

An observational report of universal GeneXpert testing of inpatients with diagnosed or presumptive TB in the Philippines

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Background: The Philippines is a high TB and multidrug-resistant TB burden country. Although the scale-up of GeneXpert testing is occurring, the benefits of universal Xpert-*Mycobacterium tuberculosis*/rifampicin (MTB/RIF) testing in inpatients have not been documented.

Methods: Routine GeneXpert testing irrespective of priority criteria for testing was conducted within a prospective cohort of all adults with known or presumptive TB admitted to a tertiary infectious diseases hospital in Manila. Study-specific TB diagnosis was decided upon bacteriological results, chest x-ray assessment, if already on anti-TB treatment (ATT) at admission and a cough duration of ≥ 2 wk.

Results: Of submitted sputum samples, 87.1% (277/318) had valid acid-fast bacilli (AFB) microscopy and Xpert® MTB/RIF results. Xpert® MTB/RIF was positive in 97.7% ($n = 87/89$) of AFB-positive patients and 25.5% ($n = 48/188$) of AFB-negative patients. Bacteriological confirmation in smear negative cases not on ATT prior to admission was 25.2% (34/135). Rifampicin resistance was detected in 26/135 Xpert positive cases (19.3%), including nine who might not otherwise have been detected, representing a 53% increase in yield.

Conclusion: Universal GeneXpert testing in this setting enhanced the yield of bacterial confirmation, revealing a high incidence of rifampicin resistance and suggesting a need for further investigations in Xpert-negative/smear-positive patients who may not have mycobacterial TB.

Keywords: adults, inpatients, TB diagnostics, Xpert® MTB/RIF

Introduction

Diagnosis of TB caused by *Mycobacterium tuberculosis* (MTB) remains challenging. Low-sensitivity sputum-smear microscopy for acid-fast bacilli (AFB) remains the major diagnostic tool in many resource-limited and high TB burden settings.^{1,2} The Xpert® MTB/rifampicin (MTB/RIF) assay is reported to have 89% sensitivity and 99% specificity in detecting adult pulmonary TB and simultaneously detects resistance to the first-line drug rifampicin.^{1,3} Xpert® MTB/RIF increases diagnostic accuracy and shortens time to initiate appropriate treatment with early detection of drug resistance. The WHO endorsed Xpert®

MTB/RIF in 2011 and its large-scale rollout is supported globally,⁴ but implementation as a primary diagnostic test remains limited due to higher upfront costs, logistical challenges and subsequent increased requirement of multidrug-resistant (MDR) treatment regimens following identification of rifampicin resistance.⁵⁻⁷ Nonetheless, Xpert® MTB/RIF as the first-line diagnostic test in place of AFB smear microscopy has been shown to be cost-effective when followed by timely treatment initiation.^{6,7}

Philippines is currently ranked third in the world for TB incidence (554/100 000) and is also a high burden country for MDR-TB.⁸ The Philippines introduced Xpert® MTB/RIF in 2011 and has recently expanded access.⁹ Based on test availability and

accessibility, current national testing policies prioritize retreatment cases, contacts of confirmed DR-TB cases, people living with HIV, prisoners, older people, children and, most recently, those with diabetes.^{4,10} In some regions, presumptive TB patients with chest x-rays (CXR) suggestive of TB are now also eligible to be tested.^{4,10} Progress and experiences in Xpert® MTB/RIF implementation have mostly been documented in routine outpatient programmatic settings.⁵ We hypothesized that universal Xpert® MTB/RIF should be implemented in a tertiary hospital setting where suspected TB patients and those already on anti-TB treatment prior to admission, often with undocumented diagnostic and treatment histories, are admitted to increase detection rates of MDR-TB and reduce time to the start of appropriate treatment regimens. Therefore, we aimed to determine the possible benefits of implementing universal Xpert® MTB/RIF, defined as testing all patients able to produce sputum, in TB ward admissions with presumptive TB and of those already initiated on an anti-TB treatment (ATT) regimen in a large tertiary-level infectious diseases hospital in Manila, Philippines. Presumptive and confirmed TB patients are admitted according to the treating physician's assessment of deteriorating clinical condition, or risk of deterioration requiring inpatient care (normally at least supplemental oxygen and fluids). At the time of the study, non-priority groups or those already on treatment at the time of admission were not routinely eligible for Xpert® MTB/RIF.

