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Relevance of Xpert MTB/RIF for detection of meningeal and pericardial tuberculosis in a context of high HIV infection prevalence in Abidjan, Côte d'Ivoire

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Abstract

Côte d'Ivoire is considered as a high burden tuberculosis (TB) country. Indeed, cases of extrapulmonary TB (EPTB), are growing because of the HIV/AIDS pandemic, in Côte d'Ivoire where the prevalence of HIV infection is among the highest in West Africa. The current study aimed to assess the relevance of Xpert MTB/RIF (Xpert) for the diagnosis of EPTB in Abidjan, Côte d'Ivoire. The rate of positivity for each extrapulmonary specimen and the prevalence of rifampicin resistant (RR) EPTB were determined. It was shown that the Xpert method improved the EPTB diagnosis particularly when compared to AFB smear microscopy. Indeed, among the specimen provided by 805 patients, 8.9% (77/866) were positive with the Xpert MTB/RIF versus 2.6% for AFB smear microscopy. Even if higher rates of positivity were found for pus and lymph node aspirates, this test particularly allowed the detection of severe forms such as meningitis and pericarditis tuberculosis. Indeed, among positive samples, 17 (22.0%) and 06 (7.9%) were cerebrospinal and pericardial fluids respectively, accounting both for about one third of the total number of EPTB cases during this study. Finally, this assay could be used as a primary test for most of the type of samples even if its sensitivity was poor in specimens like blood or bone marrow.

Keywords: TB, Diagnosis, Xpert MTB/RIF (Xpert), Côte d'Ivoire

Résumé

La Côte d'Ivoire est considérée comme un pays à forte charge de tuberculose. En effet, les cas de TB extrapulmonaire (EPTB), sont en augmentation à cause de la pandémie de VIH/SIDA, en Côte d'Ivoire où la prévalence de l'infection par le VIH est parmi les plus élevées d'Afrique de l'Ouest. La présente étude visait à évaluer la pertinence de Xpert MTB / RIF (Xpert) pour le diagnostic de l'EPTB à Abidjan, en Côte d'Ivoire. Le taux de positivité pour chaque échantillon extrapulmonaire et la prévalence de l'EPTB résistant à la rifampicine (RR) ont été déterminés. Il a été montré que la méthode Xpert améliorait le diagnostic de l'EPTB en particulier par rapport à l'examen microscopique des frottis. En effet, parmi les échantillons fournis par 805 patients, 8,9% (77/866) étaient positifs avec le Xpert MTB/RIF contre 2,6% pour l'examen microscopique des frottis. Même si des taux de positivité plus élevés ont été trouvés pour les pus et les ganglions pulmonaires, ce test a notamment permis la détection de formes sévères telles que la méningite et la péricardite tuberculeuse. En effet, parmi les échantillons positifs, 17 (22,0%) et 06 (7,9%) étaient des liquides céphalorachidiens et péricardiques respectivement, représentant tous les deux environ un tiers du nombre total de cas d'EPTB au cours de cette étude. Enfin, cette technique pourrait être utilisé comme test initial pour la plupart des types d'échantillons même si sa sensibilité était faible dans des échantillons comme le sang ou la moelle osseuse

Mots-clés: TB, Diagnostic, Xpert MTB/RIF(Xpert), Côte d'Ivoire .

