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Original article

Added value of molecular assay Xpert MTB/RIF compared to sputum smear microscopy to assess the risk of tuberculosis transmission in a low-prevalence country

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ABSTRACT

Airborne precautions are required at hospital admission for patients with suspected pulmonary tuberculosis. The isolation is maintained until 3 serially collected sputum smears are acid-fast bacilli negative, a time- and labor-intensive method with limited sensitivity and specificity, which has a great impact on patient flow management. We evaluated the possibility of replacing the result of microscopy by the semiquantitative result of the molecular point-of-care test Xpert MTB/RIF to assess patients' transmission risk to quickly guide airborne isolation decisions in low-endemic countries. The performance of the Xpert MTB/RIF, used as a first-line test, was compared to the results of microscopy for specimens ($n = 242$) collected from May 2010 to December 2014 in Lausanne, Switzerland. The sensitivity and specificity of Xpert MTB/RIF were 91.5% (65/71) and 99.6% (170/171), respectively, vs. 64.8% (46/71) and 94.2% (161/171) for microscopy. Samples with negative Xpert MTB/RIF were all smear negative for *Mycobacterium tuberculosis* (negative predictive value, 100%). The semiquantitative results of Xpert MTB/RIF—high, medium, low or very low—were found to correlate with acid-fast bacilli detection: positive predictive value of 100% (6/6), 96.5% (27/28), 52.2% (12/23) and 11.1% (1/9) respectively. Finally, when including clinical criteria, we identified 11 smear-negative but Xpert MTB/RIF–positive patients with a significant transmission potential. In conclusion, our data support the introduction of an Xpert MTB/RIF–based strategy as a replacement of smear microscopy for a faster and more accurate management of tuberculosis patients' transmission risk in a low-prevalence country. **O. Opota, CMI 2016;22:613**

Introduction

Among the prerequisites to limit the worldwide spreading of tuberculosis, rapid diagnosis of the disease is paramount to allow the rapid introduction of an efficient antituberculosis treatment, to take adequate isolation precautions and to achieve contact tracing. Tuberculosis diagnosis has been dominated for a long time by microscopy examination of sputum smears for the detection of acid-fast bacilli (AFB) and by specific mycobacterial culture. Despite its limited sensitivity and specificity, smear microscopy is historically the first microbial analysis performed when the clinical presentation of the patient is compatible with pulmonary tuberculosis and culture results are not yet available (delay of up to 6–8 weeks).

PCR-based methods developed over the last decades have significantly improved and accelerated tuberculosis diagnosis; however, such methods require a specific molecular diagnostic laboratory setup. The need for simpler PCR systems has been solved with the real-time PCR-based system Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), a simple point-of-care test (POCT) that can simultaneously detect, in 2 hours, *Mycobacterium tuberculosis* and the main mutations associated with resistance to rifampicin. Since 2013, the World Health Organization has recommended the Xpert MTB/RIF as the initial test for tuberculosis microbial diagnosis for

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patients with suspected pulmonary tuberculosis including new cases; for retreatment cases; for suspected multidrug-resistant (MDR) tuberculosis; and for HIV-infected patients with suspected tuberculosis because of its excellent sensitivity and specificity associated with an extremely short turnaround time [1,2]. At present, more than 108 countries (mainly countries endemic for tuberculosis) are routinely using this diagnostic test [3].

Studies addressing the added value of this rapid molecular test to assess patients' transmission risk and to guide airborne isolation decisions are needed. Historically, patients' infectiousness was addressed by smear microscopy; a positive smear result reinforced the suspicion of tuberculosis and was associated with a high transmission risk [4–8]. However, in a low-prevalence setting, patients with suspected tuberculosis are placed in an isolation room until three consecutive sputum smears are AFB negative because of the limited sensitivity of this method. Such a strategy can have a great impact on patient placement and can result in unnecessary prolonged stays in isolation rooms [9–11]. A significant reduction of the transmission risk of smear-negative patients compared to smear-positive patients has been observed (relative risk, 0.28 and 0.47, respectively) [12,13]. Nevertheless, several studies have demonstrated that tuberculosis transmission can occur from smear-negative patients, with a minimum relative transmission rate estimated to 0.22 [14–17]. Thus, smear examination has a limited sensitivity and specificity for tuberculosis diagnosis; it is time and labor intensive, with a great impact on laboratory routine work flow; further, it requires skilled lab technicians, and therefore it significantly disrupts laboratory routine work flow. In addition, it cannot distinguish between non-*tuberculosis* mycobacteria and *M. tuberculosis*, leading to unnecessary airborne precautions, and it is unable to detect all infectious patients.

