International Journal of Science and Research Archive

eISSN: 2582-8185

Cross Ref DOI: 10.30574/ijsra

Journal homepage: https://ijsra.net/

(Research Article)

Characterization of tuberculosis diagnostics by GeneXpert MTB/Rif in Villa Clara, Cuba

González BY [1], Mendoza AM [1], Durán MN [2], Fernández GA [1], del Valle LD [3] and Fimia DR [4, 5, *]

[1] Department of Microbiology and Sanitary Chemistry, Laboratory of the Provincial Centre of Hygiene, Epidemiology and Microbiology (CPHEM-VC) of Villa Clara, Cuba.
[2] Department of Teaching and Research, Gynaeco-obstetric Hospital "Mariana Grajales" of Villa Clara, Cuba.
[3] Parasitology Department. Regional High Specialty Hospital (HARE), Dr. Juan Graham Casasús, México.
[4] Department of Veterinary Medicine, Faculty of Agricultural Sciences, Universidad Central "Marta Abreu" de Las Villas, Villa Clara, Cuba.
[5] Department of Hygiene and Epidemiology, Faculty of Health Technology and Nursing (FHTN), University of Medical Sciences of Villa Clara (UMS-VC), Cuba.

International Journal of Science and Research Archive, 2024, 12(02), 2577–2584

Publication history: Received on 10 July 2024; revised on 19 August 2024; accepted on 22 August 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.12.2.1537

Abstract

GeneXpert MTB/RIF is a real-time polymerase chain reaction molecular test recommended since 2010 that is able to simultaneously detect the presence of *Mycobacterium tuberculosis* and Rifampicin resistance within two hours. The aim of the research was to characterize the diagnosis of tuberculosis by GeneXpert MTB/RIF in the Provincial Laboratory of Microbiology and Sanitary Chemistry of the Provincial Centre of Hygiene Epidemiology and Microbiology of Villa Clara, Cuba in the period January 2018-December 2020. A descriptive cross-sectional study was conducted. The study population consisted of 710 samples from patients suspected of tuberculosis. Of the total number of samples studied, 131 (18.5%) were positive; Ciego de Avila and Camagüey were the provinces with the highest percentage of positive results, with 53.8% and 32.0%, respectively. Sputum was the predominant sample type with the highest percentage of positivity (20.7%). The group of those previously treated had the highest percentage of positivity (40.0%). It is concluded that the provinces of Ciego de Avila and Camagüey were the provinces with the highest percentages of positivity, and sputum proved to be the most useful sample for GeneXpert MTB/RIF.

Keywords: GeneXpert MTB/RIF; Positivity; Sputum; Tuberculosis; Villa Clara

1. Introduction

Tuberculosis (TB) is an infectious disease caused by bacilli of the genus *Mycobacterium*, included in the so-called *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. caprae*, *M. microtti*, *M. pinnipedii*, *M. canettii* and *M. africanum*) and by other opportunistic mycobacterial species potentially pathogenic to humans (Bennett et al., 2016; Méndez et al., 2018).

It affects humans mainly at the pulmonary level, manifesting with chronic cough, sputum production, anorexia, weight loss, fever, night sweats and haemoptysis; it can also cause extrapulmonary disease (Fajardo et al., 2018; Medina et al., 2019; Yang et al., 2021).

M. tuberculosis is a strict aerobic, slow-growing bacterium (Bennett et al., 2016). The cell envelope of this mycobacterium is characterised by the presence of a variety of complex lipids that make up 60% of its total weight,

[*] Corresponding author: Fimia DR

giving it low permeability, which contributes to the difficulty in fighting mycobacterial diseases, endowing the microorganism with innate resistance to therapeutic agents and host defences. Tuberculosis can develop as a latent infection or as an active disease; the latent form involves a reversible state of the bacterium in which cells can remain long without dividing, while active disease corresponds to the symptomatic form in which tubercle bacilli replicate causing tissue damage (Fajardo et al., 2018; Méndez et al., 2018; Murray et al., 2021).

