Alternative respiratory specimens for GeneXpert-based tuberculosis (TB) and COVID-19 diagnosis in selected cities of Laguna, Philippines, amid and post-pandemic

Carolina B. Capili*[1], Louis Andrew M. Olazo[1], Joseph Edwin L. Bascuña[1], Chona Mae Daga[2], Mariza Garing[4], Alma G. Palparan[1], Vina Lea F. Arguelles[3], Catherine C. Dacasin[3], Soledad Rosanna Cunanan[4], and Ramon P. Basilio[1]

[1]National Tuberculosis Reference Laboratory, Research Institute for Tropical Medicine, Alabang, Muntinlupa City, 1781, Philippines
[2]Department of Epidemiology and Biostatistics, Research Institute for Tropical Medicine, Alabang, Muntinlupa City, 1781, Philippines
[3]Virology Department, Research Institute for Tropical Medicine, Alabang, Muntinlupa City, 1781, Philippines
[4]Santa Rosa City Health Office I, City of Santa Rosa, Laguna, 4026, Philippines

ABSTRACT

Diagnosis of tuberculosis (TB) and coronavirus disease (COVID-19) relies on the collection of standard specimens, yet obtaining these remains a persistent challenge in practice. TB testing typically relies on sputum, which requires patient ability to expectorate or to cough up from the lungs, while nasopharyngeal and oropharyngeal swabbing for COVID-19 can be uncomfortable or even painful. Exploring alternative specimens provides practical options in cases when standard specimen collection is not feasible, enabling timely diagnosis, patient-centered care, and offering a potential for dual testing from a single specimen. The Cepheid GeneXpert® technology supports this approach by providing a platform capable of diagnosing both TB and COVID-19.

This study evaluated the diagnostic performance of Xpert® MTB/RIF Ultra using oropharyngeal swabs (OPS) and Xpert® Xpress SARS-CoV-2 using sputum for the respective diagnosis of TB and COVID-19. Study participants presenting with signs and symptoms of either or both diseases were enrolled from selected sites in Laguna from August 2022 to September 2024. Both standard and alternative specimens were collected and tested using their corresponding diagnostic assays: Xpert® MTB/RIF Ultra and Xpert® Xpress SARS-CoV-2, with reference standards culture and conventional real-time reverse transcriptase polymerase chain reaction (RT-PCR) for TB and COVID-19, respectively. Diagnostic accuracy parameters were analyzed and compared across specimen types.

A total of 111 study participants were enrolled into these screening cohorts: 69 with TB, 4 with COVID-19, and 38 with co-infection wherein, 107 OPS specimens were analyzed using Xpert® MTB/RIF Ultra, and 35 sputum specimens were tested with Xpert® Xpress SARS-CoV-2.

Using sputum TB culture (n=24) as reference standard in diagnosing TB, OPS (n=14) in saline tested positive in Xpert® MTB/RIF Ultra yielded a sensitivity of 58.33% (95% CI: 48.52–68.14), specificity of 86.30% (95% CI: 79.46-93.14), positive predictive value (PPV) of 58.33% (95% CI: 48.52–68.14), and negative predictive value (NPV) of 86.30% (95% CI: 79.46-93.14).

KEYWORDS

Tuberculosis, COVID-19, Swab, GeneXpert Test, *Mycobacterium tuberculosis complex,* SARS-CoV 2, alternative respiratory specimens

Carolina Capili *Corresponding author
Email Address: **c.capili.ritm@gmail.com**
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Comparable studies have reported sensitivity of 36% (95% CI: 26–48) to 91% (95% CI: 80–98) and specificity of 66% (95% CI: 52–78) to 100.00% (95% CI: 97–100) in adults (Church et al., 2024).

Meanwhile, all 5 COVID-19 positive samples (Xpert® Xpress SARS-CoV-2 sputum positive vs OPS positive in RT-PCR) yielded a sensitivity of 100.00% (95% CI: 100–100), specificity of 90.00% (95% CI: 80.06–99.94), PPV of 62.50% (95% CI: 46.46–78.54), and NPV of 100.00% (95% CI: 100–100). These findings were higher compared with prior findings reporting 67% sensitivity (MacLean et al., 2023).

The use of OPS for TB diagnosis with Xpert® MTB/RIF Ultra and sputum for COVID-19 diagnosis with Xpert® Xpress SARS-CoV-2 showed diagnostic performance comparable to that of standard specimens. These alternative specimens may serve as reliable options, especially in situations where collecting standard specimens is difficult. Notably, sputum may be a practical dual-use specimen for diagnosing both TB and COVID-19 during emergency responses such as pandemics. Nevertheless, standard specimens remain the preferred choice whenever feasible due to their established diagnostic accuracy.