In this study, we aimed to determine the potential added value of the Xpert MTB/RIF PCR to address patients' transmission potential in a faster, more accurate and more reliable manner in low-prevalence settings.

Materials and Methods

Study design

The tuberculosis diagnostic laboratory of the Institute of Microbiology is part of the Lausanne University Hospital, a 1000-bed tertiary-care hospital located in Switzerland, a low-tuberculosis-prevalence country (approximately six new cases per year per 100 000 population; Swiss Federal Office of Public Health (FOPH), http://www.bag.admin.ch/). Our laboratory processes approximately 3500 samples for pulmonary tuberculosis suspicion per year. Each year, approximately 50 new cases of tuberculosis are confirmed by culture. Until 2010, the diagnosis of pulmonary tuberculosis relied on smear microscopy, on an in-house TaqMan probe–based real-time PCR [18] and on mycobacterial culture.

In May 2010, the Xpert MTB/RIF assay was implemented in our laboratory. We retrospectively compared the results of the Xpert MTB/RIF, smear microscopy and mycobacterial culture on respiratory samples collected in patients with suspected pulmonary tuberculosis from May 2010 to December 2014. During this study period, 4918 patients (11 414 samples) were tested for suspected pulmonary tuberculosis. Only samples for which these three analyses were available were included in the study. Indeed, while smear microscopy and culture are systematically performed for suspected pulmonary tuberculosis, the Xpert MTB/RIF was selectively requested by clinicians for patients with a high pretest probability of disease on the basis of clinical and epidemiologic data, or for patients with suspected infection with MDR tuberculosis, as recommended by the World Health Organization [1]. When multiple samples were available for a given patient, only the first sample was considered. As a consequence, our study is made up of spot samples collected at hospital presentation rather than of morning samples. All data were extracted from our laboratory database. Clinical reviews were extracted from the software of our hospital.

The study was approved by the local ethics committee (Commission Cantonale d'Ethique de la Recherche sur l'Etre Humain, Lausanne, Switzerland).

Microbiologic diagnosis of tuberculosis

All the microbial analyses were performed on the same sample after splitting it for AFB staining, Xpert MTB/RIF analysis and mycobacterial culture. AFB detection was achieved through a fluorescent auramine-Thiazine Red staining on a heat-fixed smear. After heat fixation on a slide, the sample was placed in a staining rack containing the 0.1% auramine staining solution for 15 minutes. After rinsing with tap water, the sample was treated with the 0.5% acid–alcohol decolourizing solution for 5 minutes and again rinsed with tap water. Counterstaining was achieved with Thiazine Red applied for 3 minutes. After a final rinse in tap water, the slides were dried and observed by fluorescent microscopy.

Smear grading was determined according to the International Union Against Tuberculosis and Lung Disease scale [19]. The staining was performed on nondecontaminated respiratory samples. Purulent sputum or bronchial aspirates were solubilized with the mucolytic agent N-acetyl-L-cysteine (2% m/v pH 6.8) to increase the homogeneity of the sample before smear preparation. Samples with a volume exceeding 3 mL were concentrated by centrifugation (30 minutes, 3000 × *g*). Mycobacterial culture was performed in a Mycobacteria Growth Indicator Tube (Becton Dickinson, Heidelberg, Germany) after sample decontamination using a solution containing N-acetyl-L-cysteine (2% m/v) and with NaOH (2% m/v) [20]. The Xpert MTB/RIF analysis was performed on non-decontaminated samples according to the manufacturer's instructions. When positive, the Xpert MTB/RIF provides a semiquantitative result defined by the manufacturer as follows: positive–very low (cycle threshold (C_t) >28), low (C_t 22–28), medium (C_t 16–22) or high (C_t <16).