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Introduction

Tuberculosis (TB) remains one of the leading causes of death due to a single infectious disease with about 10 million people newly infected in 2017 and 1.3 million death (World Health Organization 2018). There are two types of clinical manifestation of TB, which are pulmonary TB (PTB) and extrapulmonary TB (EPTB). According to the World Health Organization (WHO), EPTB refers to any bacteriologically confirmed or clinically diagnosed case of tuberculosis (TB) involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges, etc. (World Health Organization 2013b). It has been hypothesized that the ongoing pandemic of HIV/AIDS could increase the prevalence of EPTB as several authors showed an association between EPTB and HIV (Fanosie et al. 2016; Mohammed, Assefa, and Mengistie 2018; Naing et al. 2013). In its last report also, the WHO indicated that EPTB represented 14% of the 6.4 million incident cases that were notified in 2017 (World Health Organization 2018). However, one of the main challenges for diagnosis is that more EPTB are paucibacillary. Therefore, the diagnosis by the conventional method of smear microscopy is not very sensitive. Moreover, the sensitive methods of mycobacterial culture and histological examination are not widely available in resource-limited conditions (Kohli et al. 2018). For these reasons, the WHO published an updated guidance on the use of Xpert MTB/RIF, an automated diagnostic test for the detection of *Mycobacterium tuberculosis* complex (MTBc) for PTB in adults. The WHO also provided an additional guidance on the use of this test for childhood TB and EPTB (World Health Organization 2013a). With a population of around 24 million inhabitants, the incidence of TB in Côte d'Ivoire was estimated to 148 per 100,000 inhabitants in 2017 (Anon 2018b). Moreover, according to the UNAIDS, the prevalence of HIV infection Côte d'Ivoire in 2017 was estimated to 2.8% (Anon 2018a; UNAIDS 2018). This prevalence is among the highest of the West African region. Therefore, studies were conducted on EPTB in Côte d'Ivoire but the diagnosis was mainly based on clinical, radiological and/or histological evidence (Anzouan-Kacou et al. 2008; Darie, Cautoclaud, and Morlain 1990; Domoua et al. 2007; Guié et al. 2008; Niangué-Beugré et al. 1999; Ossalé Abacka et al. 2018; Varango et al. 1998). One of the reasons is that Mycobacterium culture methods are not widely available in Côte d'Ivoire. Indeed, only two laboratories are performing culture for Mycobacterium species in Côte d'Ivoire. Meanwhile, Xpert MTB/RIF is currently being implemented in all laboratories at the intermediate level mostly for PTB diagnosis with well-defined targets (children, people living with HIV/AIDS or previously treated patients). This method could thus be used as an alternative to the method using Mycobacterium culture for EPTB diagnosis. Indeed, a meta-analysis has been conducted to evaluate the Xpert MTB/RIF performance for EPTB diagnosis with culture as a gold standard. It was globally found that when testing a range of nonrespiratory sample types from both adults and children suspected of having EPTB, the Xpert MTB/RIF had an overall sensitivity of 81.3% and specificity of 99.8% (Detjen et al. 2015; Steigart et al 2014). Finally, it was concluded that even if the Xpert MTB/RIF sensitivity varies across different extrapulmonary specimens, its specificity remains high. Therefore, in people presumed to have extrapulmonary TB, Xpert MTB/RIF may be helpful in confirming the diagnosis (Kohli et al. 2018).The current study aimed to assess the relevance of Xpert for the diagnosis of EPTB in Abidjan, Côte d'Ivoire. Specifically, the rate of positivity for each extrapulmonary specimen and the prevalence of multidrug resistant (MDR) EPTB have been determined.

Materials and Methods

Study design

This retrospective study was conducted at the Center for Diagnostic and Research on AIDS and other infectious diseases (CeDReS), located at the University Hospital of Treichville, Abidjan, Côte d'Ivoire. Data from any patients suspected of having an EPTB, whatever the location, and whose samples were received at the CeDReS from

March 2015 to July 2018 were included.

Description of the Xpert MTB/RIF assay

Xpert MTB/RIF (Cepheid Inc., CA, USA) was performed according to the manufacturer's instructions. This test uses molecular probes targeting five overlapping regions of the *M. tuberculosis rpoB* gene. Theses probes were designed to detect mutations in the codons 507 to 511 (Probe A), 511 to 518 (Probe B), 518 to 523 (Probe C), 523 to 529 (Probe D), and 529 to 533 (Probe E). For the test, 1 mL of each sample is added to an equal volume of the sample reagent. These 2ml of sample mixture are added directly to the Xpert MTB/RIF cartridge. The cartridge is then loaded into the GeneXpert platform, an automated real time polymerase chain reaction instrument, as per manufacturer's instructions. At the end of the test, and in case of positivity, the instrument displays: "MTB complex detected" with the level of positivity ("High", "Medium", "Low" or "Very Low". In this case, resistance to rifampicin is also indicated as "Rif resistance detected" or "Rif resistance not detected". In the absence of detection of the MTB complex, the result displayed by the instrument is "MTB complex not detected" Assays were performed using the version G4 on the GeneXpert platform (Cepheid, Sunnyvale, CA, USA). Data of all the subjects tested for EPTB with the Xpert MTB/RIF were retrieved from the laboratory information system and from the database of the GeneXpert instruments.

