Spot Specimen Testing With GeneXpert® MTB/RIF Results In More Complete TB Diagnostic Results Than Morning Specimens

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Abstract

Background: The diagnosis of Tuberculosis (TB) using smear microscopy has been based on testing 2 specimens: one spot and one early morning sputum. Recently, the World Health Organization (WHO) recommended to replace, whenever possible, microscopy with GeneXpert® MTB/RIF performed on a single specimen. However, as the bacterial load is higher in early morning specimens than in spot specimens, one could expect lower sensitivity of GeneXpert® MTB/RIF performed only on spot specimens. In this study, we compared results of GeneXpert® MTB/RIF on spot specimens versus early morning specimens, under programmatic conditions in Cotonou, Benin.

Methods: From June to September 2018, all sputa received from presumptive TB patients at the Supranational Reference Laboratory for Tuberculosis of Cotonou were included in the study. From each patient, two specimens were collected (one spot and one early morning) and GeneXpert® MTB/RIF was performed on both specimens.

Results: In total, 886 participants were included in the study, of whom 737 provided both sputa and 149 (16.8%) gave only the spot specimen. For the 737 participants who provided both sputa, GeneXpert® MTB/RIF was positive for both specimens in 152 participants; for three participants GeneXpert® MTB/RIF was positive on spot specimen but negative on morning specimen while for another three, the test was positive on morning specimen but negative on spot specimen. The overall percentage of agreement was excellent (99.2%) with a very positive and negative percent agreement greater than 98%.

Conclusions: For TB diagnosis under programmatic conditions in Cotonou, GeneXpert® MTB/RIF in spot specimens gave similar results with the test in morning specimens. Performing GeneXpert® MTB/RIF in both specimens did not significantly increase the number of cases detected. To avoid losing patients from the diagnostic cascade, it is preferable to test sputa produced at the time of visit.

Background

Tuberculosis (TB) is still a major public health concern especially in low resources settings. In 2019, among the 10 million of people affected, there were 1.4 million deaths [1]. Since decades, the diagnosis of TB is standardized and based on World Health Organization (WHO)' recommendations. Over time, these recommendations have evolved to provide TB patients with improved diagnostic services. In 2003, for screening in TB-endemic countries, WHO recommended the use of microscopic examination of two or three sputum specimens for detection of acid-fast bacilli (AFB) for the diagnosis of pulmonary TB [2]. Testing multiple specimens yields incremental increase in sensitivity compared to culture, the reference method for TB detection, with 11.1% increase for the 2nd and 2–5% for the 3rd specimen [3, 4]. WHO therefore recommended the use of two specimens, including a morning specimen (MS), to diagnose TB in endemic countries [5, 6]. Moreover, the bacterial load of the MS was described to be higher than that of spot specimen (SS) explaining the increase in sensitivity [7–9]. Subsequently, nucleic acid amplification tests, especially the GeneXpert® MTB/RIF (Cepheid, Sunnyvale, USA) proved to be game changers for the

diagnosis of TB. Indeed, besides its performance in detecting TB that approximates culture, it is user-friendly and can detect the resistance status to rifampicin, the main first line anti-TB drug, all within 2 hours[10, 11]. WHO thus recommended in 2013 the use of GeneXpert® MTB/RIF as initial test for rapid and simultaneous detection of TB and resistance to rifampicin [12]. The recommendation supports the use of a single sputum but highlights that the use of multiples specimen may increase the diagnostic sensitivity yet recognizes resource implications. On the other hand, the preferred specimen between a SS and a MS especially in programmatic conditions in low income countries was not mentioned. Nevertheless, the use of a MS is associated with increased sensitivity when smear microscopy is used as initial diagnostic tool for examining specimens, but to the best of our knowledge there are no studies evaluating in programmatic conditions the possible added value of the MS when GeneXpert® MTB/RIF is used as initial test for diagnosing TB. One study evaluated the sensitivity of GeneXpert® MTB/RIF test on MS vs SS and showed no significant difference. However, the study was restricted to microscopy smear-negative patients and a limited sample size[13]. Furthermore, the possible impact of using a screening strategy based on MS collection for TB cases detection was not evaluated. In this study, we assessed the contribution of different specimens' collection strategies for pulmonary TB screening using GeneXpert® MTB/RIF in Cotonou, Benin.

Methods

Study design

Between June and September 2018, a prospective cross-sectional study was conducted and included all consecutive patients with presumptive pulmonary TB (new cases and relapses cases).