INTRODUCTION

The emergence of Coronavirus Disease (COVID-19) in 2020, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), rapidly escalated into a global pandemic that significantly disrupted healthcare systems and resources from other public health threats such as tuberculosis (TB). Affecting approximately 10 million people annually, TB showed significant reductions in both incidence and mortality reflecting progress in control efforts between 2015 and 2019 through the WHO's End TB Strategy (WHO-TB, 2020). However, the pandemic reversed these gains particularly in diagnostics where laboratory resources were reallocated to COVID-19 testing. This disruption was further compounded by the lack of economic, medical, and social resources needed to sustain disease control and prevention efforts during the crisis (Saunders, 2020). The delays in TB diagnosis and underreporting of TB cases had heightened the risk of transmission, drug resistance, and poor outcomes, emphasizing the urgent need for resilient and accurate diagnostic systems, especially in resource-limited settings.

One of the key challenges in diagnosing TB and its co-infection with other respiratory diseases is the limited accessibility of appropriate diagnostic tools. While rapid molecular assays have improved in terms of sensitivity and specificity of TB detection, testing can remain centralized, limiting access in resource-constrained settings (Nguyen et al., 2024). The integration of molecular diagnostic platforms for COVID-19 and TB has shown promise, however, logistical barriers such as specimen processing and infrastructure constraints hinder widespread implementation (Ong et al., 2020). Therefore, there was an urgent need for diagnostic strategies that facilitate simultaneous detection of multiple pathogens from a single specimen collection.

COVID-19 and pulmonary TB (PTB) primarily affect the lungs and present with similar signs and symptoms, but they differ in their onset. COVID-19 signs and symptoms typically appear within 2 to 14 days of exposure, while PTB symptoms can take 2 to 6 weeks or even months to years to manifest after exposure (Cioboata et al, 2023). This distinction is crucial when screening and managing these diseases, especially among high-risk patients with potential comorbidities that could lead to poorer outcomes. Studies indicate that co-infection with COVID-19 and TB is possible and it was observed that TB infection may lead to increased susceptibility to COVID-19, increased disease severity, and higher risks of mortality (Tadolini et al., 2020; Can Sarıngölü et al., 2020; Yu et al., 2020; Ruhwald et al., 2023). This highlights the importance of simultaneous testing to enable timely treatment and reduce transmission, particularly during the COVID-19 pandemic.

For PTB, sputum specimens are commonly used as *Mycobacterium tuberculosis* complex (MTBC) thrives in macrophages located in the lungs' lower tract. As for COVID-19, caused by SARS-CoV-2 infecting cells in both the upper and lower respiratory tracts, with nasopharyngeal swab (NPS) and oropharyngeal swab (OPS) being preferred specimen types for diagnosis (Rothan and Byrareddy, 2020; CDC, 2020). Testing was prioritized to the recommended specimens specific to each disease: sputum for TB using Xpert® MTB/RIF, and NPS for COVID-19 testing via RT-PCR. To address these constraints, the Philippine National TB Control Program (NTP) developed a National Adaptive Plan that implemented modifications in screening, diagnostic, and treatment adherence for TB patients aiming to maintain continuous TB services during the COVID-19 pandemic, mitigating cases of TB, COVID-19, and potential co-infections which was an increasing concern amid sustained community transmission (Singh et al., 2020). However, separate specimens for each disease also requires additional supplies, prolongs patient visits, and adds to the workload of facility staff during specimen collection.

There has been growing interest in alternative specimens for diagnosing these respiratory diseases during the pandemic wherein, studies had shown evidence on oral swab sensitivity for MTBC detection ranges from 36%(95% CI: 26–48) to 91% (95% CI: 80–98) in adults and 5% (95% CI: 1–14) to 42% (95% CI: 23–63) in children, while specificity was noted from 66% (95% CI: 52–78) to 100% (95% CI: 97–100), varying by technique and platform (Church et al., 2024). Sputum showed significantly higher SARS-CoV-2 viral loads than throat and nasal swabs (Yu et al., 2020) and achieved 100% agreement in Xpert® Xpress SARS-CoV-2 testing (Wong et al., 2020; Malczynski et al., 2020). For integrated testing, Xpert® Ultra detected 96% (95% CI: 89-99) of TB cases, while Xpert® Xpress identified 67% (95% CI: 60-73) of COVID-19 cases using sputum (MacLean et al., 2023). These results support sputum's utility for dual TB and COVID-19 diagnosis.

In the Philippines, the availability of Cepheid GeneXpert® Technology for both TB and COVID-19 offers an opportunity to assess alternative specimen types, although different cartridges and specimens are required for each disease. A local evaluation of alternative specimens, such as sputum and OPS, can provide critical data on their diagnostic performance for both TB and COVID-19. Analyzing their utility and performance can determine the reliability to diagnose either or both diseases. If these alternative specimens yield results comparable to those of routine specimens, it could enhance patient convenience, reduce testing costs, and facilitate faster diagnoses, ultimately minimizing the need for additional specimen collection, and repeat facility visits.

The overall aim of the study was to evaluate the performance of using OPS in Xpert® MTB/RIF Ultra testing and sputum in Xpert® Xpress SARS-COV-2 testing for TB and COVID-19 diagnosis, respectively.

