Impact of Laboratory Practice Changes on the Diagnosis of Tuberculosis with the Introduction of Xpert MTB/RIF in Kiribati

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Abstract

The Republic of Kiribati, Central Pacific, has the largest tuberculosis epidemic in the region. There is a national tuberculosis control program, which has used smear microscopy for acid-fast bacilli as the main diagnostic tool for many years. In 2015, an Xpert MTB/RIF machine was procured and became functional within the tuberculosis hospital. The aim of this cross-sectional study, using routinely collected data, was to determine the effects of introducing Xpert MTB/RIF on laboratory smear microscopy practices and the pattern of registered tuberculosis cases. Between February 2015 and January 2016, there were 220 Xpert MTB/RIF assays performed with 6.4% errors and 15% detection of Mycobacterium tuberculosis*: one patient showed rifampicin-resistance. One year before and after introducing Xpert MTB/RIF, the number of presumptive tuberculosis patients increased by 9% from 2,138 to 2,322. There were no changes in demographic characteristics, smear-positive results, or acid-fast bacilli grade between the two periods. The number of specimens cultured for* Mycobacterium tuberculosis *significantly declined from 638 to zero, with 76 positive MTB cultures before and none after introducing Xpert MTB/RIF. There was a significant change in the profile of registered tuberculosis cases with more children (34% versus 21%) and fewer bacteriologically-confirmed cases (29% versus 43%) – P < .001. Since the deployment of Xpert MTB/RIF in Kiribati, there have been a small number of assays performed and this has been associated with no adverse effects on smear microscopy, a stoppage in mycobacterial cultures, and a change in the types and categories of diagnosed tuberculosis.*

Keywords

Xpert MTB/RIF; tuberculosis; Kiribati; smear microscopy services; culture for Mycobacterium tuberculosis*; types of tuberculosis*

Introduction

Sputum smear microscopy for acid-fast bacilli is still the most widely used method for the diagnosis of pulmonary tuberculosis (TB) in low- and middle-income countries.[1] Although inexpensive to perform and despite attempts made to improve its sensitivity and specificity, smear microscopy is cumbersome, costly for patients (although the test is free, patients have to pay for several trips to the hospital and they also incur lost wages from time off work), and does not detect drug-resistant disease.[1,2] With over 10 million people estimated to have developed new TB globally in 2015, and 580,000 having multidrug-resistant or rifampicin-resistant (MDR or RR) TB (ie, resistant to rifampicin or both rifampicin and isoniazid), new diagnostic tools to replace or complement smear microscopy are urgently needed.[3,4]

The most important recent diagnostic development to the Xpert MTB/RIF machine and assay (Cepheid Inc, Sunnyvale, CA, USA) for use with sputum and other body specimens.[5] The cartridge-based system means there is no need for prior sputum processing, minimal laboratory expertise is needed to perform the assay, the results are provided in less than two hours, sensitivity and specificity for the diagnosis of TB is high, and the investigator is provided with information about susceptibility or resistance to rifampicin.[5-7]

In 2011, the World Health Organization (WHO) strongly recommended the widespread use of Xpert MTB/RIF, especially for individuals suspected of having MDR-TB and Human Immunodeficiency Virus (HIV)-associated TB.[8,9] In 2013, the WHO updated this guidance, recommending that Xpert MTB/RIF be used as the initial diagnostic test for all patients with presumptive TB.[10]

Kiribati is an island republic in the Central Pacific, comprising 32 coral atolls, reef islands, and one raised coral atoll stretching along the equator.[11] The population is 103,058, with South Tarawa being the Capital.[12] In 2014, the country had a GDP per capita of USD$1,605 and is recognised as one of the poorest and least developed countries in the Pacific.[13] Kiribati has the largest per capita TB rate in the region with 420 cases in 2013.[14] Estimated MDR-TB cases for that year were 4.5 and 24 per 100,000 for new and previously treated TB respectively, although there were no actual diagnosed MDR-TB cases in 2013.[14] There is a national TB control program (NTP) that has followed the WHO Directly Observed Treatment, Short-course (DOTS)strategy and has used smear microscopy as the main diagnostic tool for many years. Current TB control efforts include 6-months of directly observed chemotherapy for diagnosed TB cases using the standardized regimens recommended by WHO,[15] contact tracing, isoniazid prophylaxis for contacts under five years of age and those diagnosed with diabetes, and screening of community members for TB in identified TB hotspots. All TB control efforts take place within the NTP and no TB cases are managed in the private sector.

