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Molecular Diagnosis of Extrapulmonary Tuberculosis and Rifampicin Resistance Using Genexpert MTB/RIF in Morocco

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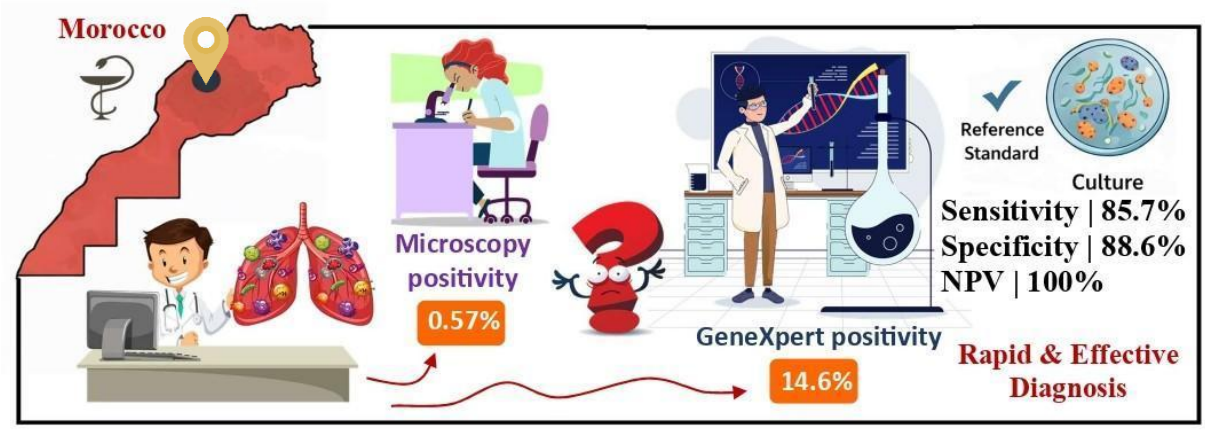
Graphical Abstract

Extrapulmonary tuberculosis (EPT) is caused by *Mycobacterium tuberculosis* and affects sites other than the lungs, and GeneXpert MTB/RIF is a WHO-recommended automated PCR assay for rapid detection of the *Mycobacterium tuberculosis* complex and rifampicin resistance. In a 36-month retrospective study including 155 EPT cases in Morocco, GeneXpert showed higher positivity than microscopy (14.61% vs 0.57%) and good performance compared to culture, with a sensitivity of 85.71%, specificity of 88.63%, and negative predictive value of 100%, supporting its use as a rapid and effective diagnostic tool for EPT.



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Abstract: Extrapulmonary tuberculosis (EPT) is a form of tuberculosis caused by *Mycobacterium tuberculosis,* affecting sites other than the lungs. GeneXpert MTB/RIF is an automated PCR-based assay for rapid detection of the Mycobacterium tuberculosis complex and rifampicin resistance and is recommended by the WHO as a reliable alternative. This study aimed to evaluate the performance of GeneXpert in diagnosing EPT in a hospital laboratory in Morocco. A retrospective descriptive study over 36 months included 155 confirmed EPT cases, with a mean age of 34.32 ± 20.67 years and a male-to-female ratio of 0.87. The most frequent site was neuro-meningeal, followed by lymphatic and digestive sites. Tuberculosis was sensitive in 98.71% of cases, with rifampicin resistance in 1.29%. Positivity rates were 0.57% for microscopy, 14.61% for GeneXpert, and 32.26% for culture. Compared to culture, GeneXpert showed a sensitivity of 85.71%, specificity of 88.63%, and a negative predictive value of 100%. GeneXpert is a rapid and effective diagnostic tool and may be considered a reference method for EPT diagnosis.

Keywords: *Extrapulmonary tuberculosis, GeneXpert MTB/RIF, PCR.*

Introduction

Tuberculosis (TB) is a major global public health challenge. According to the World Health Organization (WHO), it has probably become again the leading cause of death from an infectious agent, having been overtaken by COVID-19 over the past three years [1].

In 2023, WHO reported 10.8 million new cases of TB worldwide, distributed among 6 million men, 3.6 million women, and 1.3 million children, resulting in 1.25 million deaths [1]. This figure represents the largest number ever recorded since WHO began tracking TB globally in 1995 [2].

In 2022, approximately 2.5 million cases of tuberculosis were diagnosed in Africa, representing one new infection every 13 seconds [3]. Multidrug-resistant tuberculosis (MDR-TB) poses a serious public health threat, with only two in five people having access to treatment in 2022. Since 2000, tuberculosis diagnosis and treatment have saved 75 million lives [4].

Morocco is classified among the countries with a medium incidence of tuberculosis. In 2021, WHO estimated the number of notified cases at 35,000: an incidence rate of 94 per 100,000 inhabitants. HIV-associated tuberculosis is estimated at 410 cases **(**1.1 per 100,000 inhabitants**)** [4]. Furthermore, the distribution of cases shows a slightly higher prevalence of pulmonary tuberculosis (51%) compared to extrapulmonary forms (49%**)** [4].

Diagnosis of tuberculosis remains a challenge for clinicians and microbiologists worldwide. In particular, extrapulmonary tuberculosis (EPT) is often difficult to suspect during clinical examinations because of the diversity of its manifestations [5]. Conventional diagnostic methods still have limitations, including low sensitivity of microscopy, risk of cross-contamination, and prolonged turnaround times for culture results [6,7].

In response to these challenges, WHO approved the GeneXpert® MTB/RIF test in 2010, which allows rapid diagnosis and increased sensitivity through the detection of low amounts of the *Mycobacterium tuberculosis* complex (MTBC) genome and mutations responsible for rifampicin resistance [8-10].

Our study aims to evaluate the diagnostic performance of GeneXpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) in the rapid detection of EPT compared to culture (gold standard) and bacilloscopy.

Materials and Methods

Type, Period and Framework of the Study

This retrospective study evaluated the GeneXpert® MTB/RIF test compared to bacterial culture over a three-year period, from January 2020 to January 2023, at Ibn Sina Hospital, Rabat, Morocco**.** GeneXpert® PCR tests were performed at the explicit request of clinicians**,** and samples included

in the study met specific criteria, namely a strong suspicion of active EPT based on clinical and radiological findings [8–10].

Sample Processing and Tuberculosis Complex Detection Techniques

Sample processing and detection techniques for the *Mycobacterium tuberculosis* complex included GeneXpert® MTB/RIF testing, direct microscopic examination, and bacterial culture. For microscopic examination, smears were prepared directly from the specimens, heat-fixed, and then stained using the Ziehl–Neelsen method. When viewed under a light microscope at ×100 magnification, acid-fast bacilli (AFB) appeared pink on a blue background [7].

For culture, pre-treatment was applied according to the nature of the samples. Non-sterile samples (urine and biopsies) were decontaminated using 4% sodium hydroxide (NaOH) according to the Petroff method. Sterile samples (cerebrospinal fluid (CSF), joint fluid, pericardial fluid, ascitic fluid, or peritoneal fluid) were directly inoculated.

Each sample was inoculated onto Lowenstein–Jensen (LJ) solid medium. On this specific culture medium, typical colonies of *Mycobacterium tuberculosis*, with a rough profile and irregular edges, described as cauliflower-shaped, were observed.

GeneXPERT® MTB/RIF Test

Principle of the test

GeneXpert® MTB/RIF (GX) is an automated diagnostic test based on real-time nested PCR, allowing the simultaneous detection of the *Mycobacterium tuberculosis* complex (MTBC) and rifampicin resistance (RR). This test also provides a semi-quantitative estimate of genomic concentration (high, medium, low, very low, or trace) in less than 2 hours from clinical samples [10–12].