Globally, an estimated 10 million people (range: 8.9 - 11.0 million) were ill with TB in 2019, a number that has been declining very slowly in recent years. There were an estimated 1.2 million (range: 1.1-1.3 million) TB deaths among HIV-negative people in 2019 (up from 1.7 million in 2000,) and an additional 208 000 deaths (range: 177 000- 242 000) among HIV-positive people (up from 678 000 in 2000). Males (age ≥15 years) accounted for 56% of all TB cases in 2019 (WHO, 2021). In comparison, women accounted for 32% and children (age <15 years) for 12%. Among all cases, 8.6% were people living with HIV (PAHO, 2021).

The World Health Organization (WHO) estimated that there were 290 000 new and relapsed TB cases in the Region of the Americas in 2019. The figure represents an increase from 2018, when 282 000 cases were estimated, and corresponds to 3% of the global burden of 9.9 million cases (WHO, 2021). In 2019, 10% of patients in the Americas were estimated to have TB/HIV co-infection and 3.7% had Rifampicin-resistant or multidrug-resistant TB (RR-TB/MDR-TB). In 2019, 88.1% of TB cases in the Americas were estimated to be in 12 countries. Just over half are concentrated in three countries: Brazil (33.1%), Peru (13.4%) and Mexico (10.3%) (PAHO, 2021).

In Cuba, in 2020, a total of 532 cases of tuberculosis were reported, of which 339 were men and 133 were women. The most affected age groups were those aged 15 years and older, with only seven cases in patients aged one to 14 years, and two in children under one year of age. Pulmonary tuberculosis predominated, with 461 cases. The provinces most affected were Havana, Villa Clara, Ciego de Avila and Santiago de Cuba with 158, 51, 50 and 49 cases respectively (Health Statistical Yearbook, 2020).

The diagnosis of TB is comprehensive, as procedures such as: radiology, clinical laboratory tests, tuberculin reaction, use of pathological anatomy supported by clinical history, may suggest the presence of the pathogen, but its demonstration by culture constitutes "the gold standard" (Arévalo et al., 2015).

The difficulty of diagnosis has been a crucial obstacle to an effective response to the problems of TB in particular and then HIV-associated TB and multidrug-resistant TB (MDR-TB) (Arévalo et al., 2015).

The smear microscopy is the most widely used test in the world for the diagnosis of TB, which is characterised by being simple and quick to detect the presence of the bacillus by microscopic evaluation of a sample of the lesion (Flores, 2015; León and Gustavo, 2019).

This method detects microorganisms classified as acid fast bacilli (AFB). The detection of cases with positive smear-positive AARB (+) is crucial, as they are the most contagious and have a high mortality rate. The registration and notification of these cases allows for bacteriological surveillance until the patient is cured (Flores, 2015; León and Gustavo, 2019).

The cultivation is used to complement the diagnosis of TB. In cases of TB diagnosed by bacteriology, it detects 20-30% of cases that are not diagnosed by smear microscopy. It is a late diagnostic process due to the slow growth of the bacillus, which takes 30-60 days (Peña et al., 2014; Teran and Waard, 2015).

It is the most sensitive diagnostic test and is considered the reference test. The lintel of positivity is at 10-100 bacteria/ml, 50-100 times more sensitive than microscopy. Due to the slow growth of mycobacteria, the sample must undergo a prior process of elimination of the accompanying bacterial flora, known as decontamination, especially important in sputum, where bacteria from the oral flora are always present (Tucci, 2020).

Recent developments in technology have led to the fluorescence microscope, which uses an illumination system based on light emitted by a light emitting diode (LED) with a lifetime of up to ten thousand hours, which constitutes the LED fluorescence microscope (LED MF) (Teran and Waard, 2015).

The culture serves to complement the TB diagnosis. In cases of TB diagnosed by bacteriology, it detects the 20-30% of cases that are not diagnosed by smear microscopy. It is a late diagnostic process due to the slow growth of the bacillus, which takes 30-60 days (Peña et al., 2014).

