Xpert MTB/RIF as add-on test to microscopy in a low tuberculosis incidence setting

To the Editor:

Tuberculosis (TB) is a major public health concern worldwide. Early diagnosis, universal access to drug susceptibility testing and prompt initiation of treatment are key elements of the End TB strategy, and should therefore be implemented in all settings [1–5]. In order to reach TB elimination goals, the World Health Organization (WHO) currently recommends the use of a rapid molecular test, Xpert MTB/Rif (Xpert; Cepheid, Sunnyvale, CA, USA), as initial diagnostic tool when TB is suspected [6–8]. Although the excellent performance of this test in high TB burden areas is already supported by strong scientific evidence, few studies have been conducted so far to assess its impact on the diagnostic work-up of TB in low burden settings, sometimes with contrasting findings [7, 9, 10–12]. For example, according to Sohn *et al.* [10], Xpert testing might have limited impact in the ambulatory setting in Canada, owing to lower sensitivity and limited potential to expedite diagnosis beyond what is achieved with the existing, well-performing diagnostic algorithm.

We conducted a retrospective cohort study to assess the role of Xpert as add-on test to microscopy for TB diagnosis in a large metropolitan hospital of a medium-sized city of Northern Italy where the cumulative incidence of notified TB was 14.3 per 100 000 in 2015 (*i.e.* approximately two-fold the national rate). The study was conducted in the units of infectious diseases, respiratory diseases and respiratory endoscopy. Our primary objective was to calculate the time to treatment initiation with and without Xpert testing, to assess the impact of this tool on clinical decision-making in a plausible context. We also aimed to determine the positive and negative predictive values (PPV and NPV) of Xpert compared to smear microscopy against the reference standard (culture), in patients with presumptive TB, *i.e.* those for whom clinicians requested laboratory tests to detect *M. tuberculosis*. All patients evaluated at study sites who had at least one biological sample investigated for TB between March 1, 2016 and June 30, 2017 were included. Sociodemographic, clinical and microbiological data were extracted from digital and paper clinical charts, and from laboratory archives. We defined as pulmonary TB cases all subjects with a positive culture for *M. tuberculosis* from a respiratory sample (*i.e.* sputum, bronchial aspirate, bronchoalveolar lavage). All anonymised data were retrospectively retrieved. Since our study had no impact on the patients' clinical management, ethical clearance was not required.

A total of 1201 cases were included in the analysis, that contributed with 1067 respiratory samples and 205 non-respiratory samples. Among 1067 patients with pulmonary disease, 79 (7.4%) had microbiologically confirmed pulmonary TB. Only 26.3% (282/1067) of patients had at least one sample tested with Xpert: most of them were from infectious diseases unit (228/270, 84.4%), compared to as few as 6.8% (54/797) of patients from either the respiratory diseases or respiratory endoscopy units ($p<0.001$).

Among 282 respiratory samples, Xpert was positive in 52/65 culture-positive cases and negative in 214/227 culture-negative cases. Sensitivity, specificity, PPV and NPV were 80% (95% CI 70.3–89.7%), 98.6% (95% CI 96.1–100%), 94.5% (95% CI 91.5–97.5%), and 94.3% (95% CI 92.8–95.8%), respectively.

Among 70 non-respiratory samples, Xpert was positive in 18/23 culture-positive cases and negative in 43/47 culture-negative cases. Sensitivity, specificity, PPV and NPV were 78.3% (95% CI 61.5–95.1%), 91.5% (95% CI 83.5–99.5%), 81.8% (95% CI 73.6–90%), and 89.6% (95% CI 85.2–94%) respectively.

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Among 65 culture-confirmed PTB cases with available microscopy and Xpert results, 43 (66.2%) were smear-positive Xpert-positive, nine (13.8%) smear-negative Xpert-positive, 13 (20%) smear-negative Xpert-negative. Xpert increased the proportion of cases diagnosed with a rapid test by 21% (9/43). As expected, there were no smear-positive Xpert-negative tests among confirmed TB cases. The mean±SD time lag between sample collection and treatment initiation was 1.6±3.4 days for 47 smear-positive Xpert-positive, 1.8±2.1 days for nine smear-negative Xpert-positive, and 8.7±8.8 days for 13 smear-negative Xpert-negative patients ($p<0.0001$ for the difference between the latter group and each of the two other groups) (table 1). The mean time to treatment initiation in microscopy-negative Xpert-negative cases remained shorter than the time needed for culture to become positive (mean±SD of 17±16 days), showing that treatment was usually initiated empirically.