Statistical comparison between semiquantitative Xpert MTB/RIF method and smear microscopy

The diagnostic performance of the Xpert MTB/RIF was compared to that of smear microscopy, with the reference standard being mycobacterial culture. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and 95% confidence intervals were calculated by GraphPad Prism 6.00 for Windows (GraphPad Software, La Jolla, CA, USA). The correlation between these two diagnostic methods was determined, and the clinical characteristics of patients with discrepant results were reviewed.

Results

Patients and samples

Our study included respiratory specimens collected from 252 patients with suspected pulmonary tuberculosis. Specimens collected after the initiation of an antituberculosis treatment ($n = 10$) were excluded from our analysis because of the possible decrease in culture sensitivity (Fig. 1). Thus, a total of 242 samples from 242 patients were studied. Of these 242 samples, 71 (29.3%,

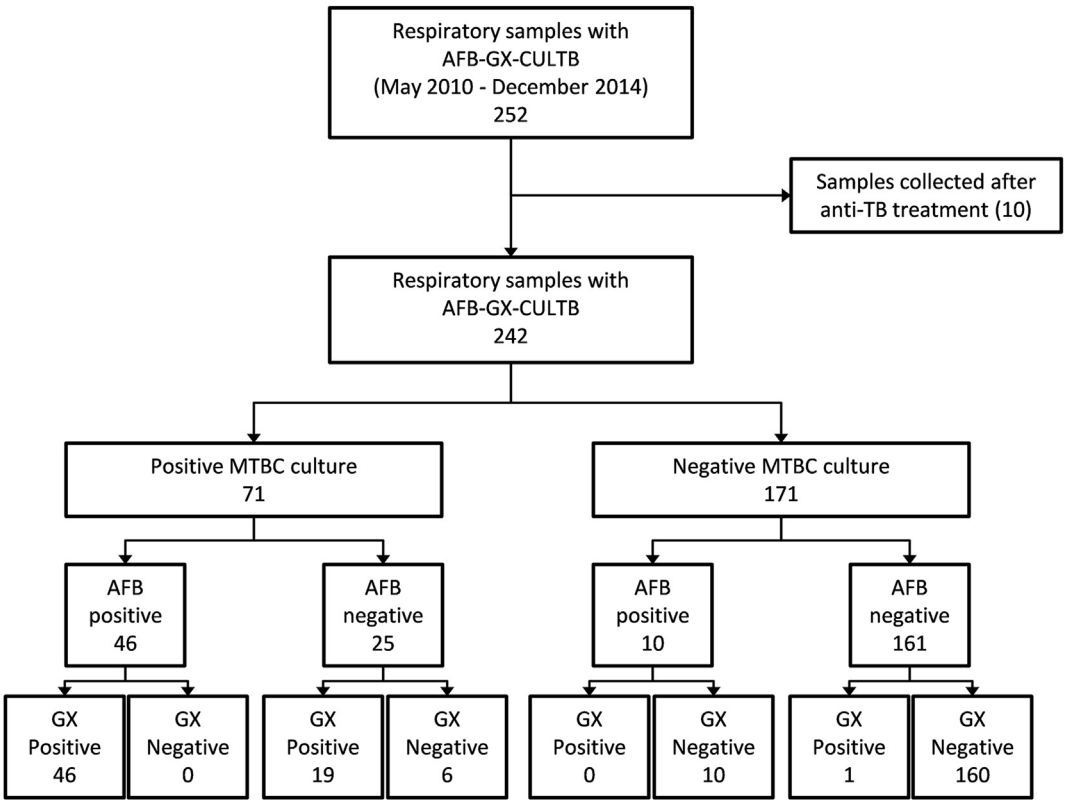

Fig. 1. Study design and sample distribution.

