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Significant Improvement in Tuberculosis Diagnosis by Detection of the Wall Lipoarabinomannan from *Mycobacterium tuberculosis* in Central African Republic (CAR)

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Abstract

Background and Objective: Tuberculosis is one of the leading causes of morbi-mortality, especially in developing countries, due to delayed diagnosis and management. The goal of this study is to assess the contribution of lipoarabinomannan (LAM) in improving tuberculosis (TB) diagnosis in the Central African Republic (C.A.R.). **Methods:** We conducted a retrospective study at the Regional University Hospital of Bria. The records of patients hospitalized, tested by Determine® TB LAM Ag (Alere, Medical Co, LTD, Chiba, Japan) immunochromatographic test for the detection of LAM in urine, associated or not with acid-fast bacilli (AFB) research by Ziehl-Neelsen stain, were selected from August to October 2020. **Results:** During this study, 152 files were selected. Among them, there were 50.0% of children aged 14 or less (≤14 years: 33.6% + 16.4%) and 50.0% of adults represented. Patients living in the displaced person camp represented a larger group (65.1%) than those in the other 2 sites. There were seventy-four patients (*i.e.* 48.7%) who did not benefit from screening for AFB. For the other seventy-eight (*i.e.* 51.3%), there were 17.1% positive results for the search of AFB. However, among the 152 patients, there was a positive HIV serology in 30.9% of cases (*i.e.* 47 out of 152) and a positive Determine® TB LAM Ag in 38.2% of cases (*i.e.* 58 out

of 152). It appears that Determine® TB LAM Ag was significantly more able to diagnose tuberculosis than AFB ($p < 0.003$). The 58 patients diagnosed with TB LAM included 20 children who could not provide sputum and HIV-infected patients ($p < 0.03$). **Conclusion:** The results of this study showed that the microscopy for AFB made it possible to make the diagnosis of tuberculosis in 17.1% of patients against 38.2% for the Alere Determine® TB LAM Ag test. This result highlights the need for routine use of LAM detection to improve the diagnosis of tuberculosis. The conduct of a subsequent study combining Xpert MTB/RIF would improve the diagnosis of tuberculosis using all 3 tests.

Keywords

Tuberculosis Diagnosis, TB-LAM, Acid-Fast Bacilli Microscopy, HIV/AIDS, Central African Republic

1. Introduction

According to the World Health Organization (WHO), about a quarter of the world's population is infected by *M. tuberculosis* and 10 million people contracted tuberculosis worldwide in 2018. The global average incidence of tuberculosis is around 130 new cases per 100,000 inhabitants. Deaths from tuberculosis have risen to 1.2 million, to which is added 0.25 million deaths among people living with Human Immunodeficiency Virus (HIV). These deaths make tuberculosis one of the top 10 causes of death worldwide and the leading cause of death from an infectious agent [1] [2]. Tuberculosis is a disease of poverty. People affected by tuberculosis face economic distress, vulnerability, marginalization, stigmatization and discrimination [1] [2]. Tuberculosis patients share these conditions with those infected with HIV; HIV is one of the main factors favoring the acquisition of tuberculosis [3]. The majority of patients live in developing countries, particularly in Africa, a continent sheltering 25% of the global number of tuberculosis patients [4] [5]. While progress has been made with the WHO strategy for the elimination of tuberculosis, efforts are still needed in order to meet the global targets for tuberculosis [6] [7] [8] [9].

One of the factors limiting this fight against tuberculosis is linked to the diagnosis, the patient's gateway to the cascade of care. Mycobacteria culture, the gold standard for diagnosis, is not sufficiently accessible in developing countries, where the diagnosis is based on screening using Zeihl-Neeslen staining. Many clinically obvious tuberculosis cases are microscopically negative, particularly in HIV + people [10]. Therefore, WHO has spurred the development of rapid or relatively rapid tests. Among these tests, Determine TB-LAM Ag, a rapid test that detects LAM, a glycopeptide of the mycobacteria wall, soluble and excreted in the urine [11], is of particular interest. LAM has high precision [12], and is complementary with GeneXpert [13] in the diagnosis of tuberculosis in HIV-infected

patients.