MATERIALS AND METHODS

This study utilized a cross-sectional design from August 2022 to May 2024 with prospective patient enrollment who were initially screened for signs and symptoms indicative of presumptive TB and/or suspected COVID-19. Study participants who met the eligibility criteria were enrolled, including age over 18 and at least

one symptom common (e,g, cough or fever) to both diseases, and were recruited as outpatients or referred from the clinics of Sta. Rosa City Health Office (CHO) I, Sta. Rosa CHO II, Biñan CHO I, Sta. Rosa Community Hospital, and Cabuyao CHO I. Study approval was obtained from the Research Institute for Tropical Medicine (RITM) - Institutional Review Board (IRB) (Protocol #2021-27), and all study participants provided written informed consent before specimen collection.

Patient Selection and Specimen Collection

Study participants were assigned to cohorts based on common signs and symptoms: TB cohort (e.g., cough >2 weeks, night sweats, fever, weight loss), COVID-19 cohort (e.g., cough, fever, chills, sore throat within 5-7 days), or TB and COVID cohort with overlapping symptoms. Study staff interviewed the study participants and assessed for their signs and symptoms through the study case report form. Study participants provided either an early morning sputum (self-collected at home as instructed by the healthcare worker or study staff) or a spot sputum; OPS specimens were collected by study staff by swabbing the oropharynx 10 times (Lima et al., 2020). The number of sputum and OPS specimens collected varied by disease cohort: presumptive TB only (1 sputum, 1 OPS in 3 mL saline for Xpert® MTB/RIF Ultra, suspected COVID-19 only (1 sputum, 1 OPS in 3 mL universal transport medium (UTM) for Xpert® Xpress SARS-CoV-2), or dual TB and COVID-19 screening (2 sputum, 2 OPS with each transport medium).

COVID-19 Testing

For Xpert® Xpress SARS-CoV-2 testing (Cepheid, Sunnyvale, California, United States of America), an oropharyngeal swab (OPS) specimen was prepared by separating 1.5 mL of UTM for testing. For sputum, a sterile swab was dipped into the specimen and then submerged in 500 µL of 0.9% saline. Testing was conducted following the manufacturer's instructions. For RT-PCR testing utilizing the MiRXES Fortitude Kit 2.1 (MiRXES, Singapore), specimens included UTM-preserved OPS and sputum (liquefied in phosphate buffer solution at a 3:2 ratio). SARS-CoV-2 RNA was extracted using either the RNeasy Mini Kit or the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany).

MTBC Testing

For Cepheid's Xpert MTB/RIF Ultra testing (Cepheid, Sunnyvale, California, United States of America), oropharyngeal swab (OPS) specimens were preserved in 1.5 mL of saline, while sputum specimens were treated with sample reagent (SR) following the manufacturer's instructions. For TB culture using the Ogawa solid medium, OPS specimens in 1.5 mL of saline and 2 mL of sputum in saline were processed using the modified Kudoh procedure and identified colony growth of MTBC through Bioline TB Ag MPT64 Rapid immunochromatographic kit (Abbott Laboratories, Illinois, United States of America).

Statistical Analysis

Data and results were anonymized and entered into a password-protected database. Statistical analyses using STATA 15 (StataCorp LLC, Texas, United States of America) included sensitivity and specificity to assess diagnostic accuracy (95% Confidence Interval (CI)), as well as positive and negative predictive values. Cycle threshold (Ct) values were analyzed for their mean and standard deviation (SD) to quantify the relative viral or bacterial load and dispersion of nucleic acid detection levels across specimens. Wilcoxon-signed rank test was done to compare the mean Ct values between OPS and sputum.

LIMITATIONS

The study was intended to be an intervention of the emergency response to increase case finding for both TB and COVID-19 during the height of the pandemic. However, due to lockdown restrictions, the transition into the implementation of Integrated Delivery of TB Services (iDOTS) phase 2 (i.e., decentralization of TB treatment/case holding from treatment centers and satellite treatment centers) and decreasing number patients seeking testing for COVID-19 (e.g. stigma), the enrollment of COVID-19 patients was lower compared to TB patients where established programs and laboratories supported the study. Additionally, saline was used and tested as a TB transport medium to determine its efficiency in supporting detection during outbreaks and preventing transmission given its affordability. This approach was also considered beneficial for low-resource settings due to its low cost.

RESULTS AND DISCUSSION

A total of 119 potential patients were invited to participate in the study. Of these, 8 individuals were excluded as 5 were lost to follow-up, while 3 had specimens that did not meet the inclusion criteria. This resulted in 111 eligible study participants who were then categorized into three cohorts: 69 (62.16%) study participants were assessed for TB signs and symptoms alone, 38 (34.23%) study participants had both TB and COVID-19, and 4 (3.60%) study participants were assessed with COVID-19 only. However, 7 TB and COVID-19 co-infected study participants consented only to submit specimens for TB testing, foregoing the COVID-19 testing due to certain limitations. This resulted to COVID-19 testing 31 co-infected study participants.