With funding and technical support from the Australian AID Program and the Pacific Community (SPC), the Kiribati NTP procured an Xpert MTB/RIF machine in early 2015, which became functional within the NTP hospital February 5, 2015. After one year of use, there has been no published information about the number of Xpert tests performed or the results. Additionally, there are a number of other issues of interest. First, we wanted to assess the community response to the introduction of this new assay—the arrival and capability of the Xpert MTB/RIF assay was published in the newspaper and aired in the news over the radio, and we wanted to know whether this may have prompted more patients with presumptive TB to come forward and submit sputum specimens. Second, we wanted to assess the impact of this new technology on the proficiency of

laboratory technicians performing smear microscopy as we were concerned that smear microscopy would be underused resulting in a decline in the quality of acid-fast bacilli detection. Third, with the introduction of Xpert MTB/RIF, a decision was made to stop sending specimens for *Mycobacterium tuberculosis* (*MTB*) culture and drug-susceptibility, and we needed to know whether this had actually happened. Finally, we were interested in assessing whether there was any association between the introduction of Xpert MTB/RIF and the diagnosed and registered types and categories of TB.

We therefore carried out a retrospective study using secondary data to assess whether the introduction of Xpert MTB/RIF was associated with a change in diagnostic practices and the profile of TB in Kiribati. Specific objectives were to determine: 1) use of Xpert MTB/RIF over one year between February 2015 and January 2016 in terms of number of tests performed along with errors and results and 2) for one year before (February 2014 to January 2015) and one year after (February 2015 to January 2016) the introduction of Xpert MTB/RIF, the numbers and characteristics of patients submitting sputum specimens along with the results, the number having *MTB* cultures performed along with positive cultures, and the types and categories of diagnosed TB.

Methods

Patient Population

All patients with presumptive and diagnosed TB registered at Kiribati NTP between February 2014 and January 2016 were included in the study and divided into the pre-Xpert period (February 2014 to January 2015) and the post-Xpert period (February 2015 to January 2016).

Study Design

This was a cross-sectional retrospective study using routinely collected data from laboratory and patient TB registers.

Setting

Tuberculosis and TB control in Tungaru Central Hospital, South Tarawa:

The study was carried out at the NTP unit, Tungaru Central Hospital, South Tarawa. Presumptive cases of TB are referred from peripheral health clinics, outpatient clinics, inpatient services and emergency units on the main and outlying islands to the NTP unit.

Diagnostic Criteria and Treatment

TB diagnosis before introduction of Xpert MTB/RIF:

All presumptive TB patients submitted two sputum specimens for smear microscopy. Those with positive smears - scanty, 1+, 2+ and 3+ acid-fast bacilli (AFB)—were diagnosed as smear-positive pulmonary TB while those with negative smears followed a clinical and radiographic algorithm for the diagnosis of smear-negative pulmonary TB. Extra-pulmonary TB was diagnosed based on clinical, microbiological and radiographic characteristics. *MTB* cultures were done on patients highly suspected to have smear-negative pulmonary TB while culture and drug-susceptibility testing was done on patients with previously treated TB, with HIV, or with persistently smear-positive sputum specimens during treatment. Drug-susceptibility testing was performed outside the island in the SA Pathology Laboratory, Adelaide, Australia.

TB diagnosis after introduction of Xpert MTB/RIF:

All presumptive TB patients still submitted two sputum specimens to the laboratory for smear microscopy. Those with positive smears were diagnosed as smear-positive pulmonary TB. Those with negative sputum smears who were highly suspected to have TB on chest radiography had one of the two sputum specimens examined by Xpert MTB/RIF. All presumptive TB patients with HIV-infection, at high risk of MDR-TB (previously treated cases, contacts of MDR-TB cases, and cases still smear-positive after three months of treatment), who were aged less than 15 years or had suspected extra-pulmonary TB had their sputum or other specimens examined by Xpert MTB/RIF, regardless of smear microscopy. No specimens were sent for culture and drug-susceptibility testing, unless the Xpert MTB/RIF showed resistance to rifampicin when culture and drug-susceptibility testing were used to confirm the result.