These diagnosis difficulties of tuberculosis are more pronounced in C.A.R.. C.A.R. is a resource-limited country; one of the 30 countries with a high burden of tuberculosis in the world: 540 cases for 100,000 inhabitants in 2018 [2]; 7900 deaths; 6600 cases of HIV/tuberculosis (TB) co-infections and 180 cases of multidrug-resistant tuberculosis [14]. The performance of the Tuberculosis Control Program (TCP) remained very poor with a therapeutic coverage of only 43%. These data mean there is a total of 14,000 undiagnosed or untreated tuberculosis cases. One of the reasons identified for this poor performance of the TCP was an insufficient laboratory network, with inadequate biological diagnostic resources, despite 80 functional diagnosis and treatment centers and around 20 GeneXpert® devices (Cepheid, Sunnyvale, USA) across the country. Therefore, the identification of other methods to improve the diagnosis of tuberculosis seems essential. The use of the Determine® TB LAM Ag test appears to be a tool to improve diagnostic accessibility. That is why this study's goal is to assess the contribution of Determine® TB LAM Ag in the improvement of tuberculosis diagnosis in C.A.R.

2. Methods

Study settings: It was a retrospective study that took place from August 1st to October 31st, 2020, at the Regional University Hospital of Bria. This hospital is a reference public health establishment in the Health Region 5 in C.A.R. It is located in the zone affected by military conflicts since 2013. These conflicts have caused massive population displacement regrouping in overcrowded camps. These conditions are favorable to the transmission of *M. Tuberculosis*. The hospital benefits from the support of 2 Non-Governmental Organizations (N.G.O): Doctors without Borders (DWB France) and International Medical Corps (IMC), allowing the supply of the Determine® TB LAM Ag test (Alere, Medical Co, LTD, Chiba, Japan) in the laboratory.

Study population: The study involved patients hospitalized for tuberculosis suspicion at the Regional University Hospital of Bria during the period of April 1st, 2019 to July 31st, 2020 (*i.e.* 15 months). Were included in the study, patients who benefited for the diagnosis of tuberculosis from the Determine® TB LAM Ag test (Alere, Medical Co, LTD, Chiba, Japan) associated or not with the microscopic search for mycobacteria by the Ziehl-Neelsen stain.

Data collection: A pre-established individual survey sheet was used to collect data from patients' medical records. This sheet collected socio-demographic (age, sex, origin), clinical and biological (results of TB LAM, AFB research, and HIV serology) data.

Laboratory analysis of the study: Three laboratory analyses were taken into account. Determine® TB LAM Ag (Alere, Medical Co, LTD, Chiba, Japan) is an immunochromatographic test for the qualitative detection by immunocapture of LAM antigen of Mycobacteria. LAM is a 17.5 kD glycolipid antigen from the

wall of mycobacteria [11] [15]. The detection antibody is labeled by conjugation to colloidal gold particles in human urine. The detection of AFB in sputum specimens was performed by Zeihl-Neelsen stain. Briefly, the sputum was smeared and successively stained with fuchsin, discolored with sulfuric acid and counterstained with methylene blue. HIV serology was performed using the sequential HIV screening algorithm combining Alere Determine® HIV-1/2 (Alere, Matsudo-shi, Japan) followed by Uni-gold® HIV (Trinity Biotech, Dublin, Ireland) in case of positivity; except for infants under 18 months who were diagnosed using PCR on the COBAS AmpliPrep/COBAS TaqMan HIV-1 test v2.0 platform (Roche Molecular Diagnostics, Basel, Switzerland). This platform has a dual target detection strategy in the *LTR* region and the HIV *gag* gene using (2 pairs of primers.). For this last analysis, dried blood spots specimens were shipped to National laboratory of Clinical Biology and Public Health.

Statistical analysis: Data were analyzed using Epi-Info 7 (WHO Geneva and Center for Diseases Control and Prevention (CDC) Atlanta). Different categories proportions of the categorical variables and the means of the quantitative variables were estimated. Pearson's Chi-square test or Fisher's exact test were used to compare the proportions of categorical variables, with a significance level of 5% (p-value less or equal to 0.05).

Ethical considerations: The study was approved by the Ethics and Scientific Committee of the Health Sciences Faculty.

3. Results

During our study, 152 patient files met the inclusion criteria were selected. Among the patients, 102 (*i.e.* 67.1%) were male with a sex ratio (M/F) of 2.0. Children 14 and younger represented 50% (33.6 + 16.4) as well as adults. There were more patients living in the displacement camp (65.1%) than in the other 2 sites (Table 1).