All study participants underwent diagnostic tests according to their screening cohort. For TB diagnosis using the Xpert® MTB/RIF Ultra test, sputum specimens showed 28 positive and 41 negative results; OPS specimens showed 13 positive and 56 negative results among study participants screened for TB only (n = 69). TB and COVID-19 co-infected study participants (n=38) tested 21 positive and 17 negative for sputum specimens; 14 positive and 24 negatives for OPS. For TB culture results, sputum specimens among TB study participants showed 10 positive, 51 negative, 5 with non-tuberculous mycobacteria (NTM), and 3 contaminated samples (n = 69). OPS specimens from the same cohort yielded no positive results and 69 negative results. Among TB and COVID-19 co-infected study participants, sputum specimens resulted in 14 positive results, 22 negative results, 1 NTM, and 1 contaminated sample (n = 38). OPS specimens from this group had 1 positive and 37 negative results (n = 38).

For COVID-19 diagnosis, study participants underwent both Xpert® Xpress SARS-CoV-2 and RT-PCR testing. Among study participants screened for COVID-19 only (n=4), all sputum and OPS specimens tested negative for SARS-CoV-2 and RT-PCR results. With TB and COVID-19 co-infected study participants (n=31), 8 sputum and 7 OPS specimens tested positive for SARS-CoV-2, while 23 sputum and 24 OPS specimens tested negative. Their RT-PCR results detected SARS-CoV-2 in 9 sputum and 5 OPS specimens, while 22 sputum and 26 OPS specimens tested negative.

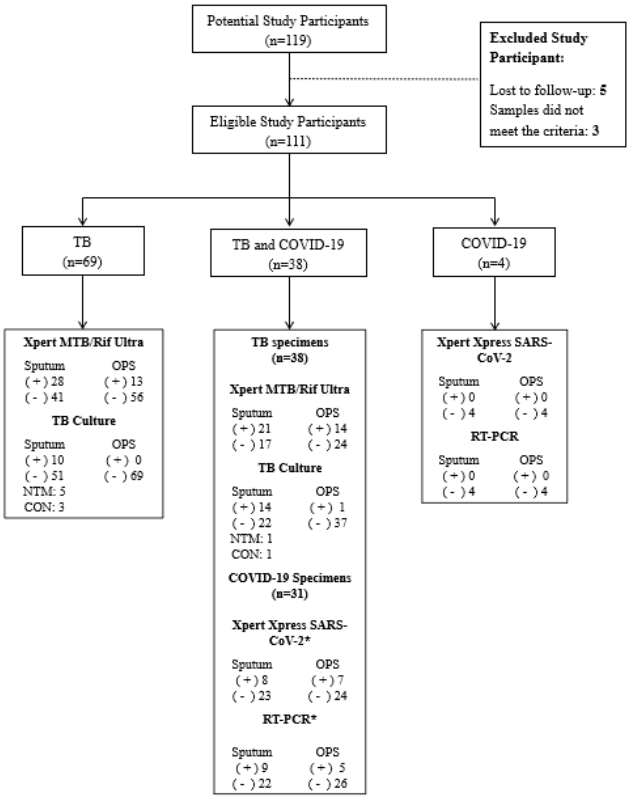

Figure 1: Study participant screening cohort and tests

NTM: Nontuberculous mycobacterium; **CON**: Contamination; * - TB & COVID-19 screened, no COVID-19 sample submitted

Demographic and Clinical Profile

Table 1 showed a total of 111 study participants wherein the largest age group was 41-60 years (49.55%), followed by 21-40 years (27.93%). Study participants over 60 years represented 19.82%, while those under 20 years accounted for just 2.70%. The gender distribution of the study participants was relatively balanced with 63 males (56.76%) and 48 females (43.24%).

Table 1: Demographic Profile (N=111)

Patient Characteristics	N	%
Age group (years)		
Less than 20	3	2.70
21-40	31	27.93
41-60	55	49.55
More than 60	22	19.82
Gender		
Male	63	56.76
Female	48	43.24

Signs and symptoms were self-reported by the study participants and assessed by study staff. As shown in Table 2, these sign and symptoms varied significantly among these groups, highlighting the overlapping and distinct clinical presentations associated with each condition.

Among study participants screened for TB alone (n=69), cough was the most common symptom (91.30%), with an average cough duration of 31.13 days. Fever was present in 42.03% of these patients, lasting an average of 6.21 days. Other frequently reported symptoms included weight loss (53.62%), difficulty of breathing (43.48%), and chest pain (37.68%).

For the COVID-19 cohort (n=4), cough was also prevalent (75%) but with a much shorter average duration of 4.67 days. Fever was equally common, observed in 75% of cases with a shorter duration (1.67 days). All patients screened for COVID-19 reported cold symptoms (100%).

For those screened for both TB and COVID-19 (n=38), cough was highly prevalent (92.11%) with a mean duration of 30.86 days, similar to the TB-only group. Fever was reported in 42.11% of these cases, lasting an average of 3.5 days. This group showed higher rates of loss of appetite (68.42%) compared to the other groups.

