Pooled testing of sputum with Xpert MTB/RIF and Xpert Ultra during tuberculosis active case finding campaigns in Lao People’s Democratic Republic

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ABSTRACT

Introduction Active case finding (ACF) of individuals with tuberculosis (TB) is a key intervention to find the 30% of people missed every year. However, ACF requires screening large numbers of individuals who have a low probability of positive results, typically <5%, which makes using the recommended molecular tests expensive.

Methods We conducted two ACF surveys (in 2020 and 2021) in high TB burden areas of Lao PDR. Participants were screened for TB symptoms and received a chest X-ray. Sputum samples of four consecutive individuals were pooled and tested with Xpert Mycobacterium tuberculosis (MTB)/ rifampicin (RIF) (Xpert-MTB/RIF) (2020) or Xpert-Ultra (2021). The agreement of the individual and pooled samples was compared and the reasons for discrepant results and potential cartridge savings were assessed.

Results Each survey included 436 participants, which were tested in 109 pools. In the Xpert-MTB/RIF survey, 25 (sensitivity 89%, 95% CI 72.8% to 96.3%) of 28 pools containing MTB-positive samples tested positive and 81 pools containing only MTB-negative samples tested negative (specificity 100%, 95% CI 95.5% to 100%). In the Xpert-Ultra survey, all 32 (sensitivity 100%, 95% CI 89.3% to 100%) pools containing MTB-positive samples tested positive and all 77 (specificity 100%, 95% CI 95.3% to 100%) containing only MTB-negative samples tested negative. Pooling with Xpert-MTB/RIF and Xpert-Ultra saved 52% and 46% (227/436 and 199/436, respectively) of cartridge costs alone.

Conclusion Testing single and pooled specimens had a high level of agreement, with complete concordance when using Xpert-Ultra. Pooling samples could generate significant cartridge savings during ACF campaigns.

INTRODUCTION

Despite being treatable and curable, tuberculosis (TB) remains one of the main infectious killers in the world, as ten million people fall ill and 1.4 million die from the disease each year.1 Its diagnosis is usually reliant on passive case finding (PCF), in which health services wait for individuals with symptoms of TB to attend a health facility to initiate the diagnostic process. Although PCF identifies most people with TB in locations with adequate access to health services, it misses those unwilling or unable to attend the clinics and is a major reason only seven of the ten million people with TB are diagnosed and notified.2 Individuals missed by passive approaches often include vulnerable populations such as internally displaced, migrant or rural populations, women, the unemployed and ethnic minorities,3,4 who may face multiple societal and economic barriers to attend the service, including catastrophic costs.5,6 It is,
thus, recognised that, to be inclusive and reduce the socio-economic impact of TB, health services need to include active case finding (ACF) approaches that involve proactive interventions to extend the reach of TB services for diagnosis and treatment. Although ACF interventions can be very effective, they are less standardised than PCF, as they address the specific barriers of multiple target populations and are more resource and time intensive than PCF.

The WHO recommends testing all individuals with presumptive TB with molecular assays, such as the Xpert Mycobacterium tuberculosis/rifampicin (Xpert MTB/RIF) and Xpert-Ultra (Cepheid Sunnyvale, California), with the latter being preferred given its higher sensitivity. Although the use of these assays is expanding, the assay cartridge unit costs of US$ 9.98 per test remains one of the main hurdles for its wider implementation in low-income and middle-income countries. Diagnostic test costs can limit the expansion of ACF activities, as they require testing large numbers of individuals with relatively lower yields than PCF.

Since 2015, the Lao National Tuberculosis Control Center (NTC) has conducted ACF by implementing intensified case finding activities to increase the detection of individuals with TB in high burden districts of the country. These activities include the sensitisation of the population, the local provision of chest X-rays for screening (independently of symptoms) and the identification of individuals with symptoms of TB who have not attended health facilities. Participants with abnormal chest X-rays or symptoms of TB are tested using Xpert MTB/RIF or Xpert-Ultra. The activities have increased case detection, although the cost of the Xpert cartridges is considered high and is the main limiting factor to implement the intervention on a larger scale.