Among the patients, seventy-four (*i.e.* 48.7%) did not benefit from the screening for AFB. For the other seventy-eight (*i.e.* 52%), the search for AFB was positive in 17.1% of cases. However, in all 152 patients, the HIV serology and Determine® TB LAM Ag (Alere, Medical Co, LTD, Chiba, Japan) was positive respectively in 30.9% (47/152) and 38.2% (58/152) of cases including 38 of those who benefited from AFB research and 20 out of 70 (*i.e.* 28.6%) who did not (Figure 1).

It emerges from the combinations of examinations 2 to 2 that 100 patients had benefited from AFB and TB LAM research. The comparison of the 2 tests showed that 12 had positive results with the 2 examinations at the same time, while 5 had positive AFB but TB LAM negative, 26 TB LAM positive and AFB negative and 58 had negative results with the 2 analyzes. Taking AFB as the gold standard, the TB LAM test had a sensitivity of 70.5%, specificity of 80.6%, positive and negative predictive values of 46.2% and 92.1% respectively; the accuracy of 69.3%. Determine® TB LAM Ag (Alere, Medical Co, LTD, Chiba, Japan) were

Table 1. Socio-demographic characteristics of the 152 patients selected.

	n	%
Sex		
Male	102	67.1
Female	50	32.3
Age (years)		
<5	51	33.6
5 à 14	25	16.4
15 à 24	8	5.2
25 à 34	20	13.2
35 à 44	11	7.2
45 à 54	22	14.4
≥55	15	10.0
Origin		
Bria Center	22	14.5
Neighboring villages	31	20.4
Displaced persons camp	99	65.1

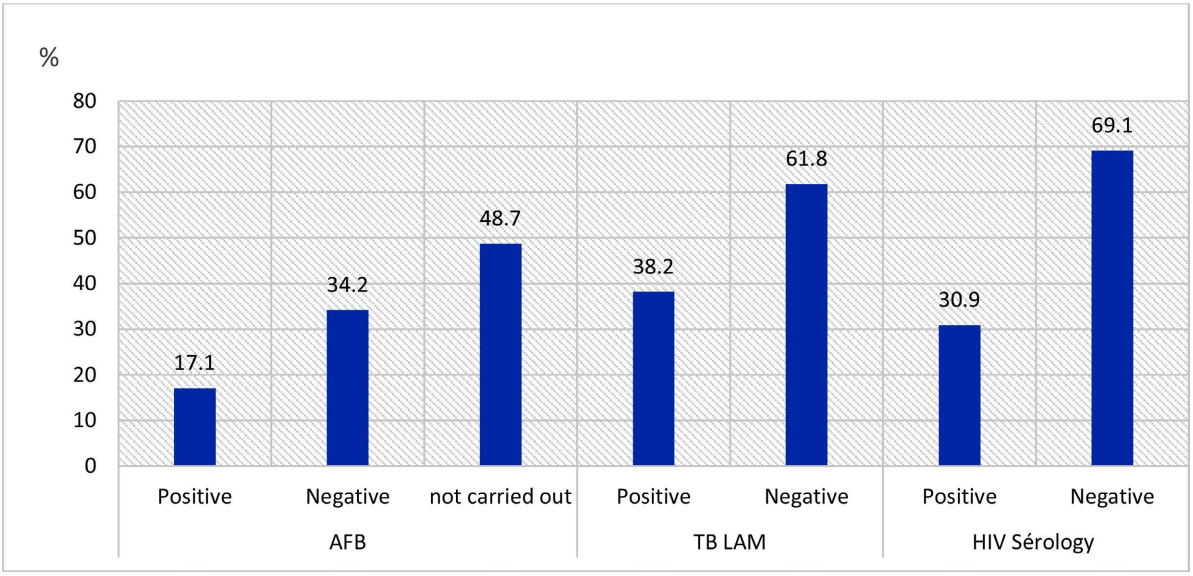

Figure 1. Distribution of the results of the AFB, TB LAM and HIV serology examinations.

significantly more able to diagnose tuberculosis than AFB ($p < 0.003$). HIV serology and LAM TB were simultaneously positive in 24 patients and negative in 71 while 34 patients had positive HIV serology and negative LAM TB, and 23 positive HIV serology and negative LAM TB. The 58 patients diagnosed by Determine® TB LAM Ag (Alere, Medical Co, LTD, Chiba, Japan) included 20 children who could not provide sputum, especially in HIV-infected patients. The

TB LAM test was able to diagnose more tuberculosis in patients co-infected with HIV ($p < 0.03$). HIV serology and AFB were positive in 6 patients and negative in 59. HIV serology was positive in 25 patients with negative AFB. On the contrary, AFB was positive in 11 HIV negative patients. There was no difference between patients infected with HIV and those who were not with respect to the diagnosis with AFB (Table 2).