Smear microscopy

Acid Fast Bacilli (AFB) smear microscopy was performed by using fluorescent staining. Briefly, a thin smear was realized on each slide, allowed to air dry, and then heat-fixed. The staining process started by slide flooding with auramine for 15 minutes. The reagent was washed off with distilled water and decolorized for 3 minutes with an acid-alcohol mix. Slides were thoroughly rinsed with distilled water and finally re-stained with potassium permanganate for 1 minute before a last wash with distilled water and air drying. Slides were examined under fluorescent microscopy at magnification x200. Results were interpreted according to the Union/WHO scale. Smears were declared negative if no AFB were observed in 30 fields (1 length), scanty from 1 to 29 AFB/1 length, 1+ from 30 to 299 AFB/1 length, 2+ from 10 to 100 AFB/ 1 field and 3+ if more than 100 AFB were observed in one field.

Data analyses

Data entry and analysis were performed with Epi Info 7.2.1.0 software (Centers for Disease Control and Prevention (CDC).). In order to analyze patient characteristics, descriptive statistics were used. Confidence intervals for the absolute difference and ratios between the two tests were calculated.by using the McNemar's test. This test has been used to determine if there were differences in rates of positivity between AFB microscopy and Xpert MTB/RIF assay. It is a 2x2 cross classification of matched responses to a dichotomous item. The McNemar test is a non-parametric statistical test, meaning that it can be used with data sets and samples that are not normally distributed.

Results

Sociodemographic characteristics of the patients

During the period of study, data from 805 patients were collected. These patients provided 866 specimens including 612 for which AFB smear microscopy was performed. The age of patients ranged from 0 to 94 years with 48 (6.0%) children (<15 years) and 462 (57.7%) aged between 15 to 45 years. The median age was 41 years and the majority of patients were male (51.9%; sex ratio: 1.08). Among patients admitted at the University Hospital, the majority were from two departments that are infectious diseases (286; 35.5%), followed by Cardiology (139; 17.3%), when 171 (21.2%) were outpatients (Table 1).

Table 1: Patients baseline characteristics

Characteristics		% [CI 95%]
Age		
Median (range)	41 (0 – 94)	
< 15 years	48	6.0 [4.5-7.8]
15-45 years	462	57.4 [54.0-60.8]
> 45 years	295	36.6 [33.4-40.0]
Sex		
Male	418	51.9 [48.5-55.4]
Female	387	48.4 [44.6-51.5]
Department of origin		
Cardiology	139	17.3 [14.8-20.0]
Infectious diseases	286	35.5 [32.3-38.9]
Medicine	95	11.8 [9.8-55.6]
Pediatric	15	1.9 [1.1-3.1]
Pneumology	57	7.1 [5.5-9.1]
Other departments	16	2.0 [1.2-3.2]
PLWHA care centers	26	3.2 [2.2-4.7]
Outpatients	171	21.2 [18.6-24.2])

Most of the specimen consisted in cerebrospinal, pleural, ascitic and pericardial fluids with 284 (32.8%), 158 (18.2%), 122 (14.6%) and 112 (12.9%) samples respectively (Table 2).

Table 2: Results of Xpert MTB/RIF in each type of specimen

Nature of specimen	Total number	*Number of positive samples (rate %)*	[CI 95%] of rate
Bone & joint aspirate	7	1 (14.3%)	[2.6-51.3]
Peritoneal fluid	125	10 (8.0%)	[4.4-14.1]
Lymph node aspirate	23	11 (42.3%)	[29.2-67.0]
Cerebrospinal fluid	284	17 (6.0%)	[3.8-9.4]
Blood marrow	32	0 (0.0%)	[0.0-10.7]
Pericardial fluid	112	6 (5.4%)	[2.5-11.2]
Pleural fluid	158	10 (6.3%)	[35-11.3]
Pus	38	20 (52.6%)	[37.3-67.5]
Blood	19	0 (0.0%)	[0.0-7.8]
Stool	19	1 (5.3%)	[0.9-24.6]
Urine	46	1 (2.2%)	[0.4-11.3]
TOTAL	866	77 (8.9%)	[7.2-11.0]

Rifampicin resistance detection using Xpert MTB/RIF assay

MTBc was detected in 77 specimens, leading to an overall positivity rate of 8.9% for Xpert MTB/RIF (Figure 1).