The assay targets the 81-bp central region of the *rpoB* gene, which is amplified and analysed using five molecular probes (A, B, C, D, and E). Each probe is specific to a different sequence of the *rpoB* gene corresponding to a rifampicin-sensitive wild-type strain and is labelled with a distinctly coloured fluorophore. In the case of a mutation within these sequences, hybridisation is disrupted, affecting the fluorescent state of the probe without altering its conformational integrity [10].

Procedure and Sample Preparation

Clinical samples are processed using a sample reagent, the Sample Reagent (SR), composed of NaOH and isopropanol [11,12]. SR is added to the sample in a 2:1 ratio, then the sample is homogenized by vortexing and incubated for 15 minutes at room temperature. This step helps to liquefy the samples and reduce the viability of MTBC, thus decreasing the biohazard [13]. A 2 mL volume of the processed sample is then transferred into the cartridge chamber using a sterile

disposable pipette, before being placed into the GeneXpert instrument. Subsequent processing is fully automated.

Statistical Data Analysis

Patient data, including sex, age, and results of different tuberculosis diagnostic methods, were entered and analysed using Microsoft® Excel® 2013 software. The performance of the GeneXpert® MTB/RIF test was evaluated by calculating its sensitivity (Se), specificity (Sp), and positive predictive value (PPV) and negative predictive value (NPV), with bacterial culture used as the reference standard.

Results

Distribution of Tuberculosis Patients by Sex

Of a total of **1,061** samples analysed, all of extrapulmonary origin, MTBC was detected in 155 clinical samples. The mean age of tuberculosis patients (EPT) was 34.32 ± 20.67 years, with extremes ranging from 4 days to 83 years. A slight female predominance was observed, representing 52.90%, or 82 patients out of 155, with a male-to-female (M/F) ratio of 0.87 (Tables 1 and 2).

Distribution of Tuberculosis Patients by Age

The positivity rates obtained for culture, microscopy, and GeneXpert® MTB/RIF were 2.26% (24/1,061), 0.57% (6/1,061), and 14.61% (155/1,061), respectively. The distribution of TB patients revealed by GeneXpert® shows that the most represented age groups are 31–40 years (17.42%), 0–10 years (16.77%), and 21–30 years (16.13%). Older age groups are less frequent, with only 1.30% of patients aged over 70 years (Table 2, Figure 1).

Table 1. Distribution of tuberculosis patients revealed by GX according to sex

Sex	Number of Patients (n)	Percentage (%)
Female	82	52.90
Male	73	46.10
Total	155	100
Sex-Ratio M/F	M/F = 0.87	

Table 2. Distribution of tuberculosis patients revealed by GX according to age

Total number of patients analysed (n)	1,061	
Number of tuberculosis patients (n)	155 (TEP)	
Positivity rate (%)	14.61%	
Extreme ages	4 days – 83 years	
Average age	34.32 ± 20.67 years	
Distribution by age	**Number of patients (n)**	**Percentage (%)**
0-10	26	16.77
11 - 20	20	12.90
21 - 30	25	16.13
31 - 40	27	17.42
41 - 50	22	14.19
51 - 60	18	11.61
61 - 70	15	9.68
71 - 80	1	0.65
81 - 90	1	0.65
Total	**155**	**100**

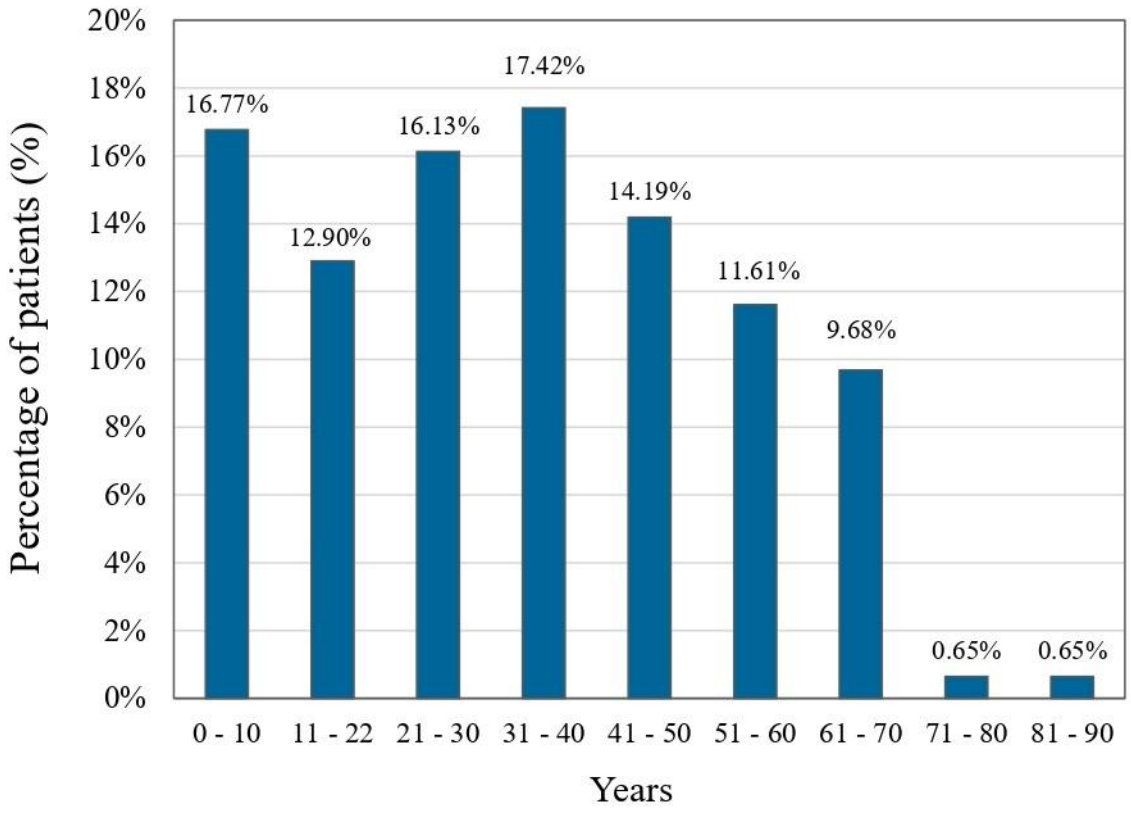

Figure 1. Distribution of tuberculosis patients revealed by GX according to age

Distribution of Tuberculosis Patients by Year

Between 2020 and 2022**,** the number of samples analysed remained stable, increasing from 351 in 2020 to 366 in 2022. By contrast, the number of positive samples decreased from 56 in 2020 to 35 in 2022. The positivity rate thus decreased from 16% in 2020 to 9% in 2022, suggesting a decrease in the incidence of tuberculosis during this period (Figure 2)**.**