4. Discussion

This study's goal is to assess the contribution of TB LAM in improving the diagnosis of tuberculosis in CAR. Therefore, to assess its adequacy in achieving the objectives of the global plan for the elimination of tuberculosis [16], we are documenting here the first routine use of Determine® TB LAM Ag (Alere, Medical Co, LTD, Chiba, Japan) in CAR. The results showed that among of 152 patients, microscopy, for lack of sputum in 51 patients (33.6%), only applied to 101 (66.4%) with a positivity of 17.1% (Figure 1). The Determine® TB LAM Ag test (Alere, Medical Co, LTD, Chiba, Japan) on the other hand was positive in 38.2% (Figure 1) of all 152 patients. Determine® TB LAM Ag (Alere, Medical Co, LTD, Chiba, Japan) significantly confirmed more diagnosis of tuberculosis than microscopy, especially in HIV + people (Table 2).

One third of patients (*i.e.* 33.6%) (Table 1) were under 5 years old. These children had not yet acquired the ability to spit in their psychomotor development. Thus, in pulmonary forms, the sputum collection requires hospitalization of the child. A nasogastric tubing is performed by a nurse in the morning, before

Table 2. Comparison of the 3 tests carried out on patients.

		Acid-fast bacilli (AFB) detection		Total	*p*
		Positive	Negative		
TB LAM	Positive	12	26	38	<0.003
	Negative	5	58	63	
	Total	17	72	101	
		TB LAM		Total	*p*
		Positive	Negative		
HIV serology	Positive	24	23	47	<0.03
	Negative	34	71	105	
	Total	58	94	152	
		Acid-fast bacilli (AFB) detection		Total	*p*
		Positive	Negative		
HIV serology	Positive	6	25	31	0.7
	Negative	11	59	70	
	Total	17	72	101	

getting up, to collect sputum swallowed during sleep. CAR is a country sorely lacking resources. It is therefore not always easy to bring together the necessary resources for this act. Hence the interest in detecting the LAM from urine, the collection only requires a urine bowl. Besides the children, the fact that nearly half of the patients came from the displacement camp, confirms the role of precarious living conditions as risk factors for tuberculosis [17]. People fleeing military conflicts are gathered in a camp, sleeping in dwellings of fortune, thus meeting promiscuity conditions. Another risk factor is the HIV infection. The HIV frequency in our study was 30.9%, which is 8 times higher than the seroprevalence in the general population in CAR. The HIV seroprevalence in CAR is 3.6% in the general population [18]. Tuberculosis appears in CAR as the first opportunistic infection. HIV, which alters the patient's immune system, makes them more vulnerable to tuberculosis. While a patient with a normal immune system has a 10% chance of developing tuberculosis throughout his life, the person immunocompromised by HIV has a 10% probability each year of developing tuberculosis [19]. Additional deaths among people living with HIV are noted when it comes to tuberculosis mortality [20]; hence the need to systematically screen for HIV in all tuberculosis cases and vice versa [21]. In CAR, only half of the 25,000 cases of tuberculosis were diagnosed in 2018 [14]. The other half undiagnosed and therefore untreated puts the population more at risk of tuberculosis transmission, and eventually risk of death and reduces the progress of countries towards the goal of global elimination phase by 2030 [6] [7] [8] [9].

HIV is an additional problem in the diagnosis of tuberculosis. With HIV, there are more cases of extra-pulmonary forms or even pulmonary forms with negative AFB microscopy [22]. In resource-limited countries like the CAR where the diagnosis of HIV is based on microscopic screening, microscopy alone is not sufficient to establish this diagnosis; not only in HIV patients whose immunosuppression makes the picture atypical [23] [24] [25] [26] but also in children unable to spit. The use of other diagnostic methods is therefore necessary to hope to diagnose the maximum number of tuberculosis cases that must be treated in order to eliminate HIV by 2030. This is where the Determine® TB test LAM Ag (Alere, Medical Co, LTD, Chiba, Japan) is of great interest. While 48.7% of patients (children) were unable to benefit from microscopy, the Determine® TB LAM Ag test (Alere, Medical Co, LTD, Chiba, Japan) was able to establish the diagnosis in 28.6% patients. For the other, the positivity of the microscopy was 17.1% against 38.2% of Determine® TB LAM Ag (Alere, Medical Co, LTD, Chiba, Japan) positive.