Among 205 patients with extrapulmonary disease, 38 (18.5%) were culture-confirmed. Of the 23 individuals for whom both microscopy and Xpert results were available, eight (34.8%) were smear-positive, while 10 (43.5%) were smear-negative and Xpert-positive: Xpert led to a 125% gain in the proportion of extrapulmonary TB cases diagnosed with a rapid test. The mean±SD time lag between sample collection and treatment initiation was 3.0±5.4 days for eight smear-positive Xpert-positive, 1.5±2.0 days for 10 smear-negative Xpert-positive, and 3.6±6.9 days for five smear-negative Xpert-negative patients (no statistically significant differences at an alpha level of 0.05 using a parametric test).

There were three cases of multidrug-resistant TB (2.9%), all correctly identified by Xpert.

In low TB incidence, high resource countries the use of Xpert in clinical practice is not determined by the procurement capacity, but rather by the evidence of cost–benefit analyses. In agreement with previous studies [11], we found 14% additional rapid diagnoses of pulmonary TB with Xpert compared to microscopy, allowing treatment to commence about 7 days earlier. The gain was much larger for extrapulmonary TB cases (+125%). In a German hospital, implementing Xpert as an add-on test in TB suspects resulted in cost savings [13]. Others had previously shown that Xpert could greatly reduce the frequency and impact of unnecessary empirical treatment and contact investigation [14]. Moreover, according to a study conducted in the USA, a single negative Xpert result is predictive of the absence of smear-positive/culture-positive tuberculosis with an NPV of 99.7%, suggesting a role in removing patients from an airborne infection isolation room [15].

Xpert use was limited to about a quarter of presumptive TB cases, with pulmonary care units making very low use of the test. Even at the infectious diseases unit, Xpert was ordered in less than 50% of presumptive extrapulmonary TB cases, despite the proven benefits of this tool. Xpert scale-up will require intensive stewardship on TB diagnostic practices in all units where patients with presumptive TB are likely to be evaluated.

TABLE 1 Mean time to treatment initiation in patients included in the study (with and without culture-confirmed tuberculosis (TB)), classified by smear microscopy and Xpert MTB/RIF results

Category	N	Time to treatment initiation days		p-value
		Mean±SD	95% CI	
Patients				
Total	1201			
Providing respiratory sample only	996			
Providing non-respiratory sample only	134			
Providing both respiratory and non-respiratory samples	71			
Culture-confirmed TB cases	102			
Pulmonary only	64			
Extrapulmonary only	23			
Pulmonary and extrapulmonary	15			
Pulmonary TB cases[#]	65			
Smear-positive/Xpert-positive	43	1.6±3.4	(0.58; 2.62)	<0.0001[¶]
Smear-negative/Xpert-positive	9	1.8±2.1	(0.43; 3.17)	<0.0001[¶]
Smear-negative/Xpert-negative	13	8.7±8.8	(3.92; 13.48)	
Extrapulmonary TB cases[#]	23			
Smear-positive/Xpert-positive	8	3.0±5.4	(−0.74; 6.74)	0.8[¶]
Smear-negative/Xpert-positive	10	1.5±2.0	(0.26; 2.74)	0.3[¶]
Smear-negative/Xpert-negative	5	3.6±6.9	(1.36; 5.84)	

[#]: with information on Xpert and time to treatment; [¶]: two-tailed; compared with smear-negative/Xpert-negative.

Our research has limitations: a low proportion of cases was investigated by Xpert, so we cannot exclude biases in the selection of samples that were submitted for testing. Moreover, we did not measure important outcomes, such as the effect of Xpert results on empirical TB treatment and on isolation practices, and we did not perform a cost–benefit analysis.

In conclusion, we provide an estimate of the benefits of Xpert compared to microscopy in the diagnosis of pulmonary and extrapulmonary TB in a low incidence setting. According to our study, Xpert plays an important role in guiding the clinicians' decision towards a prompt initiation of TB therapy even in a low burden setting, thus allowing for a greater number of potentially infectious patients to be rapidly put on treatment while waiting for culture results.

These data favour the use of Xpert as an alternative, rather than as add-on test to microscopy, in agreement with WHO recommendations [6].

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