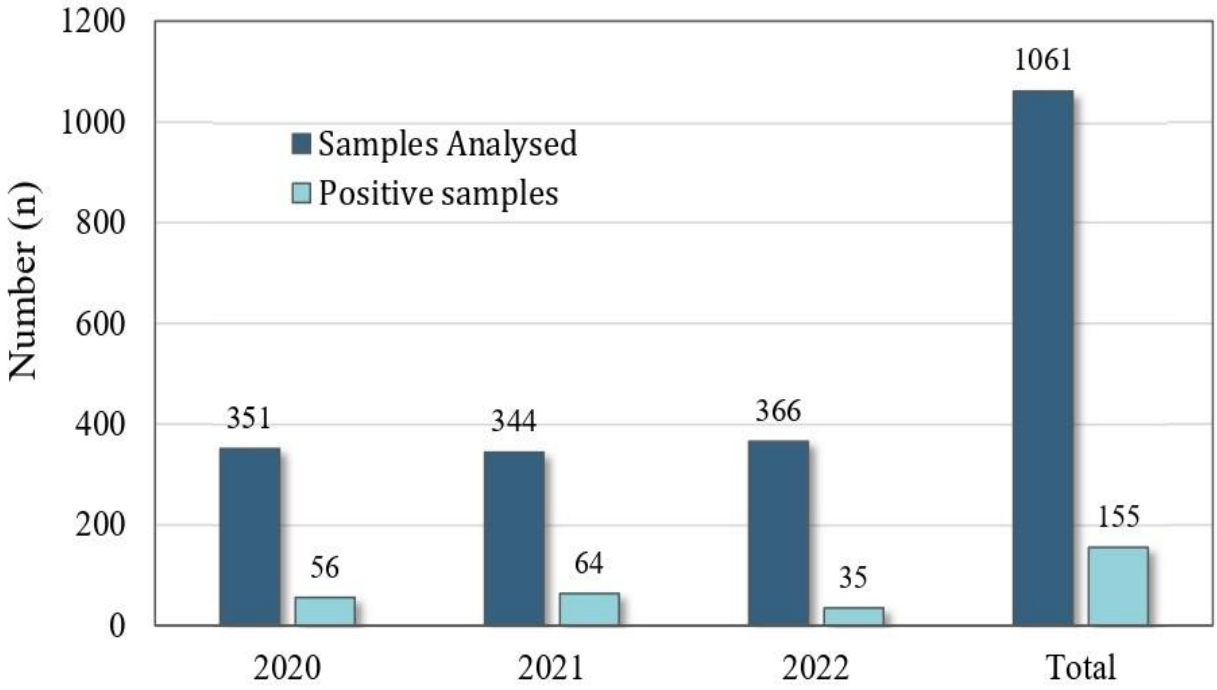

Figure 2. Distribution of tuberculosis patients revealed by GX (2020-2022).

Distribution of Tuberculosis Patients According to the Nature of the Sample

The distribution of tuberculosis patients according to the nature of the sample shows diversity in the types of samples collected. The most frequent samples concerned cerebrospinal fluid (CSF) with 54 cases, indicating a high prevalence of neuromeningeal tuberculosis (NMT)**,** followed by biopsies of cervical lymphadenopathy (45 cases).

Other specimens included urine and skin biopsies, each accounting for 11 cases. Less common specimens were also observed, such as ascitic fluid (9 cases)**,** colonic biopsies (6 cases), and pericardial biopsies (4 cases). Finally, rare specimens included liver, ileal, and peritoneal biopsies, as well as joint fluid and abscess pus, all accounting for 1 to 3 cases (Figure 3)**.**

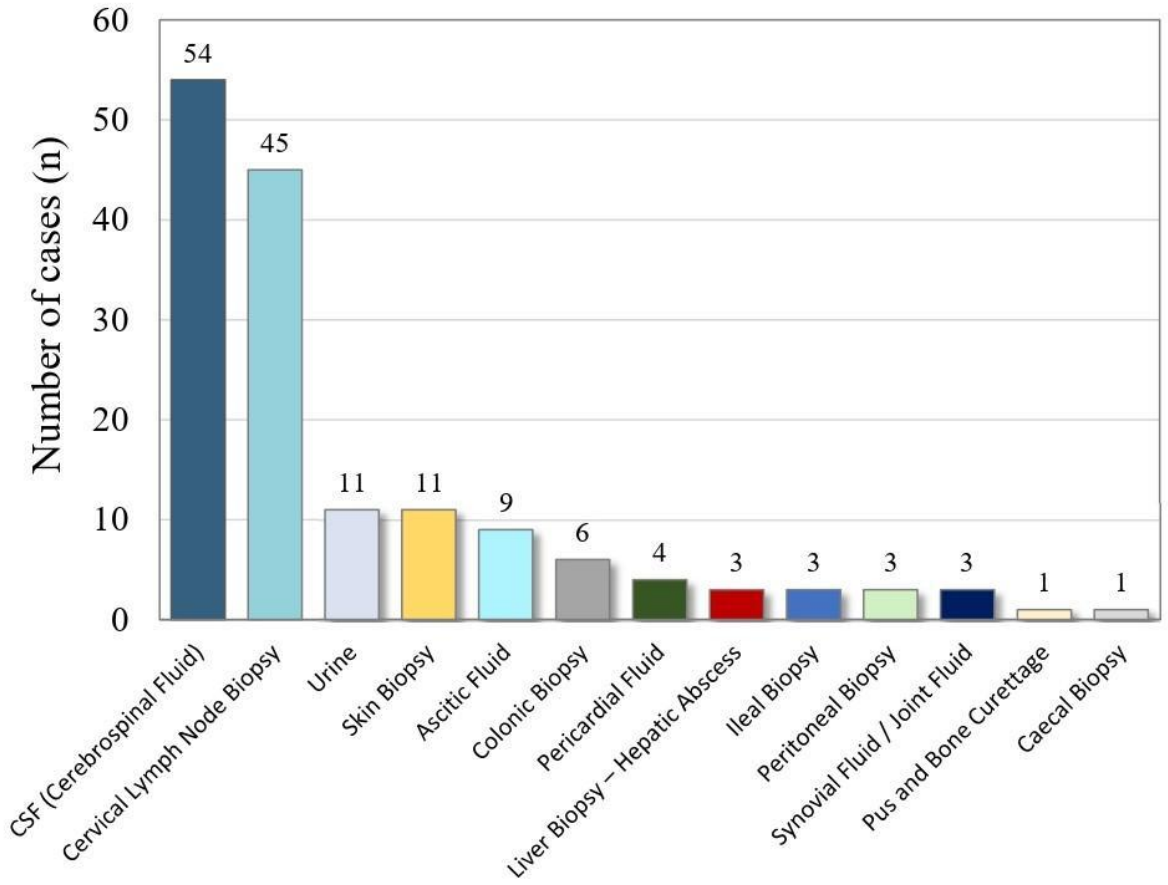

Figure 3. Distribution of tuberculosis patients revealed by GX according to the nature of the biological sample.

Distribution of Tuberculosis Patients by Location

The distribution of EPT cases revealed by GeneXpert (GX) according to location shows a predominance of neurotuberculosis, with 34.83% of cases, followed by lymph node tuberculosis at 29.03%**.** Digestive locations represent 16.78% of cases, and cutaneous and urogenital locations are also present in 7.10% of cases each (Table 3).