Materials and methods

A prospective cohort study of inpatients admitted to the TB ward at San Lazaro Hospital, serving a poor population in Manila with high TB admission and mortality rates, was conducted as previously described.¹¹ Patients were recruited from July 2016–May 2017 and followed up until in-hospital death or discharge. Research nurses assisted enrolled participants to expectorate early morning sputum samples. AFB sputum-smear microscopy (Ziehl Neelsen stain) and Xpert® MTB/RIF (Cepheid, Sunnyvale, California, USA) testing were conducted on all samples. The most recent CXR were assessed by two study clinicians to classify whether they were suggestive of TB and to score severity.¹² Symptom history and previous TB history were ascertained by patient interview. HIV testing was offered to all study participants, with additional study-specific consent. Hospital admission and final diagnoses were extracted from clinical notes.

For the purpose of this analysis, study-defined TB comprised: (1) sputum-smear positive; (2) sputum-smear negative, Xpert® MTB/RIF positive; (3) already on ATT at admission; (4) cough ≥ 2 wk and CXR suggestive of TB regardless of sputum results. Sputum-smear positive, Xpert® MTB/RIF-negative patients were defined as possible non-mycobacterial TB infection (NTM). Those with invalid or missing sputum-smear microscopy or Xpert® MTB/RIF results were excluded from analysis.

Results

Three hundred and eighteen participants who survived the first 48 h of admission provided sputum samples, of whom 87.1% ($n = 277$) had both valid AFB microscopy and Xpert® MTB/RIF

results (Figure 1). HIV status was known for 118/277 (42.2%), with 18/118 (15.3%) being HIV-positive. Xpert® MTB/RIF identified MTB in 97.7% ($n = 87/89$) of AFB-positive patients and 25.5% ($n = 48/188$) of AFB-negative patients. In all Xpert® MTB/RIF-positive patients, the prevalence of rifampicin resistance was 19.3% (26/135).

Impacts of universal Xpert® MTB/RIF testing

Figure 1 shows the numbers of patients by smear AFB result (positive/negative), split by Xpert® MTB/RIF MTB result (positive/negative), then by ATT initiated prior to admission (yes/no), then by rifampicin resistance detected by Xpert® MTB/RIF (yes/no) and finally by TB treatment category (new, relapse or treatment after loss to follow-up/previous treatment outcome unknown). The numbers of patients who were HIV-positive and those already on MDR treatment regimens upon admission are marked at the final level of TB treatment category. The numbers and proportions of participants who died during admission are shown, down to the level of rifampicin resistance detected by Xpert® MTB/RIF.

Increased yield of bacteriologically confirmed cases of TB

Of 135 participants who were sputum AFB-negative and not on ATT prior to admission, 34 (25.2%) were Xpert® MTB/RIF-positive. Fourteen of these (41.2%) did not have any of the priority criteria of HIV-positive status, aged ≥ 65 y or a history of previous TB treatment, and thus would not normally have been tested. This reduced to 13 participants if previously diagnosed diabetes was included as a priority criteria, or 11 if HbA1c $\geq 6.5\%$ at admission was included as a priority criteria (Table 1). One hundred and fifty-nine patients (57.8%) had unknown HIV status after declining testing, of whom 31 had none of the above priority criteria for testing. Two of these 31 patients were found to have rifampicin resistance (Table 1). Of 53 participants who were sputum AFB-negative and already on ATT prior to admission, 14 (26.4%) were Xpert® MTB/RIF-positive.