One approach that could increase the affordability of Xpert testing is to test several samples together using the pooling method. This procedure combines (or pools) the sputum of several individuals into one pot and tests them together with a single test. If the test is positive, the pool’s samples are retested individually to identify the positive sample(s) while if the test is negative, all samples in the pool are considered negative, resulting in 30%–40% savings in Xpert cartridge costs alone depending on the prevalence of TB in the population tested. Therefore, pooling may hold great promise for ACF, but there are few reports of its performance under operational conditions.

Here, we report a prospective study to assess the sensitivity and specificity of the pooling method using Xpert MTB/RIF and Xpert-Ultra during intensified case finding interventions, and its potential to increase the affordability of Xpert testing in Lao PDR.

METHODS

We conducted two independent prospective surveys embedded within the ACF activities of Lao’s NTC, from March to April 2020 and from January to March 2021. Both surveys were cross-sectional and used the same recruitment and testing procedures. The 2020 survey aimed to assess the performance of the pooling method when testing samples with Xpert MTB/RIF, while the 2021 survey assessed the method when using Xpert-Ultra, after its release for routine use by Lao’s NTC.

ACF was conducted in Lao’s high TB burden areas, which are programmatically defined as TB incidence ≥100 cases per 100,000 population. The 2020 survey was conducted in Vientiane Capital, Luang Prabang and Savannakhet provinces with estimated populations of 890,129, 468,375 and 1,051,675 inhabitants, respectively, and TB notification rate of 134, 88 and 102 cases per 100,000 population in 2020, respectively. The 2021 survey was conducted in Saravane and Oudomxay, with 430,428 and 333,954 population and TB notification rates of 127 and 110 cases per 100,000 population in 2020, respectively.

Both surveys were conducted in the same fashion. Before an ACF activity, the NTC team met the province and district health authorities and conducted preparation visits with the provincial TB coordinator, district TB manager and village authorities, distributed health education materials, obtained the addresses of individuals with TB and line listed household contacts. At an agreed date, the NTC team set up a digital chest X-ray machine and a four-module GeneXpert platform in the village and invited all residents to complete a questionnaire on signs and symptoms, history and treatment of TB and offered chest X-rays for screening, independently of the presence of symptoms. Individuals with abnormal chest X-rays and those who indicated having cough >2 weeks duration were asked to provide sputum samples for Xpert testing and were managed according to the decision tree shown in figure 1. Sputum samples were tested with Xpert following the manufacturer’s instructions. Sputum samples tested individually with Xpert MTB/RIF or Xpert-Ultra were processed in the village GeneXpert platform. Consecutive samples with remnant volumes ≥0.5mL were included in the pooling studies and were transported to the National TB Reference Laboratory in Vientiane using a cold chain. Samples were transported after the sample reagent had been added. Turned around time to testing was <48 hours after the sample reagents had been added and samples were maintained in a cold chain at all times. Sputum samples from four participants were pooled together, with a volume of 0.5mL of sputum each added to a pot, to obtain an aggregated volume of 2mL. Samples for a pool were selected consecutively and staff were blind to the individual Xpert test results and the pooled specimen was tested using one new Xpert cartridge.

Statistical analysis

Categorical data were summarised using descriptive statistics and χ² tests were used to test for statistically significant differences. Individuals unable to produce sputum were excluded from the analysis. The pooled samples were compared with the four Xpert MTB/RIF and Xpert-Ultra individual results and their agreement was tested using
kappa statistics. The CT values and grades (trace, very low, low, medium and high) of individual and pooled tests were compared with describe the effect of combining the samples. Cost differences were calculated on the bases of the number of cartridges required to test all specimens using pooled and individual testing.

Sample size for the surveys was not formally estimated as we were limited by the expected number of participants attending the campaigns before the COVID-19 lockdown, the capacity of staff to conduct additional testing to their routine activities and the number of spare cartridges available for research purposes.

Patient and public involvement
It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting or dissemination plans of our research.

RESULTS
The 2020 survey included 436 participants, 334 (76.6%) men and 102 (23.4%) women, and 29 (6.7%, 95% CI 4.7% to 9.4%) were Xpert MTB/RIF MTB-positive. The 2021 survey also included 436 participants, 222 (50.9%) men and 214 (49.1%) women, and 37 (8.5%, 95% CI 6.5% to 11.5%) were Xpert-Ultra MTB-positive (p value >0.1, table 1). Men were more likely to be MTB-positive than women in 2020 (26/334 (7.8%) men vs 3/102 (2.9%) women, respectively, p=0.014); but women were more likely to be MTB-positive than men in 2021 (12/222 (5.4%) vs 12/214 (11.7%), respectively, p<0.008). Each survey included 109 pools of four patients.