Osteoarticular and pericardial tuberculosis are the least common, each representing 2.58% of cases. This distribution highlights the diversity of EPT forms, with a notable concentration on neuro-meningeal and lymph node involvement (Table 3)**.**

Table 3. Distribution of tuberculosis patients revealed by GX according to the location of extra-pulmonary tuberculosis

Nature of Extrapulmonary Tuberculosis (EPT)	Number of samples analysed (n)	Number of patients Tubercular (n)	GX test positivity rate (%)	Percentage of PET localization (%)
Neurotuberculosis	289	54	18.69	34.83
Osteoarticular tuberculosis	61	4	6.56	2.58
Pericardial tuberculosis	27	4	14.81	2.58
Cutaneous tuberculosis	51	11	21.57	7.10
Urogenital tuberculosis	107	11	10.28	7.10
Digestive tuberculosis	249	26	10.44	16.78
Lymph node tuberculosis	277	45	16.25	29.03
Total	**1061**	**155**	**14.61**	**100**

Distribution of Tuberculosis Patients According To GeneXpert MTB/RIF Detection Levels

The distribution of tuberculosis patients according to GeneXpert MTB/RIF detection levels shows a majority of cases with a low detection level (39.35%) and trace levels (30.32%)**.** Very low levels represent 23.23%, and medium and high levels are less frequent, with **2**.58% and 4.52%, respectively. This distribution reflects the diversity of bacterial loads in the samples analysed, which are often paucibacillary (Figure 4)**.**

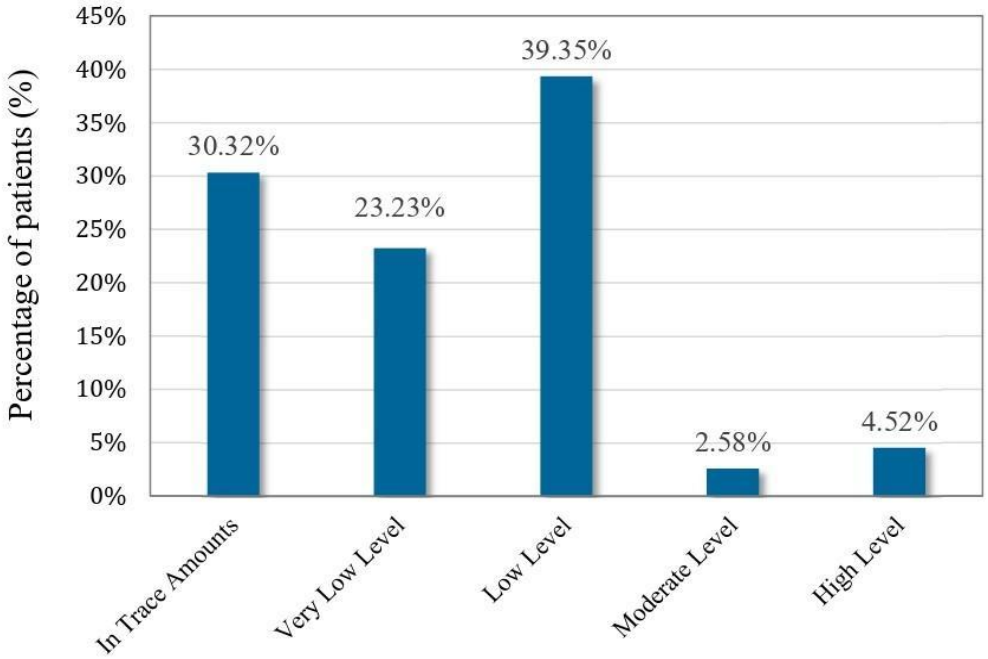

Figure 4. Distribution of tuberculosis patients revealed by GX according to the detection level of the machine

Comparison of GeneXpert MTB/RIF results versus Bacilloscopy and Culture

The positivity rates for microscopy, GeneXpert MTB/RIF, and culture were 0.57%**,** 14.61%, and 2.26%, respectively. The results of the comparison between GeneXpert and bacilloscopy revealed significant differences. Among the 155 patients identified as positive by GX**,** 6 cases showed positive bacilloscopy results, representing approximately 3.87% of cases, whereas 96.13% were classified as negative.

Comparison of GeneXpert results to culture (gold standard) reveals discrepancies in the diagnosis of EPT cases. Among the 155 GX-positive cases**,** 24 had a positive culture, representing approximately 15.48%**,** and 84.52% of cases were classified as negative.

The evaluation of GeneXpert results in relation to culture and smear tests reveals key elements in the diagnosis of tuberculosis. Among the 155 tuberculosis patients identified by GX**,** 3 patients had positive results for both culture and smear tests, representing approximately 1.94% of cases. In addition, 3 patients had a positive smear test with a negative culture, also representing approximately 1.94%**.** In contrast, 21 patients showed a negative smear test but a positive culture, corresponding to approximately 13.54%**.** The majority of cases, 82.58% **(**n = 128), had negative results for both conventional tests (Figure 5)**.**

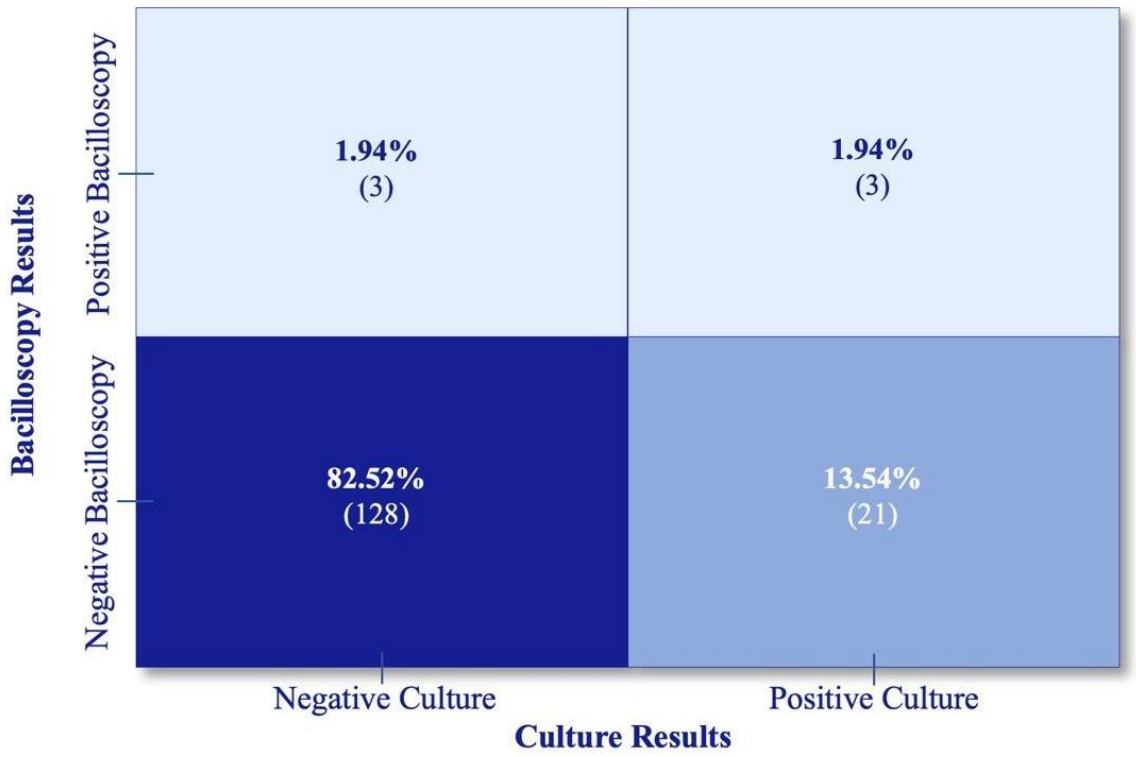

Figure 5. Confusion Matrix of Culture Results vs. Bacilloscopy Results in GX-Revealed Tuberculosis Patients

Performance of the GeneXpert® MTB/RIF Test

Compared to culture results, the GeneXpert® MTB/RIF (GX) test showed an overall sensitivity of 85.71%, an overall specificity of 88.63%, a positive predictive value of 22.84%, and a negative predictive value of 100% (Table 4).

