smear microscopy for detection of MTB, using MGIT culture as reference standard, was 3/33 (9.0%, [95% CI: 1.9, 24.3] vs. Xpert sensitivity of 21.2% overall (p<0.001)