Study setting

The study was carried out at the Centre National Hospitalier de Pneumo-Phtisiologie de Cotonou, the biggest public tertiary hospital specialized in TB in Benin. The hospital is located in the south of the country but also serves as referral center for the whole country. Bacteriological diagnosis of TB in this hospital is performed by the WHO Supranational Reference Laboratory for TB with a turnaround time of 24 hours for the GeneXpert MTB/RIF. Therefore, the patient is asked to return the day after arrival at the clinic to obtain its result.

Specimen collection

After informed consent, patients were asked to provide two sputum specimens: the first one was collected on site (spot specimen, SS) and the second was provided the next morning and brought back to the laboratory (morning specimen, MS). A systematic phone call was made to the patients who did not spontaneously bring back the second specimen.

Specimen processing

Specimens were processed with the GeneXpert®MTB/RIF (Cepheid, Sunnyvale, USA) cartridge according to manufacturer's instructions and as previously described [14]. Rifampicin (RIF) resistant results were further confirmed by repeating the test on an additional specimen as recommended for new cases, before further testing, including culture isolation and indirect phenotypic drug susceptibility testing (pDST) on Löwenstein Jensen media [15, 16].

Statistical analysis

The frequencies and percentages of presumptive patients' characteristics were presented by the number of specimens provided (both SS and MS, or SS only). Chi square and Fisher's exact tests were used to assess whether the characteristics of those who provided both SS and MS were similar to those who provided SS only.

The overall percentage of agreement, positive percent agreement (PPA) and the negative percent agreement (NPA) with 95% Wilson score confidence intervals were estimated to evaluate the performance of GeneXpert®MTB/RIF using SS and MS. For analytical purposes, SS and MS were both used as reference standard one at a time. PPA and NPA are equivalent to the sensitivity and specificity respectively if the reference standard is perfect. McNemar test was used to assess the evidence of agreement for GeneXpert®MTB/RIF results obtained from SS and MS. Subsequently, the Cohen's Kappa coefficient was used to evaluate the concordance between the bacterial loads for samples positive using GeneXpert®MTB/RIF and sputum aspects obtained from SS and MS.

Some participants only provided the SS. As the agreement assessment requires the availability of results from both SS and MS, sensitivity analyses were conducted assuming two extreme scenarios: (i) all missing MS gave the same GeneXpert®MTB/RIF results as their counterpart SS and (ii) all missing MS gave the opposite GeneXpert®MTB/RIF results to their counterpart SS. All analyses were performed using Stata version 14.2.

Results

In total 886 presumptive patients were included in the study, of whom 859 (97.0%) had never suffered from TB and 27 (3.0%) had a previous history of TB (Table 1). Male were predominant (n = 480, 54.2%). There was no evidence of difference in the distribution of age and history of TB across those who provided both SS and MS and those who only provided SS (p = 0.65 and p = 0.43, respectively). However, we found a slightly evidence of difference in the gender distribution (p = 0.02).

Table 1
Participants' characteristics by number of specimens provided

Characteristics	All enrolled participants (n = 886)	Provided spot and morning specimens (n = 737)	Provided spot specimen only (n = 149)	P
Gender, n (%)				0.02[a]
Female	406 (45.8)	351 (47.6)	55 (36.9)	
Male	480 (54.2)	386 (52.4)	94 (63.1)	
Age group in years, n (%)				0.65[a]
Below 15	62 (7.0))	15 (6.9)	11 (7.4)	
15–29	228 (25.7)	185 (25.1)	43 (28.9)	
30–44	308 (34.8)	257 (34.9)	51 (34.2)	
45–59	186 (21.0)	161 (21.8)	25 (16.8)	
60 and above	102 (11.5)	83 (11.3)	19 (12.7)	
History of TB, n (%)				043[b]
New	859 (97.0)	716 (97.2)	143 (96.0)	
Relapse	27 (3.0)	21 (2.8)	6 (4.0)	

[a] Chi square test. [b] Fisher's exact test.

Of the 886 patients, 654 (73.8%) spontaneously returned to provide the MS, 83 (9.4%) provided it after a phone call, and the remaining 149 (16.8%) did not provide it despite the phone call. Thus, 737 provided both SS and MS and 149 provided only SS.

Among the 232 patients who did not spontaneously provide the MS, GeneXpert® MTB/RIF was positive on 37 SS representing 15.9% (95% CI: 11.2–20.7) of this sub population.