Table 4. Performance of the GeneXpert® MTB/RIF Test (VPP, VPN Se and SP)

Nature of Extrapulmonary Tuberculosis (EPT)	Nature of the Collection	Number of samples analysed (n)		Number of patients Tubercular (n)		VPP (%)	VPN (%)	Se (%)	Sp (%)
Neurotuberculosis	*Cerebrospinal fluid (CSF)*	**289**		**54**		12.96	100	100	83.3
Bone tuberculosis	*Joint fluid*	45	**61**	3	**4**	25	100	100	95
	Pus and bone curettage	16		1					
Pericardial tuberculosis	*Pericardial fluid*	**27**		**4**		75	100	100	95.8
Cutaneous tuberculosis	*Skin biopsy*	**51**		**11**		0	100	0	78.4
Urogenital tuberculosis	*Urine*	**107**		**11**		18.18	100	100	91.4
Digestive tuberculosis	*Liver Biopsy – Liver Abscess*	41	**249**	3	**26**	15.38	100	100	91
	Cecal biopsy	21		1					
	Ileal biopsy	28		3					
	Colonic Biopsy	37		6					
	Peritoneal Fluid	42		3					
	Ascites fluid	79		9					
	Fluid from intervesicouterine abscess drainage	1		1					
Lymph node tuberculosis	*Cervical Lymphadenopathy Biopsy*	**277**		**45**		13.33	100	100	85.5
Total		**1061**		**155**		22.84	100	85.71	88.63

Detection of Rifampicin Resistance (RR)

Analysis of the results of the GeneXpert® MTB/RIF test, carried out on 155 samples positive for the *Mycobacterium tuberculosis* complex (MTBC), identified two cases of RR EPT, representing a resistance rate of 1.29%**.** Both cases concerned cerebrospinal fluid (CSF) samples, highlighting the severity of the neuro-meningeal form, which is often associated with a poor prognosis. Rifampicin resistance in these cases may lead to disease progression and further complicate treatment.

MTBC Detection Time (Mean Time to Execution)

The average time to detect the MTBC and RR was 2 hours using the GeneXpert test**,** whereas with Lowenstein–Jensen culture this time ranged between 28 and 42 days**.**

Discussion

Global Priorities or Tuberculosis Care and Control

Improving early detection of tuberculosis cases and strengthening diagnostic capacity for drug-resistant tuberculosis are global priorities in the fight against this infection [14]. In this study, we evaluated the sensitivity and specificity of the GeneXpert® MTB/RIF (GX) test for detecting extrapulmonary tuberculosis (EPT) and rifampicin resistance (RR). The results show that GX makes a significant contribution to the detection of the MTBC**,** particularly in extrapulmonary specimens, and to the identification of rifampicin resistance.

EPT Positivity Rate by GX

In Morocco, EPT has increased significantly in recent decades. This form of the disease can affect all organs and tissues, although the lymph nodes and pleura are most frequently affected. Globally, EPT accounts for approximately 20% of tuberculosis cases**,** according to WHO estimates [15].

The number of reported cases has increased significantly, from 258,000 in 2000 to 1,050,000 in 2020, representing an annual increase of 8%. The incidence per 100,000 population has also increased, from 4.2 in 2000 to 13.5 in 2020, with an annual increase of 7%**.** Furthermore, the proportion of patients diagnosed with EPT among all reported TB cases worldwide has increased from 7.3% in 2000 to 18% in 2020, representing an average annual growth of 5% [15] (Figure 6).

In Morocco, the notification of EPT cases has also followed a similar trend. In 1980, 5,700 cases were recorded, a number that increased to 13,800 in 2021, representing an annual increase of 2.3%**.** In addition, the proportion of EPT among new tuberculosis cases increased from 24% in 1980 to 49% in 2021, corresponding to an average annual increase of 1.6% [15] (Figure 6).

In our study, the positivity rate for the diagnosis of EPT by GX MTB/RIF was 14.61%**.** This rate is slightly lower than that observed in other cities, such as Algiers (84.53%) and Sfax (34.60%)**,** and comparable to lower rates reported in Dakar (11.76%) and Brazzaville (11.45%). Compared to other studies, our result lies within a moderate range, although it is lower than that reported in Paris

(37.50%) or Menoufia (30.10%)**.** These variations may be attributed to geographical and clinical factors specific to each study (Figure 6).

Our study reveals a relatively low positivity rate for extrapulmonary tuberculosis (14.61%**),** similar to the confirmation rate of 16% reported by the Directorate of Epidemiology and Disease Control of the Ministry of Health and Social Protection of Morocco. EPT now represents 48% of cases, compared to 28% in 1990. This low rate is associated with non-uniform and often probabilistic diagnostic strategies, increasing the risk of overtreatment and antimicrobial resistance. The Ministry of Health and Social Protection therefore highlights the need for standardized guidelines to improve the diagnosis and management of EPT [33].

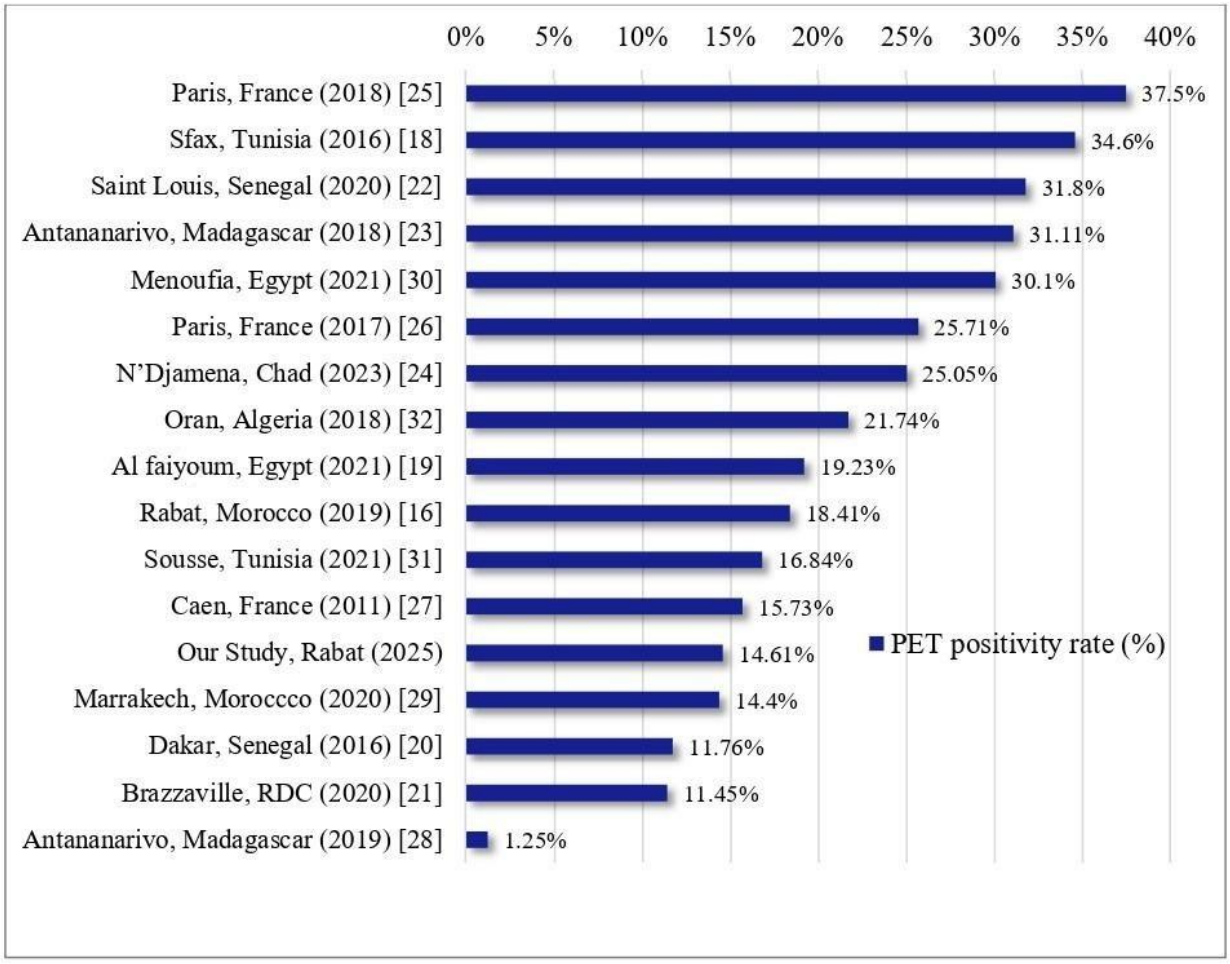

Figure 6. Positivity rates of extrapulmonary tuberculosis EPT revealed by GeneXpert MTB/RIF in different countries (Table 5)