In the era of the implementation of the global strategy "end tuberculosis by 2030" [16], notably in the CAR, very affected by the epidemic, while half of the tuberculosis cases are neither diagnosed nor treated, the results obtained With TB LAM in this study are of a particular interest. In addition to strengthening the laboratory network with the use of the simultaneous detection of resistance

to rifampicin by Xpert® TB/RIF, the problem of tuberculosis patients who do not spit or are unable to produce sputum (small children) remains to be solved. They represented 33.6% of our series (**Table 1**) and cases of extra-pulmonary tuberculosis. In these cases, the obstacle of inability to provide the sputum sample can be overcome by examining a urine sample with the Determine® TB LAM Ag test (Alere, Medical Co, LTD, Chiba, Japan). In our serie, the Determine® TB LAM Ag test (Alere, Medical Co, LTD, Chiba, Japan) was twice more efficient (38.2%) than microscopy (17.1%) as shown in the **Figure 1**. In addition to this performance superior to the one of microscopic sputum analysis, the Determine® TB LAM Ag test (Alere, Medical Co, LTD, Chiba, Japan) is a point of care [27] [28]. It is performed in a single step (deposit of 60 µL of urine) with a result returned in 25 min (rapid test) while the microscopy and the GeneXpert give their results in about 2 hours [29]. It would be even more interesting when combined with the Xpert® MTB/RIF test, a combination that increases sensitivity to 83.3% [24]. However, it was not possible in this study to combine the Xpert® MTB/RIF test. The partnership between the Central African government and the 2 NGOs DWB France and International Medical Corps (IMC), and the one involving the Global Fund Against AIDS, Tuberculosis and Malaria has allowed the diagnosis of more tuberculosis cases and confirmed the slogan "leave no one behind: unite to end TB" [20].

This study has certain limitations. The data collection which was carried out retrospectively to the hospitalization of patients does not make it possible to assess certain aspects of the context of patients' hospitalization as the survey progresses. Mycobacteria culture or PCR should have been used as a gold standard to better appreciate the diagnostic performance of Determine® TB LAM Ag (Alere, Medical Co, LTD, Chiba, Japan), especially because the concentration of bacteria must be 10^6 bacteria/mL for AFB to be positive. However, the development of the LAM TB test was not intended to replace AFB, tuberculosis screening reference test in limited resources countries, but to fill the gaps in this examination. This gap is particularly observed in children who cannot spit and in the immunocompromised patients whose immunodeficiency makes the excretion of tuberculosis bacillus very uncertain despite a productive cough. With a sensitivity of 70.5% compared to AFB microscopy, the improvement in the diagnosis of tuberculosis by the detection of TB LAM, although significant, remains partial. Comparison of TB LAM with culture or PCR would give somewhat lower sensitivity. There also remains the issue of antibiotic resistance which cannot be diagnosed by TB LAM, but better by culture which is only carried out at the national reference laboratory for tuberculosis, at least by Xpert® MTB/RIF (Cepheid, Sunnyvale, USA) which detects both *M. tuberculosis* (MTB) and resistance to rifampicin (RIF), one of the major anti-tuberculosis treatment drugs. For this, the network of 20 GenXpert® devices (Cepheid, Sunnyvale, USA) spread across the country must operate regularly with regular supply of Xpert® MTB/RIF cartridges (Cepheid, Sunnyvale, USA).

5. Conclusion

The results of this study showed that the microcopy for acid-fast bacilli made it possible to diagnose tuberculosis in 17.1% of patients compared to 38.2% for the Determine® TB LAM Ag test (Alere, Medical Co, LTD., Chiba, Japan). This result highlights the need for routine use of LAM detection to improve the diagnosis of tuberculosis. The conduct of a subsequent study combining Xpert® MTB/RIF (Cepheid, Sunnyvale, USA) would improve the diagnosis of tuberculosis using all 3 tests.

Author Contributions

CDMK, HN and GG conceived the study; HN, IG and carried out the experimentations; MMS, HDMK and HD made statistical analyses; CDMK, NENO, MMS and GG wrote the paper. All authors have read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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