Increased detection of MDR-TB

Five of 113 (4.4%) of newly diagnosed TB patients and 20/160 (12.5%) of TB patients with a history of previous TB treatment had rifampicin resistance detected by Xpert® MTB/RIF. Of 135 participants who were MTB-positive by Xpert® MTB/RIF, 26 had rifampicin resistance detected by Xpert® MTB/RIF, of whom only one was already diagnosed as MDR-TB and 5/26 (19.2%) had no previous history of TB treatment. Two patients had none of the priority criteria for Xpert® MTB/RIF testing of positive HIV status, history of previous TB treatment, aged ≥ 65 y or previously diagnosed diabetes. An additional case had missing history of previous TB treatment, which, if included, would have resulted in 11.5% (3/26) of cases that would otherwise not have been identified (Table 1). Detailed characteristics of the 26 patients with rifampicin resistance are available in Supplementary Table 1. Of the 66 patients already on first-line (drug-sensitive [DS]-TB) ATT at admission, six were identified to have rifampicin resistance (9.1%), suggesting either failure to identify MDR-TB at treatment

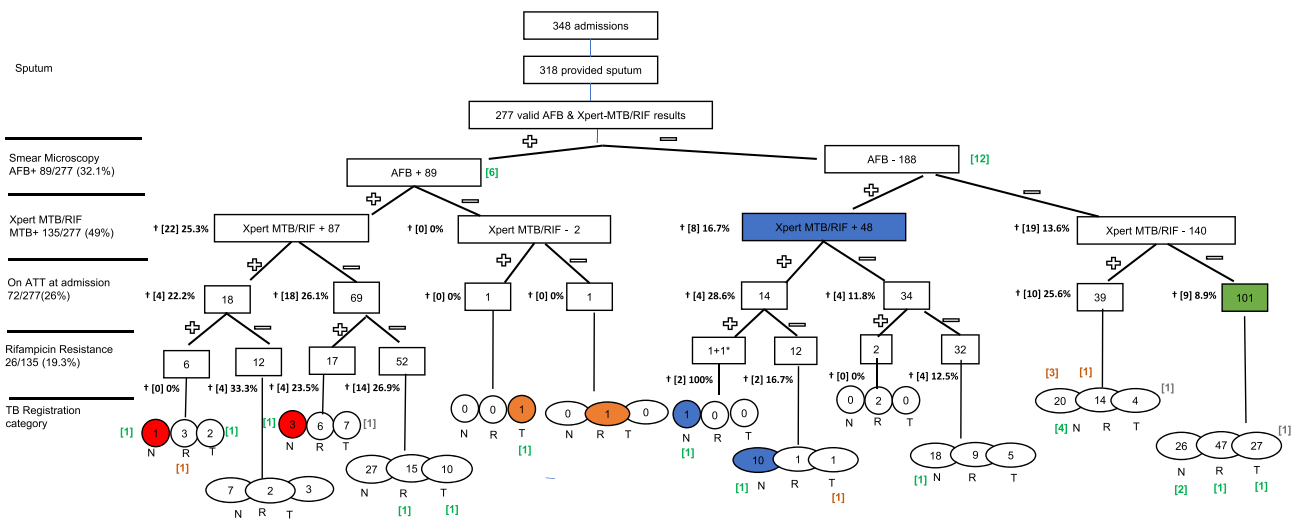


Figure 1. Bacteriological results by anti-TB treatment at admission, HIV status and TB registration category. *Rif positive+ indeterminate; [x] Number of HIV positive patients; †[x] 0% Number and percentage of inpatient deaths; [x] Number of patients on MDR treatment at time of admission; [x] Number of patients with unknown TB registration category; N: New = 114 (41.6%), R: Relapse = 100 (36.5%), T: Treatment after LTFU or previous treatment outcome unknown = 60 (21.9%) (N = 274); AFB: acid fast bacilli; ATT: anti-TB treatment. **Red circles:** indicate rifampicin resistant cases not eligible for GeneXpert testing based upon New TB category, AFB-positive and no other risk criteria (e.g. HIV infection); **Orange circles/ellipsoids:** indicate cases of possible Non-Tuberculous Mycobacteria; **Blue box:** indicates increased number of cases that were bacteriologically confirmed by GeneXpert; **Blue circle:** indicates rifampicin resistant cases not eligible for GeneXpert testing at the time of the study (New cases and AFB-negative) unless other risk factors (e.g. HIV infection); **Blue ellipsoid:** indicates bacteriological confirmation in those already on Anti-TB treatment previous to admission; **Green box:** indicates cases needing further investigation of differential diagnoses and culture if strongly suspicious of TB.

Table 1. Characteristics used to determine priority for Xpert® MTB/RIF testing

Priority testing criteria	AFB-negative, Xpert® MTB-positive patients (n = 34)	Xpert® Rifampicin-resistant patients (n = 26)
Retreatment	16 (64%)	20 (77%)
MDR-TB contact	No data	No data
HIV-positive, or pre-admission HIV diagnosis	1 (25 refused) (4%)	4 (9 refused) (15%)
Prisoner	0 (0%)	0 (0%)