Table 5: Comparative Table of GeneXpert MTB/RIF Evaluation in the Diagnosis of Extrapulmonary Tuberculosis (EPT) in Different Countries [16-32]

Author, Country	Year	Number of extra-pulmonary samples	TB positivity rate by GX (%)	Number of RR cases	VPP (%)	VPN (%)	SE (%)	Sp (%)
Our study *(Rabat, Morocco)*	***2024***	**155/1061**	**14.61**	**1.29% (n =2)**	**22.84**	**100**	**85.71**	**88.63**
Mechal et al. [16] *(Rabat, Morocco)*	*2019*	79/429	18.41	0% (n =0)	54	97	78.2	90.4
Yamouni et al. [17] *(Algiers, Algeria)*	*2024*	153/181	84.53	0% (n =0)	96.5	92.7	77	99.1
Marouane et al. [18] *(Sfax, Tunisia)*	*2016*	53/153	34.6	0% (n =0)	-	-	84.7	96.8
Hezfy et al. [19] *(Al Faiyum, Egypt)*	*2021*	40/207	19.23	5% (n =2)	96.4	100	37.1	99
Diallo et al. [20] *(Dakar, Senegal)*	*2016*	64/544	11.76	3.13% (n =2)	84.38	99.39	94.74	97.95
Bemba et al. [21] *(Brazzaville, DRC)*	*2020*	42/550	11.45	0% (n =0)	-	-	20	100
Niang et al. [22] *(Saint Louis, Senegal)*	*2020*	61/192	31.8	0% (n =0)	-	-	-	-
Rakotoarivelo et al. [23] *(Antananarivo, Madagascar)*	*2018*	56/180	31.11	3.57% (n =2)	98.3	86.6	82.4	98.8
Ngakoutou et al. [24] *(N'Djamena, Chad)*	*2023*	110/439	25.05	65.5% (n =72)	-	-	-	-
Billard-pomares et al. [25] *(Paris, France)*	*2018*	36/96	37.5	-	75	90	71	91
Mechaï et al. [26] *(Paris, France)*	*2017*	18/70	25.71	-	100	73	56.2	100
Malbruny et al. [27] *(Caen, France)*	*2011*	14/89	15.73	-	-	-	85.7	97.3
Ramamonjinirina et al. [28] *(Antananarivo, Madagascar)*	*2019*	74/5933	1.25	-	-	-	-	-
Mouhib et al. [29] *(Marrakech, Morocco)*	*2020*	18/125	14.4	-	-	-	100	89
Elbrolosy et al. [30] *(Menoufia, Egypt)*	*2021*	40/133	30.1	32.5% (n =13)	86.4	36.8	63.2	70.5
Talbi et al. [31] *(Sousse, Tunisia)*	*2021*	31/184	16.84	6.45% (n =2)	100	100	91	94
Chiali et al. [32] *(Oran, Algeria)*	*2018*	10/46	21.74	-	100	88.9	71.5	100

Distribution of PET cases revealed by GX according to sex

In our study in Rabat, the sex ratio was 0.87, with a slight female predominance (52.9% women and 46.1% men). This ratio is similar to that observed by Marouane *et al.* [18] in Sfax (0.8) and by Moufid [38] in Morocco (0.87), indicating a relatively balanced distribution between the sexes in these studies. In contrast, other studies show a more marked male predominance, with higher sex ratios: in Dakar (1.22)**,** Antananarivo (1.46)**,** N'Djamena (2.06)**,** Oran (1.56), and Marrakech (1.6), which suggests a higher proportion of men in these populations compared to women (Table 6).

Table 6. Comparative Table of Patients with Extrapulmonary Tuberculosis (EPT) Revealed by GeneXpert MTB/RIF in Different Countries by Sex and Age

Author (City, Country)	Year	Sex			Average age	Extreme Ages
		Women	Men	Sex ratio M/F		
Our study *(Rabat, Morocco)*	*2024*	**52.90%**	**46.10%**	**0.87**	**34.32 ± 20.67%**	**4 days – 83 years**
Marouane et al. [18] *(Sfax, Tunisia)*	*2016*	55.56%	44.44%	0.8	-	-
Diallo et al. [20] *(Dakar, Senegal)*	*2016*	45%	55%	1.22	-	1 – 92 years old
Rakotoarivelo et al. [23] *(Antananarivo, Madagascar)*	*2018*	40.6%	59.4%	1.46	-	-
Ngakoutou et al. [24] *(N'Djamena, Chad)*	*2023*	32.7%	67.3%	2.06	41.86 ± 16.91 years	15 – 79 years old
Ramamonjinirina et al. [28] *(Antananarivo, Madagascar)*	*2019*	39.9%	60.8%	1.52	-	-
Chiali et al. [32] *(Oran, Algeria)*	*2018*	39.1%	60.9%	1.56	37.6 years ± 4.8 years	8 – 75 years old
Moufid et al. [34] *(Rabat, Morocco)*	*2019*	53.45%	46.55%	0.87	35 years old	25 - 64 years old
Kane et al. [35] *(Ziguinchor, Senegal)*	*2017*	28.57%	71.43%	2.5	37 years old	18–67 years old
Aazri et al. [36] *(Marrakech, Morocco)*	*2018*	39%	61%	1.6	34 years old	10 - 72 years old
Bakary Semega et al. [37] *(Dakar, Senegal)*	*2020*	35%	65%	1.85	59.4 years old	1 – 86 years old

The slight female predominance observed in our study contrasts with WHO data, which show that tuberculosis generally affects more men than women, as confirmed by other similar studies on

extrapulmonary tuberculosis mentioned above. Indeed, national tuberculosis prevalence surveys indicate that the disease affects men more frequently, with greater gaps in case detection and reporting in this population [38]**.**

Distribution of PET cases revealed by GX according to age

In our study in Rabat, the mean age of patients with extrapulmonary tuberculosis (EPT) was 34.32 ± 20.67 years, with ages ranging from 4 days to 83 years. This profile is comparable to that observed in Marrakech (mean age 34 years, with ages ranging from 10 to 72 years) and Oran, where the mean age was 37.6 years, with a range from 8 to 75 years. In contrast, in studies such as the one from N'Djamena, the mean age was higher **(**41.86 ± 16.91 years**)** and the ages ranged from 15 to 79 years. Data from Ziguinchor and Marrakech also show relatively young age ranges, similar to those in our study. These differences in mean age may reflect demographic and epidemiological variations across the regions studied (Table 6).

All these studies, including our study, show that extrapulmonary TB affects individuals of all age groups, with a mean age of approximately 39 years, reflecting a widespread distribution of the disease across different age categories. This trend is consistent with recent WHO data, which indicate that TB mainly affects adults, particularly men aged 15 years and older, with the highest burden observed in the 25–54 age groups. Cases are also reported among younger and older populations, as highlighted in the 2022 WHO Global TB Report [37]**.**

GeneXpert MTB/RIF Performance Contribution

The results of our study show the diagnostic efficiency of GeneXpert MTB/RIF in detecting different types of extrapulmonary tuberculosis in terms of sensitivity and specificity. Neurotuberculosis, osteoarticular tuberculosis, pericardial tuberculosis, urogenital tuberculosis, and digestive tuberculosis displayed a perfect sensitivity of 100%, indicating complete detection of cases of these forms of tuberculosis, and their specificities ranged from 83.3% to 95.8%, reflecting a good accuracy rate in identifying these diseases without false positives (Table 4).