Agreement was evaluated using paired specimens, that is patients who provided both SS and MS. From 737 patients providing both SS and MS, 155 (21.0%) were positive with GeneXpert® MTB/RIF for SS and MS (Table 2). Using either SS or MS as reference standard, the PPA and NPA were 98.1% (95% CI: 94.5–99.3) and 99.5% (95% CI: 98.5–99.8), respectively. The overall percentage of agreement was very high (99.2%, 95% CI: 98.2–99.6). There was no evidence of disagreement between the two types of specimen (p = 0.99). There were 731 concordant and 3 discordant results with MS as well as with SS. Note that the bacterial load of these six discordant specimens ranged from very low to medium.

Table 2
Agreement between results from SS and MS using GeneXpert® MTB/RIF

Morning Specimen	Spot Specimen[#]			P[a]	Overall percentage of agreement	Positive percent agreement	Negative percent agreement
	Positive	Negative	Total		(95% CI)[b]	(95% CI)[b]	(95% CI)[b]
Total	**155**	**582**	**737[&]**	0.99	99.2 (98.2–99.6)	98.1 (94.5–99.3)	99.5 (98.5–99.8)
Positive	152	3	**155**				
Negative	3	579	**582**				
Spot Specimen	**Morning Specimen[#]**		Total	**P[a]**	**Overall percentage of agreement**	**Positive percent agreement**	**Negative percent agreement**
	Positive	Negative			**(95% CI)[b]**	**(95% CI)[b]**	**(95% CI)[b]**
Total	**155**	**582**	**737[&]**	0.99	99.2 (98.2–99.6)	98.1 (94.5–99.3)	99.5 (98.5–99.8)
Positive	152	3	**155**				
Negative	3	579	**582**				

[a] McNemar test. [b] Wilson 95% confidence intervals. [#] Used as reference standard. [&] Note that the agreement analysis included 737 presumptive TB patients who provided both SS and MS.

The sensitivity analyses including all 886 patients and assuming that all the missing MS gave the same GeneXpert® MTB/RIF results as their counterpart SS showed consistent results about the high level of agreement of the performance of GeneXpert® MTB/RIF using SS and MS (Additional file 1, Table 1-A). However, when assuming that all the missing MS gave the opposite GeneXpert® MTB/RIF results as their counterpart SS, there was strong evidence of disagreement ($p < 0.001$, Additional file 1, Table 1-B). Nevertheless, it is worth noting that the former assumption is more plausible than the latter with respect to the high level of agreement found with the 737 pairs of SS and MS.

Comparing the bacterial load of paired SS and MS that were both positive, we found evidence of some level of agreement in the bacterial load from SS and MS ($p < 0.001$, Table 3). However, the kappa coefficient was 0.35 and suggested poor agreement between SS and MS.

Table 3
Agreement between bacterial load of the positive specimens using GeneXpert® MTB/RIF on SS and MS

Bacterial load from morning specimens	Bacterial load from spot specimens				
	High	**Medium**	**Low**	**Very low**	**Total**
High	28	24	4	1	**57**
Medium	6	45	14	2	**67**
Low	0	7	12	2	**21**
Very low	0	0	5	2	**7**
Total	**34**	**76**	**35**	**7**	**152**
Observed agreement = 57.2%, Expected agreement = 33.8%, Kappa coefficient = 0.35[#], P < 0.001[&]					

[#] A kappa coefficient varies from 0 to 1. The higher the coefficient, the greater the agreement. A kappa coefficient below 0.40 can be considered as poor agreement [17]. [&]Tests the hypothesis that the bacterial loads from both specimens are randomly determined (in others words, the null hypothesis states that the level of agreement observed is simply due to chance).

Finally, four RIF resistant cases were detected on MS, of which two were also detected on SS (Table 4). After testing an additional specimen on GeneXpert®MTB/RIF for the two discordant cases , resistance status to RIF detected by the MS was excluded. Sensitivity to RIF was later confirmed using pDST. These 2 false resistant patients were new cases displaying a “very low” bacterial load.

Table 4
Resistance status to rifampicin

Morning Specimen	Spot Specimen		
	Resistant	**Susceptible**	**Total**
Total	**2**	**150**	**152**
Resistant	2	2	**4**
Susceptible	0	148	**148**

Discussion

Of the included patients, only 654 (73.8%) provided the MS spontaneously and 83 (9.4%) provided it after a phone call but the remaining 149 (16.8%) did not return, despite the phone call. However, under programmatic conditions, especially in low resources settings, an algorithm that includes a phone call to such a high number of presumptive patients may be difficult to implement because of economic implications and feasibility in routine conditions.