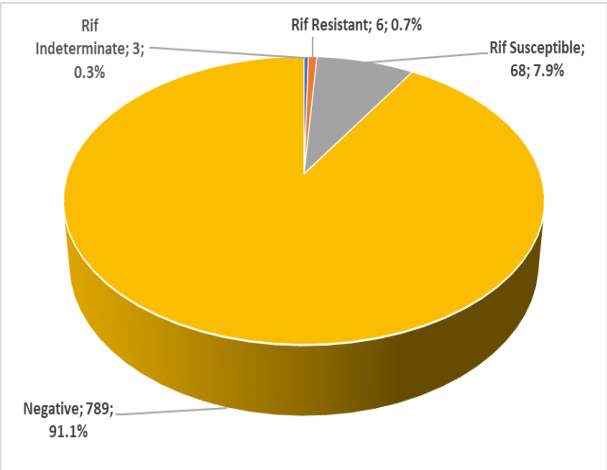

Figure 1: Global positivity rate for Xpert MTB/Rif
Legend: Results of the Xpert MTB/Rif assay for the detection of Mycobacterium tuberculosis complex (MTB). In case of positivity, susceptibility to Rifampicin (Rif) is assessed with three possible (3) options: Rif Susceptible, Rif Resistant or Rif Indeterminate.

Mutations related to rifampicin resistance was found for 6 out to 74 samples, suggesting a rifampicin resistance rate of 8.1% in positive samples when excepting those with indeterminate results. The highest rates were observed for diverse pus and lymph node aspirates, while no specimen of bone marrow or blood was found positive. Also, 17 CSF out of 284 (6.0%) and six pericardial fluid out of 112 (5.4%) were positive (Figure 2). It was observed that, the level of positivity with the Xpert MTB/RIF was low for most of the samples, except for pleural fluids and lymph node aspirates.

Smear microscopy

Considering AFB microscopy, out of 612 samples tested, 16 (2.6%) were positive (Figure 3).Five types of samples were found positive for microscopy (pleural, peritoneal and cerebrospinal fluids, lymph node aspirate and stool). Among the samples found positive for

smear microscopy, 3, 9, 2 and 2 were found scanty, 1+, 2+ and 3+ respectively. The two samples found 3+ were one cerebrospinal and one pleural fluid (Figure 4).

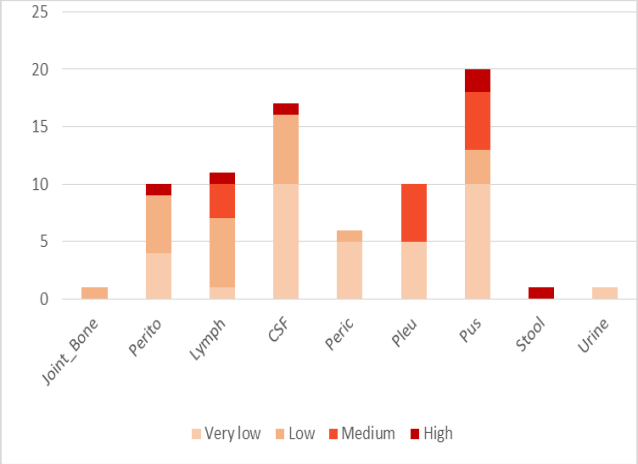

Figure 2: Level of positivity of Xpert MTB/Rif and type of specimen

Legend: Joint_Bone: joint and bone aspirate; Perito: peritoneal fluid; Lymph: lymph node aspirate; CSF: cerebrospinal fluid; Peric: pericardial fluid; Pleu: pleural fluid