Table 2: Signs and Symptoms per Screening Pathway (N=111)

Sign and Symptoms	TB Screening (n=69)	COVID-19 Screening (n=4)	TB and COVID-19 Screening (n=38)
Cough	63 (91.30%)	3 (75.00%)	35 (92.11%)
Cough duration in days (mean, SD)*	31.13 (29.30)*	4.67 (0.58)*	30.86 (33.0)*
Fever	29 (42.03%)	3 (75.00%)	16 (42.11%)
Fever duration (mean, SD)*	6.21 (6.01)*	1.67 (1.15)*	3.5 (3.26)*
Weight loss	37 (53.62%)	1 (25.00%)	15 (39.47%)
Night sweats	23 (33.33%)	1 (25.00%)	13 (34.21%)
Hemoptysis	20 (28.99%)	0 (0.00%)	7 (18.42%)
Difficulty of breathing	30 (43.48%)	1 (25.00%)	19 (50.00%)
Chest pain	26 (37.68%)	1 (25.00%)	10 (26.32%)
Malaise	12 (17.39%)	0 (0.00%)	10 (26.32%)
Myalgia	4 (5.80%)	2 (50.00%)	3 (7.89%)
Sore throat	23 (33.33%)	1 (25.00%)	8 (21.05%)
Colds	25 (36.23%)	4 (100.0%)	11 (28.95%)
Chills	11 (15.94%)	1 (25.00%)	6 (15.79%)
Loss of taste	5 (7.25%)	1 (25.00%)	7 (18.42%)
Loss of appetite	33 (47.83%)	0 (0.00%)	26 (68.42%)

Proportion of Specimens Tested per GeneXpert® Assay

Only specimens that met laboratory acceptance criteria were included in the analysis, regardless of screening cohort. A total of 107 sputum specimens were tested using the Xpert® MTB/RIF Ultra Assay for both OPS and sputum, as shown in Table 3. OPS (n=27) demonstrated a positivity rate of 25.23%, while sputum (n=49) had a positivity rate of 45.79% for detecting MTBC. Erroneous and invalid Xpert® MTB/RIF Ultra results were excluded from the analysis.

Table 3: Number of Sputum and Oropharyngeal Swabs Tested in Xpert® MTB/RIF Ultra Assay (n= 107)

Specimen type	MTBC detected (+)	MTBC not detected (-)
OPS	27 (25.23%)	80 (74.77%)
Sputum	49 (45.79%)	58 (54.21%)

Table 4 shows the positivity rate for Xpert® Xpress SARS-CoV-2 Assay for both OPS and sputum with a total of 35 specimens. OPS (n=7) demonstrated a positivity rate of 20%, while sputum (n=8) had a positivity rate of 22.86% for detecting SARS-CoV-2. Errors and invalid Xpert® MTB/RIF Ultra results were excluded from the analysis.

Table 4: Number of Oropharyngeal Swabs and Sputum Tested in Xpert® Xpress SARS-CoV-2 Assay (n= 35)

Specimen type	*SARS-CoV-2 positive (+)*	*SARS-CoV-2 negative (-)*
OPS	7 (20.0%)	28 (80.00%)
Sputum	8 (22.86%)	27 (77.14%)

Diagnostic Performance of Alternative and Standard Specimens per GeneXpert® Assay

As shown in Table 5A, OPS (n = 14) as the alternative specimen for TB diagnosis via Xpert® MTB/RIF Ultra compared to sputum positive TB culture (n=24) showed sensitivity of 58.33% (95% CI: 48.52–68.14), specificity of 86.30% (95% CI: 79.46-93.14), PPV of 58.33%, and NPV at 86.30%

When OPS (n = 27) was compared to sputum (n=49) positive Xpert® MTB/RIF Ultra showed sensitivity of 55.10% (95% CI: 45.68–64.53), specificity of 100.00% (95% CI: 100-100), PPV of 100.00% (95% CI: 100-100), and NPV of 72.50% (95% CI: 64.04-80.96).

In contrast, sputum tested (n=24) via Xpert® MTB/RIF Ultra against sputum TB culture (n=24) showed high sensitivity of 100.00% (95% CI: 100–100) but a lower specificity of 72.60% (95% CI: 63.73–81.48), with a PPV of 54.55% (95% CI: 44.64–64.45) and NPV of 100.00% (95% CI: 100–100).

Table 5A: Diagnostic Performance of OPS and Sputum Specimens in Xpert MTB/RIF Ultra Tested Against Reference Standards

Specimen	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
OPS*	55.10% (45.68–64.53)	100.00% (100-100)	100.00% (100-100)	72.50% (64.04-80.96)
OPS**	58.33% (48.52–68.14)	86.30% (79.46-93.14)	58.33% (48.52–68.14)	86.30% (79.46-93.14)
Sputum**	100.00% (100-100)	72.60% (63.73-81.48)	54.55% (44.64-64.45)	100.00% (100-100)

Reference standard: Sputum positive in XpertMTB/RIF Ultra (**n=107**) and TB Culture** (**n=97**)*

Excluded NTM and contaminated results of TB culture

As shown in Table 5B, both sputum and oropharyngeal swab (OPS) specimens demonstrated high diagnostic performance in detecting SARS-CoV-2 using the Xpert® Xpress SARS-CoV-2 assay when compared with reference standards.