Therefore, with a TB screening strategy based on the use of GeneXpert® MTB/RIF on MS, 232 (26.2%) of presumptive patients could have been lost. In addition, there were 15.9 % of positive patients among

these "lost to diagnostic follow-up". Such a strategy would be detrimental to global efforts to increase TB notifications. Indeed, giving a specimen at the hospital on the day of arrival probably creates a link between the patient and the hospital and motivates the patient to come back the next day to get the result. This is not the case with the MS.

GeneXpert® MTB/RIF ® showed a positivity rate of 21% for both SS and MS with an excellent overall percentage of agreement of 99.2% and very positive and negative percent agreement greater than 98%.This is consistent with what was previously reported [13].

Despite the poor agreement between the bacterial load of two types of samples (kappa = 0.35) suggesting that the bacterial load of MS is higher than that of SS and confirming previous studies' results based on microscopy which noted the superiority of MS over SS in terms of bacterial load [7–9], the positivity rate on GeneXpert MTB/ RIF® was similar. Indeed, due to its high sensitivity, the GeneXpert MTB/ RIF® can detect TB even in pauci-bacillary specimens. However, the relatively high positivity rate observed in this study could be explained by the fact that the study took place in a tertiary hospital. Besides, it cannot be excluded that patients may have arrived late at the hospital in a deteriorated state of health.-

There were 3 false negatives in each group (SS and MS) which could be explained by the intermittent nature of the bacilli released in sputum after cough that has been described in pulmonary TB patients[18]. Also the heterogeneous distribution of bacilli in the same specimen may have had impact, as the processed part may not contain any bacilli. A total of four cases of RIF resistance were recorded, including 2 discrepant results between MS and SS: RIF resistant on MS but susceptible on SS. When pDST was performed on strains after culture of the specimens, these two specimens were confirmed susceptible. These discrepancies have been previously described as strongly associated with "Very Low" bacterial load [19]. Indeed, the algorithm used to detect RIF resistance in GeneXpert® MTB/RIF is based on absence or delay of binding of five probes (labelled A–E) that cover the 81 bp rifampicin-resistance determining region. Thus, factors such as insufficient DNA in the specimen or silent mutation may lead to a false detection of RIF resistance [20]. To overcome these limitations, the GeneXpert® MTB/RIF Ultra has been introduced. In this cartridge, the detection of RIF resistance is based on the interpretation of the melting curves of molecular probes [21]. However, recent studies showed that for detection of RIF resistance, GeneXpert Ultra and GeneXpert® MTB/RIF had similar sensitivity and specificity [22, 23], and post-implementation population based studies are still to be performed. Another cause for the discrepant results could be the presence of minority *rpoB* mutant populations in the processed samples that were less fit to grow in culture, as was previously described for 'borderline' *rpoB* mutants [24]. While such mutations may be more frequently presenting as 'heteroresistance', which can easily be missed in GeneXpert (both MTB/RIF and Ultra requiring > 50% mutant population to recognize RIF resistance), they are not associated with lower bacterial burden than common *rpoB* mutants. Needless to say, the interpretation of rifampicin resistance in the case of a very low bacterial load should be done with great care and should follow published guidelines [16].

Conclusion

In conclusion, both SS and MS yielded similar rates of TB confirmation in presumptive patients, but a screening strategy based on MS may lead to significant loss to follow up. SS is therefore suitable as first screening tool using GeneXpert® MTB/RIF.

Abbreviations

MS	Morning Specimen
SS	Spot Specimen
pDST	Phenotypic Drug Susceptibility Testing
TB	Tuberculosis

Declarations

Availability of data and materials

The datasets used during the current study can be obtained from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Faculty of Health Sciences of Cotonou of the University of Abomey-Calavi, Benin (N°011-18/UAC/FSS/CER-SS). Informed consent was obtained from all subjects involved in the study.

Competing interests

The authors declare no conflict of interest.

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Author Contributions

FM, MF, APW, GA and DA contributed to the conception of the study and its design. SCA performed the statistical analysis. FM wrote the first draft, BCdJ, LR and DA reviewed and edited the manuscript. All the authors revised the draft, provided critical comments, approved the final manuscript and have agreed to be personally accountable for the author's own contributions.

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