71/242) were *M. tuberculosis* culture positive and 171 (78.7%, 171/242) were culture negative. This high rate of culture-confirmed positive patients is because during the period of the study, the Xpert MTB/RIF was mainly dedicated to patients with a high pretest probability of pulmonary tuberculosis. Among the 71 specimens with positive *M. tuberculosis*, 46 (64.7%, 46/71) were smear positive. Among the 171 specimens with negative *M. tuberculosis* culture, 10 (6%, 10/171) were smear positive: eight of them grew non-*tuberculosis* mycobacteria (NTM), whereas the two remaining were false-positive smear results due to fluorescent artefacts.

Sensitivity, specificity and predictive value of Xpert MTB/RIF and smear microscopy using M. tuberculosis culture as reference standard for active pulmonary tuberculosis

We first established the performance of Xpert MTB/RIF and smear microscopy in the setting of our hospital (Table 1). Using *M. tuberculosis* culture as the reference standard for active pulmonary tuberculosis, the sensitivity and specificity of the Xpert MTB/RIF were 91.5% (65/71) and 99.4% (170/171), respectively, corresponding to a PPV of 98.5% (65/66) and a NPV of 96.6% (170/176). This was significantly higher than the sensitivity and specificity of smear examination, which were 64.7% (46/71) and 94.2% (161/171), respectively, corresponding to a PPV of 82.1% (46/56) and a NPV of 86.6% (171/186) (Table 1). A single sample tested positive by Xpert MTB/RIF but negative by *M. tuberculosis* culture. This sample was from a bronchial aspirate from a patient who presented with dyspnoea, cough and chest pain. Similarly, the bronchoalveolar lavage sample of the same patient was Xpert MTB/RIF positive and culture negative. Computed tomographic scan revealed the presence of a pulmonary condensation with cavitation. An antituberculosis treatment for active pulmonary tuberculosis was initiated by clinicians.

Correlation between Xpert MTB/RIF semiquantitative results and smear microscopy results

We next decided to investigate the correlation between the semiquantitative results of Xpert MTB/RIF and smear microscopy. We first found that all the samples with smear examination positive for *M. tuberculosis* had a positive Xpert MTB/RIF test, which corresponded to an overall sensitivity of the Xpert MTB/RIF to detect smear-positive samples of 100% (46/46) (Table 2). Conversely samples with negative Xpert MTB/RIF were all smear negative for *M. tuberculosis* (NPV = 100%, 166/166). When positive, the Xpert MTB/RIF provides semiquantitative results defined by the manufacturer as follows: positive-very low (C_t >28), low (C_t 22–28), medium (C_t 16–22) or high (C_t <16). We compared the Xpert MTB/RIF semiquantitative results to smear grading results (Table 3). All samples that tested positive–high by Xpert MTB/RIF were smear positive corresponding to a PPV, for a smear positivity of 100% (6/6). Among samples with positive–medium Xpert MTB/RIF results, 27 of 28 were smear positive, corresponding to a PPV for smear positivity of 96.4%. The PPV for smear positivity of samples with positive–low and positive–very low Xpert MTB/RIF results were 55% (12/23) and 11.1% (1/9), respectively. These data show that the Xpert MTB/RIF semiquantitative results positively correlate with smear examination.

Clinical presentation of tuberculosis patients with smear-negative result and Xpert MTB/RIF positive result

The transmission potential of suspect tuberculosis patients is generally assessed on the basis of smear examination. Smear-negative patients are generally considered as less infectious. Our study identified 20 patients with positive Xpert MTB/RIF but negative smear examination. The analysis of the clinical data for