Age ≥65 y	5 (15%)	1 (4%)
Diabetes (pre-admission diagnosis)	3 (9%)	2 (8%)
Diabetes (previous diagnosis or HbA1c ≥6.5% at admission)	7 (21%)	5 (19%)
No priority testing criteria	11 (32%)	3 (12%)*
Already on DS-ATT prior to admission	0 (0%)	6 (1 on MDR regimen)

Bold indicates cases which would have been missed if testing was based on above priority criteria only.

AFB: acid-fast bacilli; DS-ATT: drug-sensitive anti-TB treatment (initiated before the current admission); HbA1c: glycated hemoglobin.

*n = 2 new TB cases with no other priority criteria plus 1 with missing information on previous history of TB treatment.

start, or development of drug resistance on treatment. All of these had one or more priority criteria (four with a previous history of TB treatment, three with a previous HIV diagnosis). In a scenario of not testing those already started on first-line ATT or new TB cases without other priority criteria, additional cases of rifampicin resistance detected by universal testing in this study

include two new TB registration cases with negative or unknown HIV status (refused), one HIV-negative patient with an unknown TB registration history, plus six cases on first-line ATT prior to admission. Together, these represent a 53% increase in yield in identifying rifampicin resistance using universal Xpert® MTB/RIF testing.

Identification of possible NTM infection

Two participants were AFB-positive (with grade +++ and ++++) but GeneXpert-negative. Both had a previous history of TB treatment and one was on ATT at admission.

Identification of probable non-TB for further investigation

Approximately half of all participants were AFB-negative and GeneXpert-negative, of whom 72.1% ($n = 101/140$) were not on ATT prior to admission. Of those 101, only 57 (56.4%) met the study criteria for TB (a cough of duration ≥ 2 wk and CXR suggestive of TB). Forty-three of these patients had a history of previous TB, of whom 30 were relapse, 11 treatment after loss to follow-up and two previous treatment outcome unknown. Of the remaining 44 patients, one was clinically diagnosed with extra-pulmonary TB.

Inpatient mortality

There were 49 inpatient deaths among the 277 individuals included in this analysis (17.8%). The distribution of inpatient deaths by the different diagnostic groups and by treatment status at admission is shown in Figure 1. There was some evidence of increased risk of inpatient death for those who were already on ATT prior to admission (8/82 [25.0%] vs 31/205 [15.1%]; OR = 1.87, 95% CI 0.97 to 3.61, $p = 0.061$), but no evidence of an effect of rifampicin resistance, with six deaths in the 27 with rifampicin resistance (including one indeterminate result; 22.2%) and 26 deaths in the 114 without rifampicin resistance detected (22.6%) or 43 deaths in 250 (17.2%, $p = 0.52$) compared with everyone without rifampicin resistance.