Registration and Treatment:

Diagnosed patients were registered as new or previously treated and as bacteriologically confirmed pulmonary TB (smear-positive, culture-positive or Xpert-positive), not-bacteriologically confirmed pulmonary TB and extra-pulmonary TB. Anti-tuberculosis treatment followed standard WHO TB treatment guidelines.[15,16]

Data Variables, Sources of Data and Data Collection

Data variables included: 1) for the use of Xpert MTB/RIF - laboratory register number, year, month, age, sex, Xpert test number, an error (unsuccessful result caused for example by the reaction tube being filled improperly, a reagent probe integrity problem, maximum pressure limits exceeded, or module failure), a positive TB diagnosis, and a positive rifampicin resistance result. The data source was the NTP laboratory register for the Xpert MTB/RIF assay; 2) for laboratory sputum smear and culture examination—laboratory registration number, year, month, age, sex, sputum result, highest positive sputum grade (3+, 2+, 1+ or scanty), culture done, and culture positive for *MTB*. Drug-susceptibility results were not collected as these were done overseas in Australia and the results were inconsistently documented in Kiribati. The data source was the NTP laboratory register for sputum smear microscopy; 3) for registered TB patients –TB registration number, year, month, age, sex, type of TB (bacteriologically confirmed, not bacteriologically confirmed, extra-pulmonary), and category of TB (new, relapse, failed previous treatment, returned after default, other recurrent TB, transfer-in). The data source was the TB patient register. Data collection was carried out between February and June 2016 using paper-based questionnaire form.

Analysis and Statistics

Data were single-entered into Epinfo Version 7.0 (Centers for Disease Control and Prevention, Atlanta, USA). A descriptive analysis of the use of Xpert MTB/RIF was performed using absolute numbers, frequencies and proportions. Comparisons were made before and after the introduction of Xpert MTB/RIF using the chi-square test or chi-square test for trend with respect to numbers and characteristics of presumptive TB patients and their laboratory parameters and numbers, types and categories of TB, with differences at or below the 5% level being regarded as significant.

Ethics Approval

Permission for the study was obtained from the Kiribati National Tuberculosis Program through the director of public health and ethics approval was obtained in writing from the Ethics Advisory Group, International Union Against Tuberculosis and Lung Disease, Paris, France. Patient consent was not required as secondary data were used throughout.

Results

The results of Xpert MTB/RIF assays are shown in Table 1. Of the 220 assays performed, 185 were in persons aged ≥ 15 years while 35 were in children < 15 years. Just over 6% of assays had errors. From the remainder of the successful assays, there were 31 (15%) showing MTB: 2 were in children (6% positive detection) and 29 (16% positive detection) were in persons aged ≥ 15 years. All but one sample showed sensitivity to rifampicin (that one sample had rifampicin mono-resistance diagnosed by culture and drug-susceptibility testing).

Characteristics of patients with presumptive TB and their laboratory results before and after the introduction of Xpert MTB/RIF are shown in Table 2. There was a 9% increase in the number of patients identified with presumptive TB after Xpert MTB/RIF was introduced, although no differences were noted in gender or age group distributions between the two groups. Although there was a slight decrease in smear-positive detection in the post Xpert period, this was not statistically significant and AFB grading distribution in those with positive sputum smears was also not significant. The number of MTB cultures performed in the post Xpert period dropped to zero.

Characteristics of patients registered with TB for one year before and after the introduction of Xpert MTB/RIF are shown in Table 3. The main differences in the post Xpert MTB/RIF period compared with the previous period were in age group distributions where significantly more children were registered with TB and in types of TB where significantly fewer patients were registered with bacteriologically confirmed TB.