It is the most sensitive diagnostic test and is considered the reference test. The lintel of positivity is at 10-100 bacteria/ml, 50-100 times more sensitive than microscopy. Due to the slow growth of mycobacteria, the sample must undergo a prior process of elimination of the accompanying bacterial flora, known as decontamination, especially important in sputum, in which bacteria from the oral flora are always present (Tucci, 2020).

Immunochromatographic tests are another method of TB diagnosis, which are an advance in culture-based identification methods. The newest is based on the MPT64 antigen and is marketed under three different brand names: Capilia TB (TAUNS, Japan and Nippon Becton Dickinson Co, Ltd, Japan), SD TB Ag MPT64 Rapid (Standard Diagnostics, Korea) and BD MGIT TBc Identification Test (Becton Dickinson). It is based on the reaction of monoclonal antibodies against the MPT64 antigen, one of the predominant proteins excreted by *M. tuberculosis* complex, with the exception of some substrains of *M. bovis* BCG (Moure, 2013).

It is a simple and inexpensive method and has become an alternative to nucleic acid probes in routine practice. Meta-analysis studies demonstrate a sensitivity of 97-99% and specificity of 99-100% in clinical isolates, with no statistically significant differences between the three commercially available methods (Moure, 2013).

Molecular techniques are the most recent and validated advances in TB diagnosis. These tests even allow typing of mycobacteria in samples where culture methods and other conventional detection techniques are negative (Diz, 2020).

The most common molecular methods reported in the literature are:

- Transcription-mediated amplification (TMA): Amplified *M. tuberculosis* Direct test (AMTD, Gen probe).
- Conventional DNA amplification by PCR: Amplicor *M. tuberculosis* test (Roche).
- Strand displacement amplification (SDA): BD ProbeTec ET Direct TB System (DTB, Becton Dickinson).

Solid-based hybridisation assays: RIF INNO-Lipa. TB kit (Innogenetics, Gent, Belgium), MTBDR plus genotype and *Mycobacterium* Direct (MD) genotype assays (Hain Life science, Nehren, Germany).

Real-time PCR (RT PCR): Cobas Taqman, MTB test (Roche), GeneXpert MTB/RIF (Cepheid Diagnostics, Geneva, Switzerland) and Light Cycler PCR (Roche) (Diz, 2020).

GeneXpert MTB/RIF is a real-time polymerase chain reaction (PCR) molecular test recommended by WHO since 2010 that is able to simultaneously detect the presence of *M. tuberculosis* and rifampicin resistance (TB-RR) within two hours. It can be used on pulmonary (sputum) and extrapulmonary samples from patients with TB symptoms, including pleural fluid, cerebrospinal fluid and lymph node aspirate. Blood, faeces, ascitic fluid and pericardial fluid samples should not be processed by this method. In 2013, the GeneXpert MTB/RIF test began to be implemented in Latin American countries such as Brazil, Colombia, Costa Rica, Haiti, Guatemala, Guyana, Suriname, Mexico and El Salvador. In Honduras, it began to be used in 2016 (Flores, 2015).

For the National Reference and Research Laboratory for Tuberculosis, Leprosy and Mycobacteria (LNRI TBLM) and the National Control Programme (PNC) in Cuba, it is a priority to have tools that allow timely diagnosis of both TB and drug resistance (Martínez et al., 2019).

The NCP together with the LNRI TBLM developed guidelines based on WHO recommendations, targeting vulnerable groups (VGs) most likely to contract TB and develop resistance to anti-TB drugs. The use of molecular testing in VGs, such as HIV AIDS patients, could have a positive impact on the timely diagnosis of TB, as most of them are smear-negative, as well as in prison and ex-prison patients. In addition, it would allow rapid detection of rifampicin resistance in staff exchanging with countries with a high burden of resistant TB (Martinez et al., 2019).