Sputum (n= 7) tested for Xpert® Xpress SARS-CoV-2 compared against OPS (n=7) of the same assay yielded high sensitivity of 100.0%, specificity of 96.43% (95% CI: 90.28 -100), PPV of 87.50% (95% CI: 76.54-98.46), and NPV of 100.00%.

Using OPS (n=5) in RT-PCR as the reference standard, sputum (n=5) tested in Xpert® Xpress SARS-CoV-2 yielded 100%, sensitivity and 90.00% specificity (95% CI: 80.06–99.94), with PPV of 62.50% (95% CI: 46.46–78.54). OPS (n=5) also showed 100%, sensitivity and slightly higher specificity at 93.33 (95% CI: 85.07-100.00). No false negatives were observed for both types of specimens.

Table 5B: Diagnostic Performance of OPS and Sputum Specimens in Xpert® Xpress SARS-CoV-2 Assay Tested Against Reference Standards (n=35)

Specimen	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Sputum*	100.00% (100-100)	96.43% (90.28 -100)	87.50% (76.54-98.46)	100.00% (100-100)
Sputum**	100.00% (100-100)	90.00% (80.06-99.94)	62.50% (46.46-78.54)	100.00% (100-100)
OPS**	100.00% (100-100)	93.33% (85.07-100)	71.43% (56.46-86.39)	100.00% (100-100)

*Reference standard: OPS positive in and Xpert® Xpress SARS-CoV-2 assay*and RT-PCR***

This level of agreement suggests that the alternative specimens, OPS in the Xpert® MTB/RIF Ultra assay and sputum in the Xpert® Xpress SARS-CoV-2 assay, demonstrated limited consistency with their respective reference standards. The observed kappa values of 0.48 and 0.57 indicate moderate reliability compared to conventional specimen types. This could be due to several factors, such as variability in specimen quality, differences in the pathogen load between specimen types, or sensitivity limitations in detecting lower pathogen levels.

Furthermore, this study characterized bacterial and viral loads by analyzing cycle threshold (Ct) values as described in Table 6.

The Xpert® Xpress SARS-CoV-2 assay targets the nucleocapsid (N) gene, with Ct <40 indicating a positive result, indirectly proportional to viral load. The Xpert® MTB/RIF Ultra assay targets the MTBC-specific IS1081–IS6110 insertion sequences, with Ct <35 indicating positivity, and can also serve as a proxy for mycobacterial load.

For the Xpert® MTB/RIF Ultra, sputum had an average Ct value of 17.55 with a standard deviation (SD) of 2.52, suggesting a relatively consistent performance in this specimen type. In contrast, OPS specimens yielded an average Ct of 20.74 (SD = 2.22) which suggests lower bacterial loads compared to sputum.

The Xpert® Xpress SARS-CoV-2 test on sputum had an average Ct value of 23.26 (SD = 4.60) while OPS had an average Ct value of 28.12 (SD = 7.04), similar for Xpert® MTB/RIF Ultra on viral load detection.

Table 6: Average Cycle Threshold (Ct) Values of Xpert® MTB/RIF Ultra and Xpert® Xpress SARS-CoV-2 using each type of specimen

Specimen type	Xpert® MTB/RIF Ultra Mean (SD)	Xpert® Xpress SARS-CoV-2 Mean (SD)
Sputum	17.55 (2.52)	23.26 (4.60)
OPS	20.74 (2.22)	28.12 (7.04)

Table 7 further illustrates the relationship between signs and symptoms and Ct values across specimen types, showing that both sputum and OPS consistently yielded lower Ct values in the Xpert® MTB/RIF and Xpert® Xpress SARS-CoV-2 assays.
Study participants with fever and chest X-ray findings also showed lower Ct values, aligning with active infection. Notably, longer cough duration (>2 weeks) corresponded with lower Ct values in sputum for both TB and COVID-19, further supporting a higher pathogen load in symptomatic individuals. The Ct values between oropharyngeal swab (OPS) and sputum samples did not differ significantly in association with patients' signs, symptoms (cough and fever), and chest X-ray findings.

Table 7: Ct Values by Specimen Type According to Common Clinical Presentation and Chest X-ray Findings

Sign or Symptom	**Xpert® MTB/RIF**		**p-value**	**Xpert® Xpress SARS-CoV-2**		**p-value**
	Sputum	**OPS**		**Sputum**	**OPS**	
Cough						
More than 2 weeks	9.32 (9.05)	7.15 (10.80)	0.0664	4.69 (10.05)	6.12 (13.09)	0.1104
10-14 days	6.67 (8.69)	4.54 (8.86)	0.2153	11.78 (17.95)	4.64 (10.38)	0.4441
Less than 10 days	6.50 (9.81)	3.52 (8.36)	0.2853	8.15 (15.48)	7.74 (15.19)	0.5268
Fever	10.59 (8.36)	8.00 (11.17)	0.0947	6.26 (12.81)	4.92 (12.06)	0.572
Chest-Xray findings: indicative of PTB or COVID-19/ pneumonia	9.78 (8.93)	7.91 (11.00)	0.1284	5.60 (11.97)	6.48 (13.49)	0.1753

Discussion

The simultaneous detection of MTBC and SARS-CoV-2 was crucial during the COVID-19 pandemic, given their overlapping clinical presentations and shared risk factors. An integrative diagnostic framework that enabled the detection of both tuberculosis (TB) and emerging pathogens from a single specimen collection is hypothesized to improve diagnostic efficiency. Molecular assays, such as Cepheid's GeneXpert® platforms, offer potential solutions through comprehensive pathogen detection while streamlining specimen collection and processing (Wumkes et al., 2017; Ciobata et al., 2023). This approach may address the challenges associated with multiple specimen collections for different diagnostic tests, which can increase patient burden and delay treatment initiation during pandemic.