Table 1. Number of Xpert MTB/RIF tests done between February 2015 and January 2016 in Kiribati along with errors and results

Characteristics	N	(%)
Xpert tests done	220	
Xpert tests with errors	14	(6.4)
Xpert tests completed with no errors	206	(93.6)
Xpert results showing Mycobacterium tuberculosis (MTB)	31	(15.0%)[a]
MTB showing rifampicin resistance	1	(3.2%)[b]
MTB showing no rifampicin resistance	30	(96.8%)[b]

[a]denominator = Xpert tests completed with no errors (n=206)
[b]denominator = Xpert results showing Mycobacterium tuberculosis (MTB) (n=31)

Table 2. Demographic and laboratory characteristics of patients presenting for the investigation of tuberculosis before and after the introduction of Xpert MTB/RIF on Kiribati

Characteristics	Before Xpert n (%)	After Xpert n (%)	*P*-Value*
All Patients	2138 (100)	2322 (100)	
Gender			
Male	1167 (55)	1225 (53)	.20
Female	969 (45)	1094 (47)	
Not Known	2 (<1)	3 (<1)	
Age Group in Years			
1-14	261 (12)	312 (13)	.07
15-49	1027 (48)	1142 (49)	
50-69	519 (24)	551 (24)	
70+	114 (7)	122 (5)	
Not Known	187 (9)	195 (9)	
Sputum Smear Examination			
Positive AFB	157 (7)	137 (6)	.80
Negative AFB	1981 (93)	2171 (93)	
No Result Documented	0	14 (1)	
Grade of AFB			
3+	38 (24)	34 (25)	.47
2+	32 (21)	27 (20)	
1+	46 (29)	53 (38)	
Scanty	41 (26)	23 (17)	
Culture Done for MTB			
Culture Performed	638 (30)	0 (0)	<.001
Culture Not Performed	1498 (70)	2315 (99)	
No Result Documented	2 (<1)	7 (7)	
Culture positive for MTB	76 (12)	0	

*using chi-square test or chi-square test for trend
AFB = acid-fast bacilli; *MTB* = *Mycobacterium tuberculosis*

Table 3. Demographic and clinical characteristics of patients diagnosed with tuberculosis before and after the introduction of Xpert MTB/RIF on Kiribati

Characteristics	Before Xpert n (%)	After Xpert n (%)	*P*-Value
All Patients	472 (100)	550	
Gender			
Male	248 (53)	295 (54)	.70
Female	224 (47)	255 (46)	
Age Group in Years			
1-14	99 (21)	186 (34)	<.001
15-49	252 (53)	267 (49)	
50-69	108 (23)	87 (16)	
70+	13 (3)	10 (1)	
Category of TB			
New	446 (94)	524 (95)	.85
Relapse	12 (3)	7 (1)	
Failed Previous Treatment	2 (<1)	3 (<1)	
Returned After Default	0	0	
Other Recurrent TB	12 (3)	15 (3)	
Transfer In	0	1 (<1)	
Type of TB			
Bacteriologically Confirmed	201 (43)	161 (29)	.47
Not bacteriologically confirmed	221 (45)	304 (55)	
Scanty	60 (12)	85 (167)	

*using chi-square test or chi-square test for trend
TB = tuberculosis

Discussion

This is the first study from Kiribati reporting on 12-months usage of the newly introduced Xpert MTB/RIF assay and assessing whether this had any effect on numbers of patients with presumptive TB, laboratory practices and the types and categories of diagnosed TB.

Given the size of the TB epidemic in Kiribati, the number of Xpert MTB/RIF assays performed per 100,000 people was relatively small compared with what has been observed in several African countries.[17,18] In terms of Xpert MTB/RIF results, error rates were similar and MTB detection rates slightly higher than those found in sub-Saharan Africa. One published study from Fiji on the use of Xpert MTB/RIF in the Pacific region showed similar findings to those of our study.[19] It was reassuring that only one case of rifampicin mono-resistance was found in Kiribati and this is in line with findings from Fiji where there were no detected cases of MDR-TB.