In Cuba, molecular diagnosis of tuberculosis using GeneXpert MTB/RIF was implemented in 2014 at the National Reference Laboratory of the "Pedro Kourí" Institute of Tropical Medicine. Currently, the country has three laboratories with GeneXpert MTB/RIF technology located in the provinces of Havana, Villa Clara and Holguín, which provide regional services covering the rest of the country's provinces. In Villa Clara, this technology was implemented in 2018 in the Provincial Laboratory of Microbiology and Sanitary Chemistry of the Provincial Centre of Hygiene, Epidemiology and Microbiology. To date, no study has been conducted to characterise the diagnosis of GeneXpert MTB/RIF in the laboratory, which has motivated the development of this research, with the objective of characterising the diagnosis of tuberculosis by GeneXpert MTB/RIF in the Provincial Laboratory of Microbiology and Sanitary Chemistry of the Provincial Centre of Hygiene, Epidemiology and Microbiology of Villa Clara in the period January 2018-December 2020.

2. Materials and Methods

A descriptive cross-sectional study was conducted at the Provincial Laboratory of Microbiology and Sanitary Chemistry of the CPHEM of Villa Clara from 2018 to 2022.

The study population consisted of 710 samples of patients suspected of tuberculosis, which underwent the GeneXpert MTB/RIF technique in the period January 2018 - December 2020. The information was obtained from the registry books of the Mycobacteria Department, for which a documentary observation guide prepared by the author was used. The data obtained were entered into a database. The samples received in the laboratory were subjected to the GeneXpert MTB/Rif technique according to the established Standard Operating Procedures (SOP). The data corresponding to each variable were entered into files and processed with the help of the following programmes: SPSS, version 22.0 for Windows, EPIDAT, version 3.1 and Microsoft Excel version 2016. Absolute and relative (percent) frequencies were used as summary measures for qualitative variables. The results of the study were shown in text and tables.

The research was conducted as described in its initial protocol and the data recorded were used only for scientific purposes in accordance with the ethical principles of research as set out in the Declaration of Helsinki (2013) and subsequent revisions. The conduct of this research work is ethically justified by the provision of necessary information that will contribute to better diagnosis, management and treatment of infectious diseases.

3. Results

Out of a total of 710 samples tested with GeneXpert MTB/RIF, 131 were positive for 18.5% (Table 1).

Table 1 GeneXpert MTB/RIF positivity in the period January 2018 to December 2020

GeneXpert MTB/Rif Positive	Number	%
Yes	131	18.5
No	579	81.5
Total	710	100.0

Source: Patient registry of the CPHEM Laboratory in Villa Clara.

The province with the highest number of samples processed was Villa Clara with 484. Although the number of samples processed in the rest of the provinces was far from Villa Clara, the highest percentages of positivity corresponded to Ciego de Avila and Camagüey, with 53.8% and 32.0% respectively (Table 2).

Table 2 GeneXpert MTB/RIF positivity according to provinces in the central region

	Gene X pert MTB/Rif positive				
Provinces		**Yes**		**No**	**Total**
	Number	**%***	**Number**	**%***	
Cienfuegos	20	21.7	72	78.3	92
Villa Clara	76	15.7	408	84.3	484
Sancti Spíritus	4	8.7	42	91.3	46
Ciego de Ávila	7	53.8	6	46.2	13
Camagüey	24	32.0	51	68.0	75
Total	131	18.5	579	81.5	710

*Percentage calculated in relation to the total of the row; **Source**: Patient registry of the CPHEM Laboratory in Villa Clara.

Sputum was the predominant sample type with the highest percentage of positivity at 20.7%. Although the remaining samples were processed in smaller numbers, they obtained percentages of positivity close to that of sputum (Table 3).

Table 3 GeneXpert MTB/RIF positivity according to sample type

	Gene X pert MTB/Rif positive				
Type of samples		**Yes**		**No**	**Total**
	Number	**%***	**Number**	**%***	
Sputum	122	20.7	467	79.3	589
Biopsy material	3	17.6	14	82.4	17
LCR	1	20.0	4	80.0	5
Others	5	5.1	94	94.9	99
Total	131	18.5	579	81.5	710

*Percentage calculated in relation to the total of the row; **Source**: Patient registry of the CPHEM Laboratory in Villa Clara; **Legend**: LCR: Cerebrospinal Fluid.