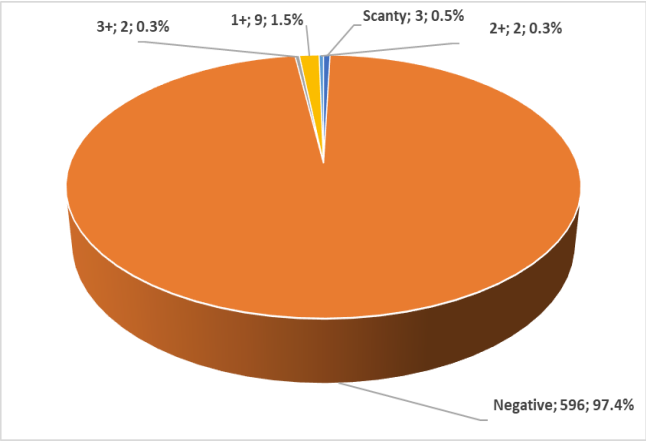

Figure 3: Global positivity rate for Microscopy

Legend: Result of acid-fast bacilli (AFB) microscopy after fluorescent (auramine) staining. Interpretation according to the Union/WHO scale. Smears were declared negative if no AFB were observed in 30 fields (1 length), scanty from 1 to 29 AFB/1 length, 1+ from 30 to 299 AFB/1 length, 2+ from 10 to 100 AFB/ 1 field and 3+ if more than 100 AFB were observed in one field.

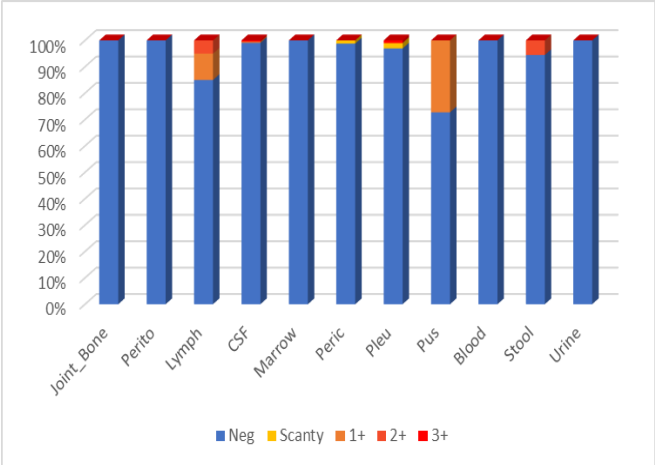

Figure 4: Level of positivity of AFB microscopy and type of specimen

Comparative analysis of both smear microscopy and Xpert MTB/RIF

In these samples tested for microscopy, 54 were positive for Xpert MTB/RIF, leading to higher positivity rate for Xpert MTB/RIF than AFB microscopy (8.8% vs 2.6%). Application of McNemar test gave an absolute difference of 6.2% (95% CI [4.0%-8.4%]) and ratio Xpert MTB/RIF of 3.4 (95% CI[2.2-5.2]). Xpert MTB/RIF and AFB microscopy allowed to obtain different positivity rates according to specimen types (Figure 5).

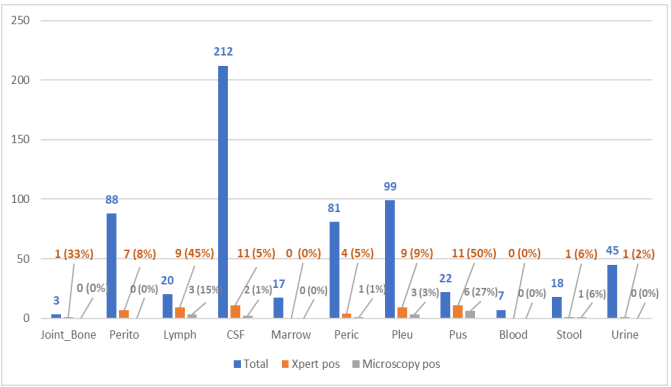

Figure 5: Xpert MTB/RIF and AFB microscopy positivity levels in the different types of specimens
Total: Total number of specimens, Xpert Pos: Positive for Xpert MTB/RIF, Microscopy pos: Positive for AFP microscopy

Thus, blood and bone marrow had no positive samples for both tests and for stools, one sample was positive for both assays. Except these cases, Xpert MTB/RIF positivity rates were higher, than those obtained with AFB microscopy for all the other types of specimens. Among those, considering specimens with big number of samples, higher differences were observed for peritoneal (8% vs 0%), cerebrospinal (5% vs 1%), pericardic (5% vs 1%) or pleural (9% vs 3%) fluids.