Sputum and NPS and OPS are standard specimens for testing, TB and COVID-19, respectively, with GeneXpert® technology reliant on specimen type for optimal performance. During the COVID-19 pandemic, TB programs adapted to integrate COVID-19 testing due to its transmission risk, allowing for the exploration of alternative specimen types, such as oropharyngeal swabs (OPS) and sputum, for dual diagnosis.

This study evaluated the diagnostic performance of OPS using the Xpert® MTB/RIF Ultra assay for TB and sputum tested with the Xpert® Xpress SARS-CoV-2 assay for COVID-19 among 111 study participants presenting with common respiratory signs and symptoms such as cough and fever. Most study participants (Table 1) were male (n=63, 56.76%) with an age group of 41-60 years, consistent with WHO (2024) reports on global TB population profile. Study participants were categorized into three cohorts (Figure 1): TB only (n=69, 62.16%), COVID-19 only (n=4, 3.60%), and TB and COVID co-infection (n=38, 34.23%), each presenting distinct signs and symptoms. Our findings showed that most of them had a cough lasting an average of 30.86 days (SD 33.0) (Table 2), with overlapping symptoms between TB and COVID-19, consistent with findings from prior studies on TB and

COVID-19 co-infection with a mean duration of 30 -32 days (MacLean et al., 2023; TB/COVID-19 Global Study Group, 2022).

The association between RT-PCR Ct values and clinical symptoms is relevant in SARS-CoV-2 infections, as it helps indicate active infection and viral load. Symptoms such as cough and fever have been found to be strongly associated with lower Ct values, suggesting higher viral burden. (Saglik et al., 2022; Heudobler et al., 2023; Yang et al., 2025). Lower Ct values tested in MTB/RIF Ultra have been associated with more severe PTB symptoms, notably cough and cavitation, and have been proposed for MTBC bacterial load in place of smear microscopy negatives on median 25.5 (interquartile range (IQR) 22–29) (Martin-Higuera et al., 2023). The association of Xpert® MTB/RIF Ultra and Xpert® Xpress SARS-CoV-2 Ct values (Table 7) was described in this study. Lower Ct values were observed for both sputum and OPS specimens; however, OPS generally yielded lower Ct values across all cough durations for both diseases. Despite this trend, there was no significant difference between using sputum and OPS.

For the detection of MTBC, sputum served as the standard specimen. WHO (2013) recommended Xpert® MTB/RIF Assay as a screening diagnostic tool because of its high sensitivity of 88% (95% CI: 84–92%) and specificity of 99% (95% CI: 98–99%) using sputum specimens. With the transition to the Xpert® MTB/RIF Ultra assay, Dorman et al. (2018) reported similar sensitivity at 88% (95% CI: 85–91%) but a slightly lower specificity of 96% (95% CI: 94–97%). Other specimens, such as tongue, oral mucosa, and OPS, were investigated as viable alternatives for MTBC detection using the Xpert® MTB/RIF Ultra. OPS specimens yielded moderate diagnostic results ranging sensitivity of 36% (95% CI: 26–48) to 91% (95% CI: 80–98) and specificity of 66% (95% CI: 52–78) to 100% (95% CI: 97–100) in adults in systematic review studies (Church et al., 2024). Our findings showed a sensitivity of 58.33% (95% CI: 48.52–68.14) and specificity of 86.30% (95% CI: 79.46-93.14) for OPS specimens (n=14/24), tested with Xpert® MTB/RIF Ultra against TB culture as reference standard, as shown in Table 5A. OPS demonstrated an average Ct value of 20.74 (SD = 2.22) in the Xpert® MTB/RIF Ultra Assay (Table 6), demonstrating its sensitivity to low bacterial loads, as demonstrated by Lima et al. (2019) in semi-quantitative comparisons. These results were comparable to those from single oral swab studies, where sensitivity was 43% (n = 15/33, 95% CI: 29–62%) (Lima et al., 2019) and 45% (n = 55/128, 95% CI: 34–52%) (Mesman et al., 2019). Further studies found higher sensitivity reaching 73.3% - 91.8% and specificity 91.5% - 100% (95% CI: 92.5–100%) (Wood et al., 2015; Luabeya et al., 2019). Co-infection may also affect the performance of diagnostics to detect other pathogens. Studies have demonstrated that TB patients exhibit altered immune responses to SARS-CoV-2, potentially affecting the reliability of diagnostic tests (Jhaveri et al., 2022).