Xpert MTB/RIF survey
In 2020, 28 (25.7%) pools contained one or more Xpert MTB/RIF MTB-positive sample (27 pools with one and one pool with two MTB-positive samples) and 81 (74.3%) pools contained solely MTB-negative samples (table 2). The pool with two MTB-positive and 24 of 27 pools with one MTB-positive sample tested MTB-positive and three tested MTB-negative, resulting in a sensitivity of 89% (25/28, 95% CI 72.8% to 96.3%). All 81 pools containing solely MTB-negative samples tested MTB-negative in the pooled assay (specificity 100%, 95% CI 95.5% to 100%). Therefore, the accuracy performance of the 109 pools in correlation to the 436 individual results resulted in 97.3% agreement (kappa: 0.925). Among the 27 pools containing single MTB-positive samples, five contained very low, 15 low, 6 medium and one high MTB grades. The pooled MTB grade was similar to the individual test in four (14.8%), one grade lower in 21 (77.8%), two grades lower in one (3.7%) and one grade higher in one (3.7%) of the pools. Of the five pools containing very low individual MTB-grades, three tested MTB-not detected and two very low MTB-grade in the pooled assay (table 3).
The CT values for the Xpert MTB/RIF probes for both individual and pooled testing are shown in Table 4. The median CT values for probes A-E ranged from 23.4 to 24.8 for the individual tests and from 30.6 to 33.6 for the pooled tests, with an increase in CT values ranging from 5.4 to 7.1.

Two of the MTB-positive samples were RIF-indeterminate and 27 RIF-negative. Of the 28 pools with
Table 3  Correlation of Individual and pooled Xpert MTB grades (positive pools only include those with only one positive Xpert)

<table>
<thead>
<tr>
<th>Pooled Xpert MTB/RIF</th>
<th>Not detected n (%)</th>
<th>Trace n (%)</th>
<th>Very low n (%)</th>
<th>Low n (%)</th>
<th>Medium n (%)</th>
<th>High n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not detected</td>
<td>81 (100%)</td>
<td>NA</td>
<td>5 (60%)</td>
<td>15 (80%)</td>
<td>6 (100%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Very low</td>
<td>0</td>
<td>NA</td>
<td>2 (40%)</td>
<td>12 (80%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>2 (13.3%)</td>
<td>6 (100%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Medium</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>1 (6.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| Pooled Xpert Ultra   | 77 (100%)          | 2 (100%)    | 5 (80%)        | 13 (46%) | 1 (67%)      | 6 (33%)   |
| Not detected         | 77 (100%)          | 0           | 0              | 0        | 0            | 0         |
| Trace                | 0                  | 2 (100%)    | 4 (80%)        | 7 (54%)  | 1 (100%)     | 2 (33%)   |
| Very low             | 0                  | 0           | 1 (20%)        | 6 (46%)  | 0            | 4 (67%)   |
| Low                  | 0                  | 0           | 0              | 0        | 0            | 0         |
| Medium               | 0                  | 0           | 0              | 0        | 0            | 0         |
| High                 | 0                  | 0           | 0              | 0        | 0            | 0         |

Bold values are frequencies and do not indicate statistical significance.

Xpert MTB/RIF, Xpert Mycobacterium tuberculosis/rifampicin.

MTB-positive samples, 25 pools contained one MTB-positive RIF-negative sample, one had two MTB-positive RIF-negative samples and two had one MTB-positive RIF-indeterminate samples. Of the 25 MTB-positive RIF-negative pools, three tested MTB-negative and did not report RIF results and 22 tested RIF-negative. The pool containing two MTB-positive RIF-negative samples tested RIF-negative and the two pools containing RIF-indeterminate samples tested RIF-negative in one and RIF-indeterminate in the other.