In contrast, cutaneous tuberculosis has a sensitivity of 0%, meaning that no cases were detected by culture (gold standard), and a relatively high specificity of 78.4%**,** suggesting that negative results are reliable, and that this form of tuberculosis appears difficult to diagnose (Table 4).

Lymph node tuberculosis also shows an excellent sensitivity of 100%, with a specificity of 85.5%, indicating a good diagnostic performance for this form. In summary, EPT forms, with the exception

of cutaneous tuberculosis, appear to be well diagnosed by tests exhibiting both high sensitivity and solid specificity (Table 4).

This variation in the sensitivity of the GX test according to the type of sample could be explained by the fact that the mycobacterial load, which varies across different compartments of the body, constitutes the main determinant of the positivity of the GX test [20].

Other studies also show variable sensitivity of the GX test according to the location of EPT. Comparison of results remains complex because of the heterogeneity of the populations studied, patient selection criteria, type of tuberculosis, quality and nature of clinical samples, and the gold standard used [16].

In our study conducted in Rabat, we observed an overall sensitivity of 85.71% and an overall specificity of 88.63%**,** which demonstrates a good capacity to detect positive cases and maintain high accuracy in identifying negative cases. Compared to other cities, our study lies in the upper average, and more impressive results have been reported elsewhere, such as Dakar (94.74% sensitivity and 97.95% specificity), which presents an excellent compromise between sensitivity and specificity. Marrakech shows a perfect sensitivity of 100%, with a slightly lower specificity (89%) (Figure 7).

Conversely, cities such as Brazzaville and Oran show a perfect specificity of 100%, but with much lower sensitivity (20% and 71%, respectively). Compared to sites such as Sfax and Sousse, which report high specificities (>96%), our study shows a good balance between case detection and accuracy, although it does not reach exceptional values for sensitivity or specificity. In sum, our study stands out for good overall performance, with a reasonable balance between the two key test parameters (Sensitivity and Specificity) (Figure 7).

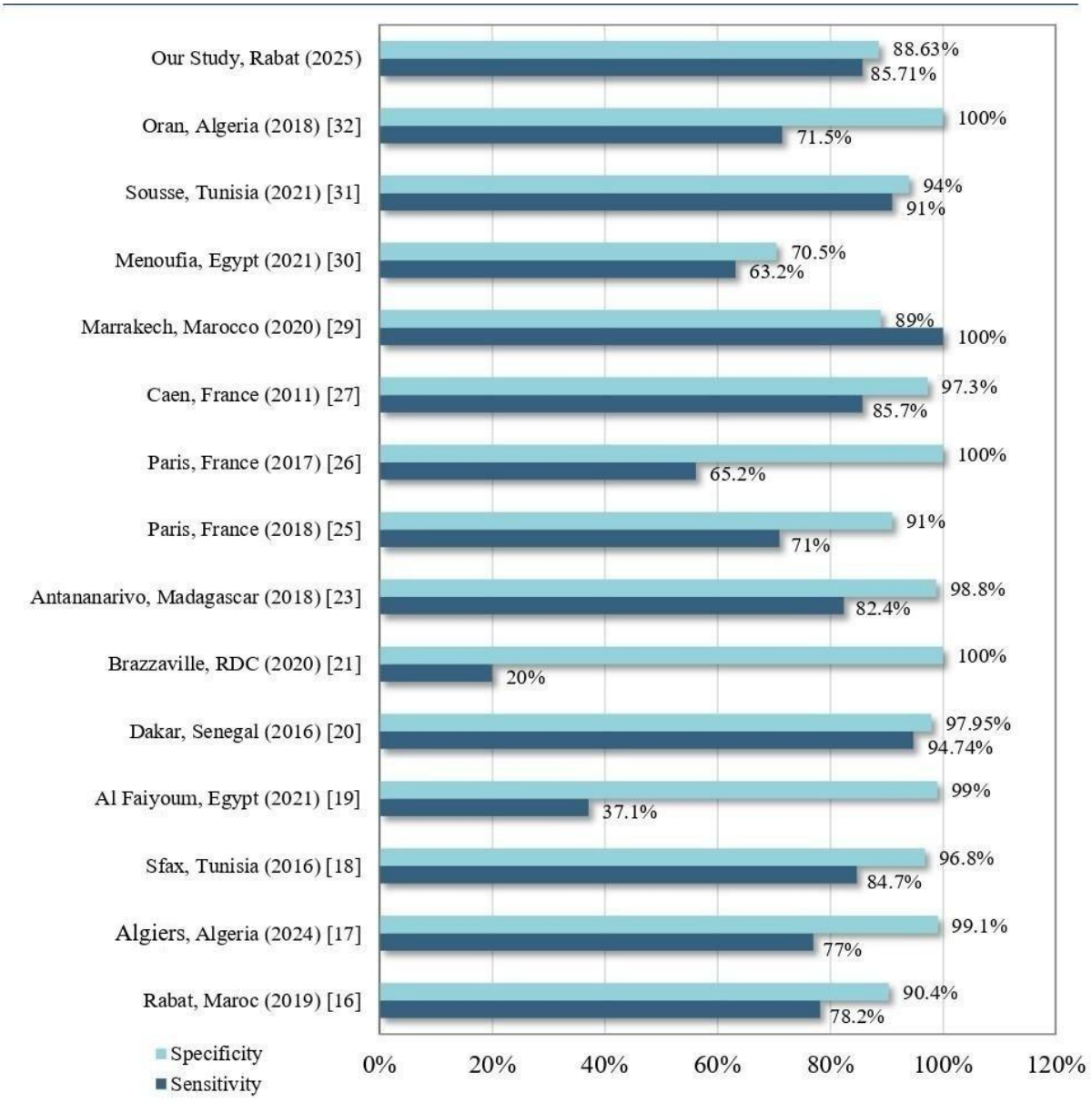

Figure 7. Contribution of performance (Se, Sp) of GeneXpert MTB/RIF in the diagnosis of Extrapulmonary Tuberculosis (EPT) in different countries (Table 6)

Detection of Rifampicin Resistance by GeneXpert MTB/RIF

In comparing the rifampicin resistance rates in *Mycobacterium tuberculosis* strains across studies from different sites, it is noted that the resistance rate observed in our study **(**1.29%**)** is relatively low compared to other cities such as N'Djamena (65.50%) and Menoufia (32.50%), where resistance rates are much higher (Figure 8).

In contrast, other sites such as Algiers, Sfax, Brazzaville, and Saint Louis report zero resistance rates, suggesting better treatment efficacy there. Cities such as Al Fayoum (5%)**,** Dakar (3.13%), and Antananarivo (3.57%) show moderate resistance rates. The relatively high rate observed in Sousse (6.45%) and the very high rate reported in N'Djamena (65.50%) highlight significant

variations in the prevalence of rifampicin resistance, which could be related to local factors such as treatment practices or the circulation of resistant strains (Figure 8).

Our results are consistent with WHO data, which report that, over the period 2020–2022, the number of multidrug-resistant tuberculosis (MDR-TB) and rifampicin-resistant tuberculosis (RR-TB) cases remained relatively stable at the global level. This stability may be attributed to several factors, including persistent challenges in early detection and effective treatment of these resistant forms of tuberculosis [40].