The technique was most frequently applied in inmate or ex-inmate patients and patients with other associated diseases. Regarding positivity, the groups with the highest percentage were those previously treated with 40.0%, followed by health workers with 28.0%, prisoners or ex-prisoners with 27.6%, alcoholics with 25.9% and HIV-positive patients with 24.5% (Table 4).

Table 4 GeneXpert MTB/RIF positivity according to vulnerable groups

	Gene X pert MTB/Rif positive				
Vulnerable groups		**Yes**		**No**	**Total**
	Number	**%***	**Number**	**%***	
TB patient contact	10	16.4	51	83.6	61
VIH	12	24.5	37	75.5	49
Prisoner and ex-prisoner	35	27.6	92	72.4	127
Previously discussed	20	40	30	60.0	50
Foreign	1	33.3	2	66.7	3
Personal exchange from countries with high TB burden	0	0	1	100	1
Health worker	7	28	18	72.0	25
Child	1	7.7	12	92.3	13
Other associated diseases	11	10.4	95	89.6	106
Smoker	6	8.2	67	91.8	73
Alcoholic	7	25.9	20	74.1	27
Prolonged internment	0	0.0	8	100	8
Others**	22	14.0	135	86.0	157

*Percentage calculated in relation to the total of the row; **Patients not defined in the indication, so this category is not taken as predominant; **Source**: Patient registry of the CPHEM Laboratory in Villa Clara.

4. Discussion

In the present study, positivity for the GeneXpert MTB/RIF technique was similar to that obtained by other authors in other geographical latitudes (López and Ramos, 2017; Sanabria, 2018; Ortiz et al., 2019), in a study on lung samples, where they obtained a positivity of 20.5%.

In the present investigation, Villa Clara was the province with the highest number of samples processed, but with lower positivity rates than Ciego de Avila, Camagüey and Cienfuegos. This result corresponds to the proximity of Villa Clara to the laboratory, which facilitates the access of health personnel to the services of the Molecular Biology Laboratory and suggests excess in the prioritisation and selection of patients for the GeneXpert MTB/RIF technique (Atehortúa et al., 2015; Argueta et al., 2019; Medina et al., 2019).

Ciego de Avila and Camagüey were the provinces with the highest percentages of positivity, despite the small number of samples processed. According to the Health Statistical Yearbook, during the years 2019 and 2020, the province of Ciego de Avila showed the highest incidence rates of tuberculosis in the central region of the country, with values of 9.4 and 11.4 per 100 thousand inhabitants respectively, which coincides with the present study. However, Camagüey had the lowest incidence rates in the region in both years. Villa Clara showed incidence rates of 6.3 and 6.6 per 100,000 habitants.

In this study, 82.9% of the samples used corresponded to sputum, which also obtained the highest positivity, results that coincide with those achieved by other authors (Zahoor et al., 2018; Heredia, 2020; Yang et al., 2021). In Medellin, Colombia, in 2021, in a study about the contribution of the use of GeneXpert MTB/RIF and its cost-effectiveness in the diagnosis of pulmonary tuberculosis and rifampicin resistance compared to non-molecular diagnostic methods, bronchoalveolar lavage was found to be the most processed sample type, with 1198 out of 1574, and with the highest positivity, with 152 for 64.1% (Cadavid et al., 2018).

In Cuba, studies on the impact of GeneXpert MTB/RIF for the diagnosis of tuberculosis, the highest number of positive samples have been in respiratory samples, mostly sputum; where, the vulnerable group that has contributed the highest number of samples has been prison or ex-prison patients (Fajardo et al., 2018; Méndez et al., 2018; Health Statistical Yearbook, 2020).

In a study on the resistance profile of *M. tuberculosis* to first-line antituberculosis drugs and their combinations in Barranquilla, Colombia, in 2020, with respect to the associated risk factors in a group of patients studied (2701), 98.4% of whom suffered from pulmonary tuberculosis, it was found that 5.78% had concomitant HIV infection (Agredo and Osorio, 2020).