Xpert-Ultra survey
In 2021, 32 (29.4%) pools contained MTB-positive samples and 77 (70.6%) solely MTB-negative samples. Twenty-seven of the 32 MTB-positive pools contained one and five contained two MTB-positive samples and all tested positive in the pooled assay (sensitivity 100%, 95% CI 89.3% to 100%). All 77 pools containing only MTB-negative samples tested MTB-negative (specificity 100%, 95% CI 95.3% to 100%), resulting in 100% agreement (Kappa: 1). Among the 27

Table 4  Median CT values of individual and pooled Xpert MTB/RIF and Xpert Ultra probe results

Xpert MTB RIF

<table>
<thead>
<tr>
<th>Probe</th>
<th>Individual results n=29</th>
<th>Min–max</th>
<th>Pooled results n=25</th>
<th>Min–max</th>
<th>ΔCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe D</td>
<td>24.6 (22.7–27.3)</td>
<td>19.1–35.2</td>
<td>32.3 (28.5–34.2)</td>
<td>21.0–38.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Probe C</td>
<td>23.7 (22.0–26.7)</td>
<td>18.9–34.7</td>
<td>30.3 (27.4–31.8)</td>
<td>20.0–35.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Probe E</td>
<td>24.8 (23.0–28.1)</td>
<td>20.5–36.2</td>
<td>33.9 (29.3–34.9)</td>
<td>21.2–39.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Probe B</td>
<td>24.6 (22.9–27.3)</td>
<td>20.1–33.8</td>
<td>30.1 (27.3–32.5)</td>
<td>20.9–34.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Probe A</td>
<td>23.3 (22.0–26.0)</td>
<td>20.5–34.1</td>
<td>31.1 (27.1–32.9)</td>
<td>19.7–34.6</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Xpert Ultra

<table>
<thead>
<tr>
<th>Probe</th>
<th>Individual results n=37</th>
<th>Min–max</th>
<th>Pooled results n=32</th>
<th>Min–max</th>
<th>ΔCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe IS1081</td>
<td>19.6 (17.1–22.6)</td>
<td>16.0–32.0</td>
<td>24.9 (22.2–26.5)</td>
<td>19.9–29.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Probe rpoB1</td>
<td>21.6 (17.9–24.9)</td>
<td>0–32.0</td>
<td>0 (0–30.2)</td>
<td>0–34.9</td>
<td>NA</td>
</tr>
<tr>
<td>Probe rpoB2</td>
<td>21.3 (17.9–25.8)</td>
<td>0–32.1</td>
<td>0 (0–29.8)</td>
<td>0–35.3</td>
<td>NA</td>
</tr>
<tr>
<td>Probe rpoB3</td>
<td>23.3 (19.2–27.0)</td>
<td>0–33.7</td>
<td>0 (0–32.9)</td>
<td>0–39.8</td>
<td>NA</td>
</tr>
<tr>
<td>Probe rpoB4</td>
<td>25.7 (21.2–29.7)</td>
<td>0–35.7</td>
<td>0 (0–33.5b)</td>
<td>0–37.7</td>
<td>NA</td>
</tr>
</tbody>
</table>

Xpert MTB/RIF, Xpert Mycobacterium tuberculosis/rifampicin.
 pools with single MTB-positive samples, two contained trace, 5 very low, 13 low, 1 medium and 6 high MTB grades. The pooled MTB grades were the same as the individual grades in three (11%), one grade lower in 10 (42%), two grades lower in seven (29%), three grades lower in five (21%) and four grades lower in two (8%) of the pooled assays (table 3). The Xpert-Ultra probes CT values are shown in . Probe IS1081/IS6110 had median CT of 19.6 for individual and 24.9 for pooled results, with a median increase of 4.6. Probes rpoB1-B4 median CT values ranging from 19.6 to 25.7 for the individual tests, but CT values were not available for the pools. Among the 37 MTB-positive samples, 30 (81%) were RIF-negative and 7 (18.9%) were RIF-indeterminate and were distributed in 32 pools. Twenty-five of the 32 pools contained only RIF-negative and 7 contained RIF-indeterminate samples. Fifteen of the 25 pools containing only RIF-negative samples tested RIF-indeterminate and 10 RIF-negative, while all seven pools containing RIF-indeterminate samples tested pooled RIF-indeterminate.