Table 1
Comparison of diagnostic performance

Examination	*Mycobacterium tuberculosis*–positive culture, % (95% CI) for:			
	Sensitivity	Specificity	PPV	NPV
Smear microscopy	64.8 (52.5–75.8) 46/71	94.2 (89.5–97.2) 161/171	82.1 (69.6–91.1) 46/56	86.6 (81.0–91.1) 171/186
Xpert MTB/RIF	91.5 (82.5–96.8) 65/71	99.4 (96.8–100) 170/171	98.5 (91.84–100) 65/66	99.6 (92.7–98.7) 170/176

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

Table 2
Detection of smear-positive samples with Xpert MTB/RIF[a]

Examination	Smear positivity detection, % (95% CI) for:			
	Sensitivity	Specificity	PPV	NPV
Xpert MTB/RIF	100 (92.3–100) 46/46	89.3 (83.9–93.3) 166/186	69.7 (57.1–80.4) 46/66	100 (97.8–100) 166/166

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.
[a] Smear-positive samples negative for *Mycobacterium tuberculosis* culture, corresponding to samples positive with non-*tuberculosis* mycobacteria or containing fluorescent artifacts, were excluded from this analysis ($n = 10$).

Table 3
Correlation between Xpert MTB/RIF semiquantitative result and smear microscopy results

Xpert MTB/RIF result	Smear microscopy result					Prediction of smear positivity		
	Negative	Scanty	1+	2+	3+	Total smear positive[a]	Total samples	Predictive value of smear positivity (95% CI)
Positive–high		1	1	1	3	6	6	PPV 100% (54.1–100)
Positive–medium	1	6	14	5	2	27	28	PPV 95.4% (81.6–99.9)
Positive–low	11	7	3	2		12	23	PPV 52.2% (30.6–73.2)
Positive–very low	8		1			1	9	PPV 11.1% (0.3–48.2)
Negative	166	8[b]	2[c]			0	176	NPV 100%[a] (97.8–100)
Total	186	22	21	8	5	46	242	

CI, confidence interval; NPV, negative predictive value; NTM, non-*tuberculosis* mycobacteria; PPV, positive predictive value.
[a] After exclusion of NTM and mycobacterial-negative samples.
[b] *Mycobacterium tuberculosis* culture negative (six NTMs and two samples with one to two acid-fast bacilli).
[c] *M. tuberculosis* culture negative (two NTMs).

this group of patients revealed that most of them (14/20) were symptomatic (cough, sputum, pulmonary infiltrate, weight loss, asthenia; Table 4). Remarkably, among these smear-negative patients, 11 (55%) of 20 presented with pulmonary cavitation, which is associated with a high transmission potential but would have been misclassified as poorly infectious on the basis of an initial negative smear examination. Finally, among these 11 smear-negative but Xpert MTB/RIF–positive patients, the molecular test identified one patient infected with a MDR isolate (patient 2; Table 4).

Discussion

To date, sputum smear microscopy remains the first microbial analysis both for tuberculosis diagnosis and assessment of patient infectiousness, which guide airborne isolation measures [3–6,8]. However, smear microscopy is time and labor intensive, requires specialized technicians and has a limited sensitivity. In addition, smear microscopy displays limited specificity because AFB staining cannot distinguish between *M. tuberculosis* and non-*tuberculosis* mycobacteria.

In most laboratories, sputum smear microscopy is still performed to assess the degree of infectivity of patients, as it is still considered the microbiologic reference standard when deciding whether to isolate the patient. This strategy has a great impact on patient placement and hospital costs, especially in regions with low tuberculosis prevalence. In the present study, we compared the performance of the Xpert MTB/RIF to microscopy to determine the potential added value of the molecular POCT as a first-line test for tuberculosis diagnosis as well as to assess patients' transmission potential and to decide whether the patient needs to be isolated.