Discussion

Since the first evaluation of Xpert MTB/RIF for EPTB by Hilleman et al. in 2011 (Hillemann et al. 2011), many other studies were undertaken. A first systematic review was conducted in 2014 and its conclusions allowed the World Health Organization to recommend Xpert MTB/RIF over conventional tests for diagnosis of TB in lymph nodes and other tissues, and as the preferred initial test for diagnosis of TB meningitis (Denkinger et al. 2014). Moreover, one of the objective of a recent and exhaustive meta-analysis that was performed in 2018 and included 66 studies was to determine the diagnostic accuracy of Xpert MTB/RIF for the detection of EPTB by site of disease in people suspected of having EPTB (Kohli et al. 2018). The results exhibited that this method has been largely evaluated and demonstrated its relevance in the diagnosis of EPTB with a high sensitivity, particularly for TB lymphadenitis and TB meningitis but a lower sensitivity for pleural TB. Moreover, the specificity was very high. Finally, it was suggested that Xpert MTB/RIF could be a replacement for standard practice. The current study was then conducted in this perspective to assess the relevance of a routine use of this method in the context of low availability of culture which is the gold standard.

Regarding sociodemographic characteristics, the number of children suspected to have EPTB was low and the median age was quite high. Indeed, according the National Tuberculosis Program, patients between 15 to 45 years of age accounted for more than 69% of incident cases in the country from 2014 to 2017 (unpublished data). Also, Ossalé Abacka mentioned in his study in Ivory Coast that patients at an advanced age were more affected by EPTB than younger ones (Ossalé Abacka et al. 2018).

This study showed that MTBc was detected in various extrapulmonary locations except for blood and bone marrow certainly because of its poor sensitivity in this case (Pohl et al. 2016). An analysis of EPTB cases confirmed by the Xpert MTB/RIF revealed that the rate of positivity was higher in patients suspected of having TB lymphadenitis, a situation that was also found by other investigators (Kohli et al. 2018; Metaferia et al. 2018), followed by bone and joint aspirate, peritoneal and pleural fluids. In addition to the previous sites listed, studies conducted in Ivory Coast reported other locations such as cutaneous or cervical TB (Darie et al. 1990; Guié et al. 2008). It is useful to notice that MTBc was detected once in a stool but this case accounted for pulmonary tuberculosis as sputum can be swallowed by patients and then be transferred to the gastrointestinal tract (Cordova et al. 2010).

A large number of CSF and pericardial fluids were analyzed with around 6% rate of positivity. These results mean that TB meningitis was found as the most frequent EBTB and both of meningitis and pericarditis TB accounted for about one third (29.9%) of the total EPTB cases during this study. Then, a special focus must be made on meningeal and pericardial locations of TB, which are the most severe forms of EPTB with high rates of morbidity and mortality (Golden and Vikram 2005). In terms of performance, the overall positivity rate was higher for Xpert MTB/RIF than AFB microscopy, meaning that the molecular method was (3 times) more sensitive as expected and previously reported (Alvarez-Uria et al. 2012; Li et al. 2017; Metaferia et al. 2018; Tortoli et al. 2012).

While considering the types of specimens, an improvement of the sensitivity rates was observed for all of them, with the exception of blood and bone marrow for which both assays were negative for all the samples. However, the sensitivity of this method can be improved by optimizing the quality of the samples. For example a concentration step for CSF increases Xpert MTB/RIF sensitivity with unchanged specificity as reported by Denkiger et al. (Denkinger et al. 2014). Also, a blood lysis-centrifugation approach has been developed and can improve the detection of MTBc in blood (Banada, Koshy, and Alland 2013). Moreover, the level of positivity for Xpert MTB/RIF was low for most of the extrapulmonary samples except for lymph node aspirates and pus, confirming that EPTBs are paucibacillary (Lee 2015). However, and surprisingly despite the low rate of positivity of microscopy, just a few positive samples displayed rare AFB (scanty) when most of them were at least 1+ positivity with this method.

Finally, among the 74 samples with an interpretable result, the rate of rifampicin resistance was 8.1%. This value was high when compared to the rate observed during the last survey conducting conducted in Ivory Coast in 2016, which was established to 4.6% in new cases and 22.0% in previously treated patients (N'Guessan et al. 2018). It could thus be hypothesized that some of the patients should have been previously treated for tuberculosis. Globally, the Xpert MTB/RIF assay was more sensitive than microscopy for almost all types of extrapulmonary specimens that have been tested. Therefore, it can be recommended for the diagnosis of EPTB. However, this is not applicable for blood and bone marrow that should be pretreated.

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Conflict of interest

Authors have no competing interests to declare.

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