Final hospital-defined diagnosis vs study-defined TB

Thirty-six of 268 patients (13.4%) in this analysis who had a recorded hospital diagnosis of TB did not have TB according to our study definition. Of those 36 patients, two were possible NTM infections and five did not have a CXR suggestive of TB but only a cough of 2 wk.

Discussion

The 25% increased rate of bacteriological confirmation in sputum AFB-negative patients using Xpert® MTB/RIF is similar to that reported elsewhere.¹ The prevalence of rifampicin resistance in new TB diagnoses in this setting (4.4%) was higher compared with the national estimate of 1.7% (95% CI 1.1 to 2.5%) of rifampicin resistance or rifampicin and isoniazid resistance in new cases,⁸ or compared with the 2012 National Tuberculosis Drug Resistance Survey of 2.43% (95% CI 1.75 to 3.37%) for rifampicin resistance detected by phenotypic drug sensitivity testing.¹³ Universal Xpert® MTB/RIF testing detected 135 cases of MTB and two cases of rifampicin resistance in patients who otherwise would not have been detected if applying the current priority criteria for testing. Six cases of rifampicin resistance in patients on first-line (DS-TB) ATT were also detected at admission.

In some regions Xpert® MTB/RIF priority testing has been extended to people who are AFB-negative but with a CXR suggestive of TB.^{1,4,10} In this study population this would not have resulted in any additional rifampicin resistant cases being detected, as the two patients who were rifampicin resistant-negative for AFB each had other criteria for testing (i.e. a history of previous TB treatment and known HIV-positive status).

Universal Xpert® MTB/RIF testing also assisted in identifying a large group of admissions unlikely to have TB but who were mostly treated as clinical TB, highlighting potential overdiagnosis^{1,10} and exposure to unnecessary toxic TB treatments.^{1,10,14} NTM accounted for 3.2% of specimens collected and 17.2% of smear-positive Xpert-negative specimens in the Philippines 2016 TB prevalence survey.¹⁵ Although sputum handling errors could not be ruled out, it seems likely that the two smear-positive Xpert-negative cases in this study were NTM infections. In settings such as this, where bacterial culture is not routinely available, Xpert in combination with slide microscopy may be useful in selecting patients for culture in the diagnosis of NTM.

The limitations of this study include a lack of information regarding MDR-TB contact, which is a priority criteria for Xpert® MTB/RIF testing, no available culture confirmation of TB or NTM, or drug sensitivity testing. Also, we were not able to compare time to starting appropriate ATT regimens as a result of implementing universal Xpert® MTB/RIF testing. The basis of previous TB diagnoses for patients on ATT at admission could not be ascertained for the majority of cases due to a missing National TB Program (NTP) treatment card or traceable NTP number. Although we did attempt to trace TB treatment outcomes for patients post-discharge, due to the relatively high rate of loss to follow-up,¹¹ we have not attempted to include this outcome here.

The high prevalence of rifampicin resistance in this setting supports the use of universal Xpert® MTB/RIF. Additionally, for individuals already on first-line ATT requiring hospitalization, high clinical suspicion of drug resistance is justified and supports the use of universal Xpert® MTB/RIF in inpatient admissions. This is particularly the case when the basis of TB diagnosis and treatment adherence are unknown. Despite national Xpert® MTB/RIF guidelines, availability cannot be assumed in settings with unregulated private healthcare providers and poor mobile urban populations. Unselective Xpert® MTB/RIF testing in these kinds of settings may be cost-effective for TB programs due to reduced delays to starting appropriate treatment and reductions in TB mortality and transmission.⁷

Supplementary data

Supplementary data are available at [Transactions](#) online.

Authors' contributions: The study was conceptualized by NL, CP, KA and SEC. Study conduct and supervision were performed by NL, VP, FPM, LR, RWC and SEC. Data analysis and curation were carried out by VP, AMT, NL and SEC. AMT and SEC wrote the original draft. All authors contributed to the review and editing of the final manuscript.