We found that in the setting of our hospital, which is located in a low-prevalence country, the sensitivity and specificity of the Xpert MTB/RIF were higher than the sensitivity and specificity of smear microscopy. These results are in line with all the studies conducted so far that have evaluated the performance of the Xpert MTB/RIF [2,21,22]. We next compared the semiquantitative result of the Xpert MTB/RIF with those of conventional microscopy using the international smear grading system [19] and found that the results of the Xpert MTB/RIF could be used as a predictor of smear result. Samples with high, medium, low and very low Xpert MTB/RIF results corresponded to PPV of smear positivity of 100%, 96.5%, 52.2% and 11.1%, respectively. In addition, we reported that all cases with a negative Xpert MTB/RIF result corresponded to negative smear examination (NPV = 100%). Finally, we observed that 55% of tuberculosis patients with negative smear microscopy but positive Xpert MTB/RIF results had a clinical presentation suggestive of high

Table 4
Clinical presentation of patients with positive Xpert MTB/RIF result and negative smear examination

Patient no.	Sex, age (years)	Specimen source	Smear result	MTBCGX	*rpoB* Xpert MTB/RIF	*Mycobacterium tuberculosis* culture	Cavitation	Radiologic findings	Clinical presentation
1	F, 20	Sputum	Negative	Positive medium	Negative	Positive	Yes	Lung infiltrate with cavitation	Cough, weight loss
2	M, 19	Induced sputum	Negative	Positive low	Positive	Positive	Yes	Lung infiltrate with cavitation	No symptoms
3	F, 20	Sputum	Negative	Positive low	Negative	Positive	Yes	Lung infiltrate with cavitation	Cough, weight loss, HIV infection, pregnancy
4	M, 23	Sputum	Negative	Positive Low	Negative	Positive	Yes	Lung infiltrate with cavitation	Cough, haemoptysis, weight loss, HIV infection
5	M, 38	Bronchial aspirate	Negative	Positive low	Negative	Positive	Yes	Lung infiltrate with cavitation	No symptoms
6	M, 36	Sputum	Negative	Positive Low	Negative	Positive	Yes	Miliary lung infiltrate with cavitation	Cough, weight loss, asthenia, fever, immunosuppressive therapy (infliximab)
7	M, 33	Bronchial aspirate	Negative	Positive low	Negative	Positive	No	Miliary lung infiltrate	Cough, haemoptysis, weight loss, HIV infection
8	F, 47	Bronchial aspirate	Negative	Positive low	Negative	Positive	No	Miliary lung infiltrate	Weight loss, asthenia
9	M, 49	Bronchial aspirate	Negative	Positive low	Negative	Positive	No	Lung infiltrate	HIV infection, lymphoma
10	M, 50	Induced sputum	Negative	Positive low	Negative	Positive	NA	NA	NA
11	F, 39	Induced sputum	Negative	Positive low	Invalid	Positive	NA	NA	NA
12	M, 21	Bronchial aspirate	Negative	Positive very low	Negative	Positive	Yes	Lung infiltrate with cavitation	Cough
13	M, 27	Sputum	Negative	Positive very low	Negative	Positive	Yes	Lung infiltrate with cavitation	Cough, haemoptysis, weight loss
14	M, 33	Induced sputum	Negative	Positive very low	Invalid	Positive	Yes	Lung infiltrate with cavitation	Cough, weight loss
15	F, 26	Bronchial aspiration	Negative	Positive very low	Negative	Positive	Yes	Lung infiltrate with cavitation	Cough, haemoptysis
16	M, 44	Bronchial aspiration	Negative	Positive very low	Negative	Negative	Yes	Lung infiltrate with cavitation	Cough, weight loss, asthenia
17	M, 37	Sputum	Negative	Positive very low	Negative	Positive	No	Lung infiltrate with pleural effusion	Cough, HIV infection
18	M, 46	Bronchial aspirate	Negative	Positive very low	Negative	Positive	No	Lung infiltrate	Cough, haemoptysis, weight loss, asthenia
19	M, 47	Sputum	Negative	Positive very low	Negative	Positive	No	Lung infiltrate	Weight loss, asthenia
20	F, 36	Sputum	Negative	Positive very low	Negative	Positive	NA	NA	NA

NA, not available.

transmission potential. Indeed, the tuberculosis infectious dose is lower than ten bacilli, whereas microscopy sensitivity ranges from 5000 to 10 000 AFB/mL, suggesting that microscopy would miss many potentially infectious patients.