**Xpert MTB/RIF and Xpert Ultra costs**

The cartridges cost for testing individually the 436 participants with Xpert at US$9.98 per test was US$4351.28 for each survey, as shown in table 5. The pooling method in 2020 required 109 Xpert MTB/RIF cartridges to test 109 pools and 100 cartridges to test individual samples of 25 MTB-positive pools. The total of 209 (109+100) cartridges for pool testing would cost US$2085.82, resulting in US$2265.46 (52%) saving in cartridge costs. Similarly, testing 109 pools with Xpert-Ultra in 2021 required 109 cartridges to test the pools and 128 cartridges to test individually the 32 positive pools. The total of 237 cartridges would cost US$2365.26, resulting in US$1986.02 (46%) savings in cartridge costs. If the number of cartridges is kept fixed, the pooling method could test more patients than testing samples individually, as 436 cartridges would allow testing 909 and 802 individuals with Xpert MTB/RIF and Xpert-Ultra, respectively—an effective test per patient cost of US$4.78 and 5.42, respectively (table 5).

**DISCUSSION**

Our surveys compared pooling with single testing during ACF for TB in a low-income country. Our results confirm that testing individual and pooled samples with the GeneXpert platform can achieve a high level of concordance. Concordance was higher with Xpert-Ultra than with Xpert MTB/RIF, which is in agreement to regional studies evaluating pooling with Xpert-Ultra in Cambodia20 and Vientiane, Lao PDR (Iem et al, in press). Discrepancies between individual and pooled Xpert MTB/RIF tests only occurred among pauci-bacillary samples with high Xpert CT values, suggesting that some samples with low DNA concentrations fall below the assay’s limit of detection and that the better agreement of Xpert-Ultra is due to its higher sensitivity. Consequently, some patients with paucibacillary disease could be missed by pooling, especially if testing is based on Xpert MTB/RIF.

The pooling strategy can lead to significant cost savings and facilitate testing of more individuals for a given number of cartridges. In our setting, pooling samples would double the number of people tested with the same number of cartridges. This is higher than in PCF studies, where pooling is reported to save up to 40% of cartridges.19 Cartridge savings are a function of the proportion of people with MTB-positive results and their distribution within the pools. If the proportion positive is low, a low number of pools would need to be retested, resulting in higher cartridge savings. For example, in a survey in Lao’s district clinics, 12% of individuals tested Xpert-positive, and pooling resulted in 38.3% and 41.7% cartridge saving costs with Xpert MTB/RIF and Xpert-Ultra, respectively (Iem et al, in press), while in our survey setting, the proportion of positives was 8.5%, which led...
to higher savings. The proportion of participants with positive tests in ACF is often lower than reported from studies using PCF, typically below 5% depending on the target population, and lower to 10%–20% of individuals attending TB clinics in PCF. Both tools can identify individuals with and important to highlight that pooled RIF results are unreliable and should not be used for clinical management.

Further studies could explore ways to further improve the efficiency of pooling when combined with other screening tools, such as CREactive protein (CRP) and digital chest X-rays with Computer-aided diagnosis (CAD). Both tools can identify individuals with and without the traditional symptoms of TB, although their relatively lower specificity requires confirming the diagnosis with more specific molecular assays. Although using tests combinations could increase assay costs, individuals with a positive CRP or abnormal chest X-rays CAD could be confirmed using the pooling method, and its efficiency gains could increase the affordability of tests combinations.

In conclusion, we have shown pooling samples for TB diagnoses during ACF campaigns, which can replicate testing samples with individual tests. The approach can facilitate testing higher numbers of patients with lower cartridge costs, increasing the affordability of testing with molecular assays. The high level of agreement between individual and pooled samples obtained with Xpert Ultra demonstrates that pooling can be reliable and contribute to achieve the WHO End TB strategy targets in resource-limited settings.

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Contributors

The study was designed by LEC, JC, VI, KK and JAMK. Patients screening and enrolling, individual sample testing on Xpert MTB/RIF and Xpert Ultra were conducted by PC, SaS, SoS, PS, and SiS in the field during the ACF campaign. VI performed the pooled testing. Data collection and analysis were conducted by VI, KK, LEC, JD and JC. VI, JD, TW, JC and LEC wrote the first draft of the manuscript. All authors made substantial contributions to the writing and editing of the manuscript. LEC is responsible for the overall content and is the guarantor of the study. The final version has been read and approved by all named authors.

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Competing interests

The authors have no conflicts of interest to declare.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

The study was approved by the Lao NTC and the Liverpool School of Tropical Medicine Research Ethics Committee, UK (Ethical waiver 20–037), and informed consent waiver was obtained.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available upon reasonable request. Not applicable.

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