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Ethical approval: This study was ethically approved by the institutional review boards of Nagasaki University (NEKKEN) and San Lazaro Hospital. Research nurses obtained written consent from all participants.

References

- 1 World Health Organisation. Xpert MTB/RIF Implementation Manual: Technical and Operational 'how-to'; practical considerations. Geneva: World Health Organisation; 2014.
- 2 World Health Organisation. Global Tuberculosis Report. Geneva: World Health Organisation; 2018.
- 3 Li S, Liu B, Peng M, et al. Diagnostic accuracy of Xpert MTB/RIF for tuberculosis detection in different regions with different endemic burden: A systematic review and meta-analysis. *PLoS One*. 2017;12(7):e0180725.
- 4 Department of Health Philippines. Manual Procedures of the National Tuberculosis Control Program. 5th Edition. Geneva: World Health Organisation; 2014.
- 5 Ardizzoni E, Fajardo E, Saranchuk P, et al. Implementing the Xpert(R) MTB/RIF diagnostic test for tuberculosis and rifampicin resistance: Outcomes and lessons learned in 18 countries. *PLoS One*. 2015;10(12):e0144656.
- 6 Khaparde S, Raizada N, Naire SA, et al. Scaling-up the Xpert MTB/RIF assay for the detection of tuberculosis and rifampicin resistance in India: An economic analysis. *PLoS One*. 2017;12(9):e0184270.
- 7 Menzies NA, Cohen T, Lin H-H, Murray M, Salomon JA. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. *PLoS Med*. 2012;9(11):e1001347.
- 8 World Health Organisation. Tuberculosis Country Profile. World Health Organisation; 2019. <https://www.who.int/tb/country/data/profiles/en/> [accessed 26 August 2019].
- 9 Carlos C. Xpert/Rif Country Rollout in the Philippines: Impact and Lessons Learned. Philippines: Research Institute for Tropical Medicine. [http://www.stoptb.org/wg/gli/assets/html/GLI5/Philippines%20Presentation%20-%20GLI%20Partners%27%20meeting,FINAL%20\(4-10-13\)%20\(1\).pdf](http://www.stoptb.org/wg/gli/assets/html/GLI5/Philippines%20Presentation%20-%20GLI%20Partners%27%20meeting,FINAL%20(4-10-13)%20(1).pdf).
- 10 Philippine Coalition Against Tuberculosis (PhilCAT), Philippine Society for Microbiology and Infectious Diseases (PSMID), Philippine College of Chest Physicians (PCCP). Task Force: Clinical Practice Guidelines for the Diagnosis, Treatment, Prevention and Control of Tuberculosis in Adult Filipinos: 2016 Update (CPGTB2016). Manila: Philippine Coalition Against Tuberculosis & Lung Disease; 2016.
- 11 Lee N, White LV, Marin FP, et al. Mid-upper arm circumference predicts death in adult patients admitted to a TB ward in the Philippines: A prospective cohort study. *PLoS One*. 2019;14(6):e0218193.
- 12 Ralph AP, Ardian M, Wiguna A, et al. A simple, valid, numerical score for grading chest x-ray severity in adult smear-positive pulmonary tuberculosis. *Thorax*. 2010;65(10):863-9.
- 13 Department of Health Philippines. Second National Drug Resistance Survey on Tuberculosis in the Philippines - Technical Report 2014. Manila: Philippines Dept of Health; 2015.
- 14 Yang CY, Guo H-R, Cheng Y-Y, Huang R-M, et al. Factors associated with misdiagnosis of smear-negative tuberculosis: an experience in Taiwan. *Respir Care*. 2012;57(5):753-7.
- 15 Department of Health Philippines. National Tuberculosis Prevalence Survey 2016 Philippines. Manila, Philippines: Department of Health - Disease Prevention and Control Bureau; 2018.