Our results suggest an added value of the Xpert MTB/RIF compared to smear microscopy to assess the transmission potential of tuberculosis patients because when negative, the smear microscopy will be negative too, confirming the rather low risk of contagiousness of the patient; and when positive, the semiquantitative result of the Xpert MTB/RIF can be used to distinguish patients with a definitively high risk of being contagious (when Xpert MTB/RIF is positive-high or medium) from those who are less contagious (when Xpert MTB/RIF is positive-low or very low). Our study identified six *M. tuberculosis* culture-confirmed patients with initial negative Xpert MTB/RIF. These patients had also an initial negative smear examination; interestingly, none of the consecutive smear examination of these patients was positive. Future studies including a larger number of samples and patients should confirm that a single negative PCR-based assay is synonymous to three negative smear examinations.

Smear status has historically been the initial microbiology test to address patients' infectiousness and was also used to aid health care decisions regarding patient isolation as well as contact investigations [5,7,8]. Relying on the correlation between the semiquantitative results of the Xpert MTB/RIF and smear microscopy results, our study supports the use of the molecular POCT both to initiate tuberculosis diagnosis and to assess patients' transmission potential, as patients with negative Xpert MTB/RIF can be considered not infectious or poorly infectious and do not warrant specific airborne isolation, whereas patients with positive Xpert MTB/RIF should be considered as potentially infectious, and thus airborne isolation should be maintained or immediately introduced if not yet in place. Conversely, smear examination should be discontinued for the diagnosis of *M. tuberculosis* infection and isolation decision; its use should now be limited to suspected infections with NTM that are not detected by the Xpert MTB/RIF. Thus, in our hospital, smear examinations are now only performed in batches once a day (open days) by a group of expert technicians in the mycobacteria laboratory, as smear examination remains useful to initiate the microbial diagnosis of infections due to NTM.

The additional cost for hospitals represented by an Xpert MTB/RIF-based strategy should be compared to the cost of excessive isolation due to the poor sensitivity and specificity of a smear-based strategy in a low-prevalence country. As reported by Lippincott *et al.* [23], an Xpert MTB/RIF-based strategy will improve the accuracy of decisions on airborne isolation, which would lead to a significant reduction of airborne isolation of patients with suspected tuberculosis.

A limitation of our analysis is that during the study period the Xpert MTB/RIF was mainly dedicated to patients with a high pretest probability of pulmonary tuberculosis or with suspected MDR tuberculosis in order to rapidly guide isolation decision. As a consequence, we report a high rate of culture-confirmed positive patients (29.3% of the study population) despite the fact that our study is conducted in a low-prevalence country. Thus, our data, obtained in a low endemic country (in contrast to previous studies on the same topic conducted in high-prevalence countries), suggest that the correlation between quantitative PCR and smear status can be generalized to any area and certainly to any population. Indeed, the sensitivity of smear examination may vary between different laboratories and geographic location, which is unlikely to be the case for nucleic acid-based methods. In any case, the definition of low- and high-prevalence countries based on geographical borders is seriously challenged by current population migrations, which might lead to the presence of high-risk groups in historically low-