Although progress has been made in implementing strategies to control drug-resistant TB, the management of MDR-TB and RR-TB remains complex and costly, requiring the use of second-line drugs, which are often expensive and associated with significant side effects. These stable figures may also reflect gaps in prevention, diagnosis, and treatment efforts in some regions, despite WHO recommendations to strengthen surveillance and therapeutic strategies [40]**.**

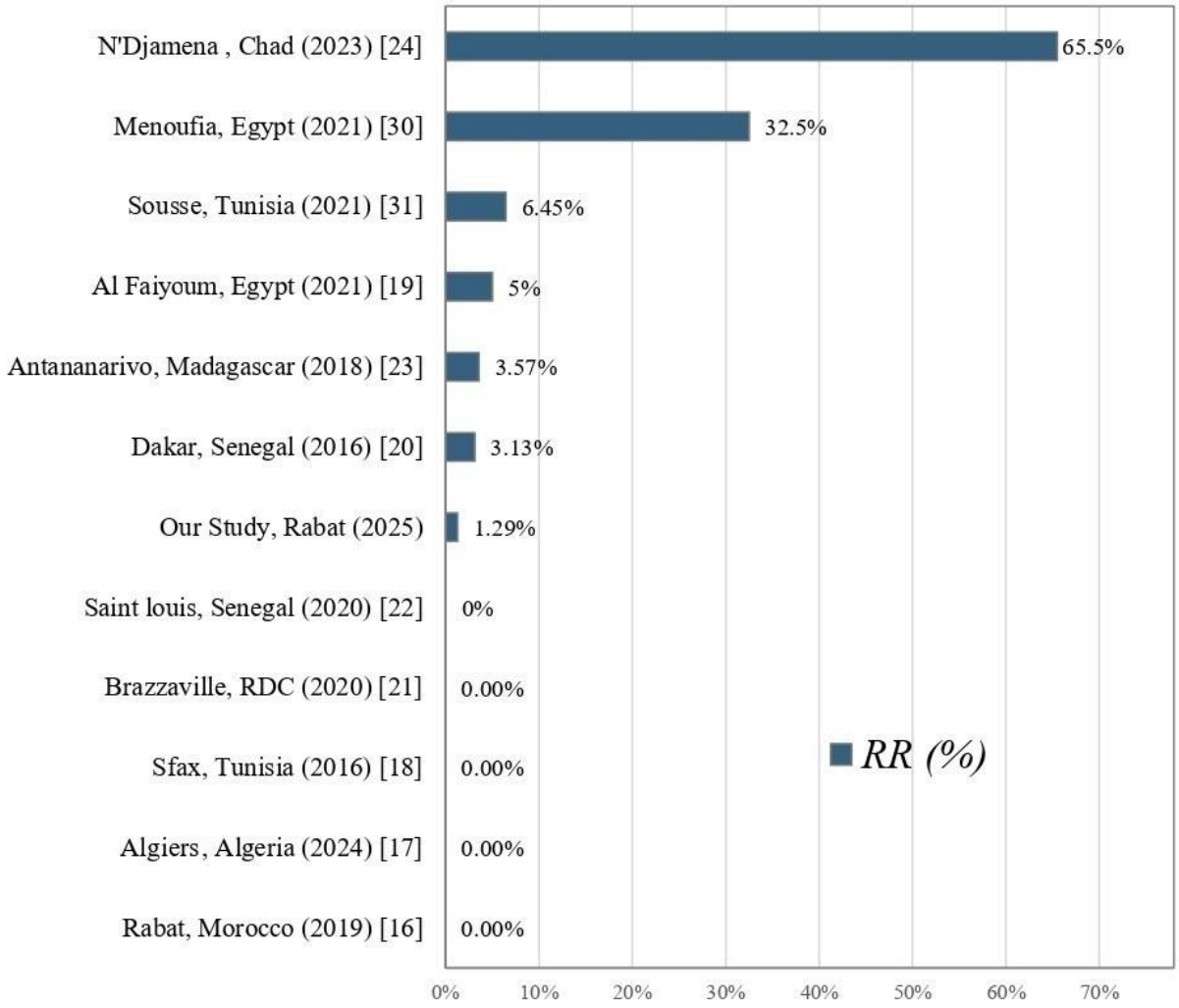

Figure 8. The rate of Rifampicin Resistance (RR), revealed by GeneXpert MTB/ RIF, in different African countries (Table 5)

General Discussion

Our study aimed to evaluate the diagnostic performance of the GeneXpert® MTB/RIF molecular test in the early diagnosis of extrapulmonary tuberculosis, as well as in the rapid detection of rifampicin resistance. The results obtained highlight the considerable contribution of GX to the diagnosis of tuberculosis and the detection of rifampicin resistance, which is a growing problem. This test allows a significant shortening of the detection time, thus facilitating early patient management, in accordance with WHO recommendations.

This study showed very good sensitivity of GX compared to culture (gold standard)**,** particularly in EPT diagnosis, where the sensitivity of GX varied according to the location of the infection. GeneXpert has the advantage of being easy to use, less dependent on user skills, and significantly reducing the risk of contamination through its closed system.

Furthermore, a negative GX result does not exclude the diagnosis of tuberculosis, and the detection of rifampicin resistance should be confirmed by a phenotypic method. The systematic use of GX, coupled with culture and integrated with clinical, radiological, and histological data, would improve tuberculosis diagnosis, particularly in Morocco where the disease is endemic. The GX test should be considered as the initial diagnostic test in cases of suspicion of extrapulmonary tuberculosis.

WHO recommended the use of GeneXpert MTB/RIF in 2010 for the diagnosis of pulmonary tuberculosis and subsequently extended this recommendation in 2013 to include extrapulmonary tuberculosis [2]. These recommendations are based on the rapid turnaround time of GeneXpert results, as well as its demonstrated performance in terms of sensitivity and specificity for the diagnosis of both pulmonary and extrapulmonary tuberculosis.

Limits of the Study

A major limitation of our study is the lack of confirmation of resistance cases detected by the GeneXpert test, because of the absence of a reference method such as GenoType MTBDRplus. This limits the accuracy of the results, particularly with regard to the risks of false-positive and false-negative results. In addition, the lack of data on patients' HIV status prevents us from assessing the impact of TB–HIV co-infection on drug resistance.

Conclusion

The results of this study confirm that the GeneXpert MTB/RIF test is a tool of choice for the diagnosis of extrapulmonary tuberculosis, because of its excellent performance in terms of sensitivity and specificity. It is particularly useful in cases of tuberculosis with negative microscopic examination, where it significantly improves diagnostic sensitivity and facilitates early medical management, in accordance with WHO recommendations.

These results support the integration of GeneXpert MTB/RIF into national tuberculosis control programmes. The effectiveness of this test in assessing antibiotic susceptibility varies according to the tuberculosis incidence rate. It is particularly relevant in low-incidence countries, where its sensitivity exceeds 90%**,** whereas its effectiveness decreases in highly endemic regions, with sensitivity reported to be as low as approximately 50%**.**

Finally, in all cases, the susceptibility results provided by GeneXpert MTB/RIF should be confirmed by another molecular test**,** as recommended by the Centers for Disease Control and Prevention (CDC)**.**

Compliance with Ethical Principles

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with international ethical standards for biomedical research involving human beings.

Participant Consent

All participants or their legal representatives provided informed consent prior to their inclusion in the study.

Confidentiality and Data Protection

The personal information of the participants was anonymized and handled confidentially, in accordance with applicable data protection laws and regulations.

Conflicts of Interest

The authors declare that they have no conflicts of interest related to this study.

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