There was a small increase in the number of patients presenting with presumptive TB after the introduction of Xpert MTB/RIF. This period coincided with active TB case finding in the community and this may have been the main reason for the increase in presumptive TB cases rather than the introduction of new technology. Although general concerns were raised several years ago that the introduction of Xpert MTB/RIF might adversely affect sputum smear microscopy services,[20] we found no significant effect in Kiribati. It was also reassuring to see that no sputum specimens were submitted for MTB culture after Xpert MTB/RIF was introduced in accordance with national recommendations.

The main differences in the types and categories of TB before and after Xpert MTB/RIF were a higher proportion of children diagnosed with TB and a lower proportion diagnosed with bacteriologically confirmed TB. We do not know why there was an increase in children diagnosed with TB in the post Xpert MTB/RIF period, but it was not due to the new technology which only resulted in two pediatric confirmed cases in the year. The lower proportion diagnosed with bacteriologically confirmed TB may have been due to more children diagnosed who tend to be smear-negative,[21-23] and no MTB cultures performed which were not compensated for by Xpert MTB/RIF positive cases. The small discrepancies between the numbers with bacteriologically-confirmed TB in the TB registers and numbers with smear-positive AFB in the laboratory registers are not surprising as it takes time for patients diagnosed in the laboratory to be registered and started on anti-TB treatment, so the time periods for patients in each register do not exactly match.

An important strength of this study was that the NTP Unit in Tungaru Central Hospital, South Tarawa, provided services for presumptive TB patients coming from over 90% of Kiribati, and the study was therefore nationally representative. The conduct and reporting of the study also adhered to STROBE and RECORD guidelines.[24,25] Limitations related to the operational and retrospective nature of the study with missing data for some of the variables in the laboratory register. We also did not collect data on why patients with presumptive TB were referred for Xpert MTB/RIF (because this was not recorded consistently in the forms or registers) as this would have been important and helpful to understand why few tests were done in the first 12 months.

There are a number of programmatic implications from this study. First, there should be a scaling up of the Xpert MTB/RIF technology as the number of tests performed in the first 12 months was small. Kiribati has now procured a second instrument in 2016 and this has become functional since the conclusion of the current study. Current WHO recommendations are that Xpert MTB/RIF is used for all patients with presumptive TB,[10] and Kiribati needs to decide whether to widen its use to all patients. Second, there needs to be an improvement in the Xpert MTB/RIF register so that reasons for being tested are being recorded. Third, if the country decides to scale up Xpert MTB/RIF to all presumptive TB patients in the country, a decision would have to be made about smear microscopy services. This study suggests that the quantity and quality of these services has not been adversely affected and it would seem prudent to continue in the first few years with these services in case there are technical or other issues with the Xpert instruments. The skill base for performing smear microscopy would thus be

retained. Finally, a decision will also need to be made about whether to re-establish the use of *Mycobacterium tuberculosis* culture and drug-susceptibility testing. Before the introduction of Xpert MTB/RIF, culture and drug-susceptibility testing were performed in patients with previously treated TB, with HIV, or with persistently smear-positive sputum specimens during treatment. The main purpose of this was to identify and diagnose MDR-TB, including rifampicin-resistant TB, both of which are treated with MDR-TB treatment regimens.[4] Since the introduction of Xpert MTB/RIF, no cultures or drug-susceptibility testing were carried out with the molecular assay replacing this function, thus saving money and removing the logistic challenges of transporting the specimens to the SA Pathology Laboratory, Adelaide, Australia. However, the downside is that there is no information about isoniazid or other primary drug resistance, excluding rifampicin. In the 2010 WHO Tuberculosis Guidelines,[15] and further endorsed in the most recent 2017 WHO Tuberculosis Guidelines,[26] the recommendation is that ethambutol can be added to the continuation phase of isoniazid and rifampicin if there are high levels of isoniazid resistance. This is something that the Kiribati NTP may wish to consider including the re-establishment of culture and DST.

In conclusion, despite the introduction of Xpert MTB/RIF in Kiribati, only a small number of Xpert tests were performed with an MTB case detection rate of 15%. Sputum smear microscopy services were unaffected while the numbers of specimens being sent for MTB culture dropped to zero. The pattern of registered TB changed with fewer numbers of bacteriologically confirmed TB. Reasons for these changes and programmatic implications are discussed.

Conflict of Interest

None of the authors identify any conflict of interest.

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