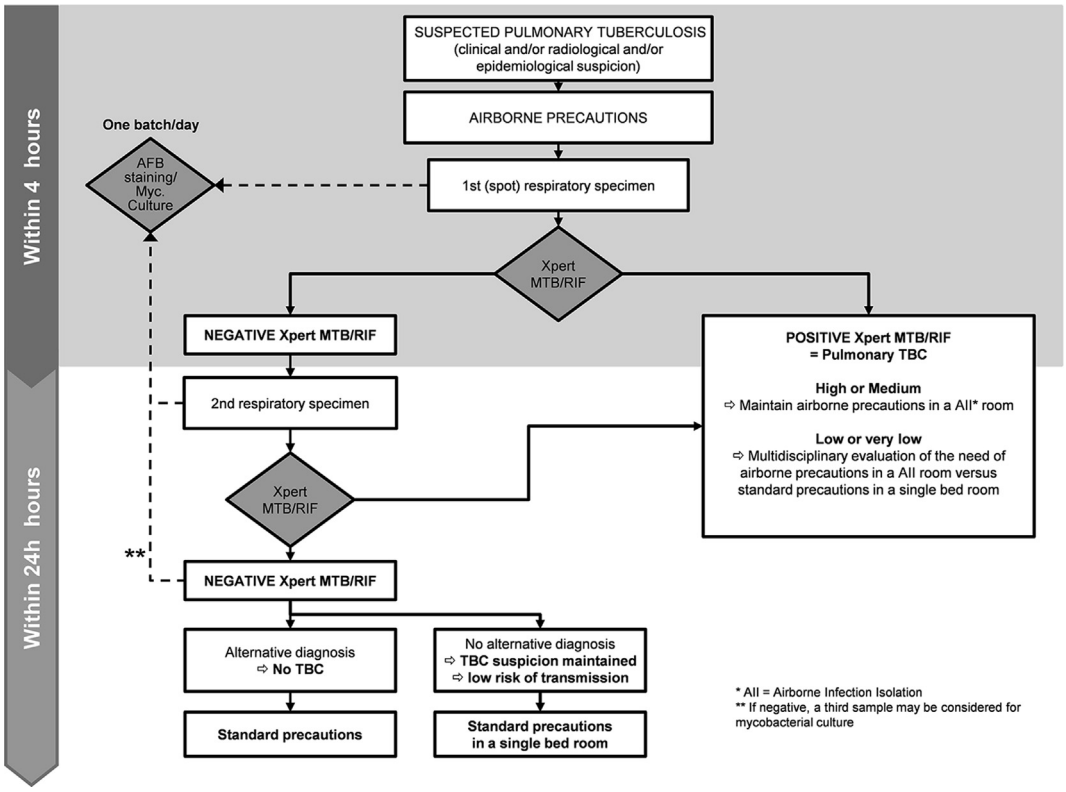

Fig. 2. Proposed work flow for pulmonary tuberculosis diagnosis based on molecular point-of-care test.

prevalence regions [24]. Another limitation of all the studies conducted so far on PCR-based diagnosis of pulmonary tuberculosis is the dependence on smear microscopy to address the transmission potential of infected patients. A breakthrough study would define the direct relationship between *M. tuberculosis* DNA load and patients' infectious potential.

On the basis of our study and on previous studies addressing the clinical performance and the cost-effectiveness of the Xpert MTB/RIF, and to follow the World Health Organization recommendations to use the Xpert MTB/RIF as first-line test to initiate pulmonary tuberculosis diagnosis [1], the diagnostic work flow of pulmonary tuberculosis has been adapted in our hospital (Fig. 2). Patients with a significant pretest probability of pulmonary tuberculosis (clinical presentation, epidemiology) are isolated. The microbial diagnostic is initiated by the Xpert MTB/RIF performed in the microbiology laboratory on spot sputum samples. A negative result does not rule out an infection but suggests a limited infectious potential of the patient. An individual evaluation by a pneumology specialist and/or an infectious disease specialist will then assess the need to maintain isolation and the need for a second Xpert MTB/RIF to increase the sensitivity of the analysis [2]. A third Xpert MTB/RIF has a limited impact on the sensitivity and NPV of the molecular POCT [2]. Nevertheless, an additional respiratory specimen might be collected for a third mycobacterial culture because culture remains the most sensitive assay and a third sample might help identify a few additional cases. This work flow takes advantage of the increased sensitivity and specificity of the Xpert MTB/RIF but also takes into consideration the fact that culture remains the most sensitive method.

Our study demonstrates that an Xpert MTB/RIF-based strategy is more efficient than smear-dependent strategies for both tuberculosis diagnosis and initial evaluation of patient infectiousness.

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Transparency Declaration

All authors report no conflicts of interest relevant to this article.

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