The Xpert® Xpress SARS-CoV-2 Assay had an overall sensitivity of 97% (95% CI: 96–98%) and specificity of 97% (95% CI: 96–98%) according to a systematic review done by Cao et al. (2022) that utilized various specimen types. Validation reports using NPS and OPS demonstrated a positive percent agreement (PPA) of 99.5% (n = 219/220, 95% CI: 97.5–99.9%) and a negative percent agreement (NPA) of 95.8% (n = 250/261, 95% CI: 92.6–97.6%). OPS alone demonstrated a strong level of agreement values for SARS-CoV-2 detection, with a PPA of 96.1% (95% CI: 91.3–98.4%) and a NPA of 96.2% (95% CI: 90.9–98.6%) (Hou et al., 2020).

Evidence suggested that lower respiratory tract specimens, such as sputum, potentially had higher sensitivity than NPS for detecting SARS-CoV-2 on the Xpert® Xpress SARS-CoV-2 assay. Studies using sputum showed a sensitivity of 67% (95% CI: 60–73%) (MacLean et al., 2023) and 100% for both PPA and NPA (Malczynski et al., 2020; Wong et al., 2020). Our findings aligned with these studies, as we compared sputum tested on Xpert® Xpress SARS-CoV-2 against OPS tested with RT-PCR in Table 5B. This comparison yielded a 100.0% (95% CI: 100-100) and specificity of 90.00% (95% CI: 80.06–99.94). Sputum specimens demonstrated an average Ct value of 23.26 (SD = 4.60) in the Xpert® Xpress SARS-CoV-2 Assay (Table 6), indicating that it can detect higher viral loads compared to OPS, as shown by Malczynski et al. (2020) with a Ct value of 31.5 (SD = 7.5).

CONCLUSION

This study highlighted the utility of OPS and sputum specimens in detecting MTBC and SARS-CoV-2 among presumptive TB and suspected COVID-19 patients. Sputum showed significantly higher positivity rates and sensitivity than OPS tested in the Xpert® MTB/RIF Ultra assay, reinforcing sputum's value as a primary specimen for MTBC detection. Similarly, while SARS-CoV-2 detection rates were comparable between specimen types, sputum demonstrated slightly higher positivity and sensitivity than OPS for the Xpert® Xpress SARS-CoV-2 assay. Notably, OPS demonstrated moderate sensitivity and specificity for MTBC detection, and sputum for COVID-19 yielded a high sensitivity for SARS-CoV-2 detection, suggesting their potential as alternative diagnostic specimens and dual diagnosis when standard specimens are unavailable or impractical to collect, such as during public health emergencies or the recent pandemic. To further enhance OPS utility, enriched transport medium for OPS may be recommended or studied to better preserve MTBC viability during longer storage and delayed testing. This approach could optimize diagnostic accuracy and flexibility in low-resource settings.

These findings also underscore the importance of specimen type in optimizing diagnostic accuracy and offer practical insights for improving TB and/or COVID-19 diagnostic workflows. Further research is recommended to validate these findings across larger and more diverse populations to better inform specimen selection in diagnostic protocols for infectious diseases.

The lessons learned from the COVID-19 pandemic should inform future policies aimed at improving TB control and ensuring that diagnostic tools are both accessible and adaptable in times of crisis. Alternative specimen collection and multiplex testing approaches hold the potential to improve TB diagnosis and co-infection management, especially in the context of future outbreaks and even pandemics. Preparedness strategies must focus on integrating single-specimen diagnostic technologies into routine TB programs. Expanding access to point-of-care testing (POCT) and alternative specimen collection can bridge diagnostic gaps in remote and underserved areas. (Nguyen et al., 2024).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

Carolina B. Capili, RMT
Contributed to the conceptualization, methodology design, manuscript drafting and editing, data collection and management, visualization, institutional coordination, and project administration.

Louis Andrew Olazo, RMT, MSMT
Contributed to the conceptualization, methodology design, manuscript drafting and editing, data collection, and result validation.

Joseph Edwin L. Bascuña
Contributed to the conceptualization, manuscript drafting and editing, data collection, fieldwork, and data management.

Chona Mae Daga, RMT, MPH
Drafted and edited the manuscript, led the visualization of study results, and performed data analysis and interpretation.

Mariza Garing, RMT, MSCLS
Contributed to methodology design, manuscript editing, and study site coordination, and conducted experiments and data collection.

Alma G. Palparan, RMT
Contributed to the conceptualization, secured funding, coordinated institutional support, edited the manuscript, and managed project activities.

Vina Lea F. Arguelles, RMT, MPH
Designed the study methodology, edited the manuscript, conducted experiments and data collection, and validated results.

Catherine C. Dacasin, RMT, MSMT
Designed the study methodology, edited the manuscript, conducted experiments and data collection, and maintained research data in Virology.

Soledad Rosanna Cunanan, MD
Provided supervision and leadership, edited the manuscript, and advocated for the study's implementation at participating sites.

Ramon P. Basilio, MD
Contributed to the conceptualization, secured funding, supervised the project, coordinated institutional support, edited the manuscript, and managed research activities.

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