In the present study, the groups of those previously treated, health workers, prisoners and ex-prisoners showed the highest percentages of positivity, which is consistent with results obtained by other authors in this regard (Jima et al., 2020; Montalvo et al., 2020; Yang et al., 2021). In Villa Clara, the use of GeneXpert MTB/RIF prioritises vulnerable groups, mainly prisoners and ex-prisoners, HIV-positive patients and previously treated patients. This explains why these groups are the predominant ones in the study, and with higher percentages of positivity.

5. Conclusion

Despite an exhaustive review of the subject at national and international level, no studies were found that demonstrate the prevalence of groups vulnerable to tuberculosis diagnosed using the GeneXpert MTB/RIF technique, which would allow a more concrete comparison with the results obtained, and where sputum proved to be the most useful sample for carrying out GeneXpert MTB/RIF.

Compliance with ethical standards

Acknowledgments

To Prof. David del Valle Laveaga for his financial contribution towards the publication of this manuscript.

Disclosure of conflict of interest

No conflict of interest exists among the Authors.

Statement of ethical approval

The research was subject to ethical norms that allowed minimising the possible harm to the people included in the study, as well as to the technical staff of the Provincial Laboratory of Molecular Biology of the CPHEM of Villa Clara who participated in the collection of samples, as well as in their processing, in order to generate new knowledge without violating the ethical principles established for these cases.

References

[1] Méndez FL, Carmona DY, Escalona RC, Moreno PL, Ortega PJA. (2018). Epidemiological behaviour of tuberculosis. Rev Med Electrónica. 40(2): 335-345.

[2] Bennett JE, Dolin R, Blaser MJ. (2016). Mandell, Douglas, and Bennett's Principies and Practice of lnfectious Diseases. 8th ed. Spain: Elsevier©.

[3] Fajardo DGE, Reyes GOM, Varela VDE y Medina RKF. (2018). Pulmonary tuberculosis and current laboratory diagnostic methods. Rev Fac Medical Sciences. 15(2): 35-44.

[4] Murray PR, Rosenthal KS, Pfaller MA. (2021). Medical Microbiology. 9th ed. Spain: Elsevier©.

[5] World Health Organization (WHO). (2021). Global Tuberculosis Report 2020: An Overview [Global tuberculosis report 2020: executive summary]. Geneva, Switzerland. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://creativecommons.org/licenses/by-nc-sa/3.0/igo/deed.es

[6] Pan American Health Organization (PAHO). (2021). Tuberculosis in the Americas. Regional Report 2020. Washington, D.C. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://doi.org/10.37774/9789275324479.

[7] Health Statistical Yearbook. (2020). Havana, Cuba. ISSN: electronic version 1561-4433. Available at: http://www.who.int/classification/icd/icd10upsdates/en/

[8] Arévalo BAR, Alarcón TH, Arévalo SDE. (2015). Diagnostic methods in Tuberculosis, the conventional and technological advances in the 21st century. La Paz Medical Journal. 21(1): 75-85.

[9] Flores CHS. (2020). Diagnostic-microbiological update on pulmonary tuberculosis [doctoral thesis]. Riobamba: Publication and Scientific Exchange Services, National University of Chimborazo, Ecuador. Available at: http://dspace.unach.edu.ec/handle/51000/7294

[10] Leon N, Gustavo E. (2019). Sensitivity and specificity of diagnostic tests for tuberculosis [master thesis]. Machala: Repository of the Academic Unit of Chemical and Health Sciences, Technical University of Machala, Ecuador. Available at: http://repositorio.utmachala.edu.ec/handle/4

[11] Teran RH, de Waard J. (2015). Recent advances in tuberculosis diagnosis in the clinical laboratory. eJIFCC. 26(4): 310-325.

[12] Peña C, Césped G, Wolff R, Álvarez V, Garay B, Medina P, et al. (2014). Bacteriological diagnosis of pulmonary tuberculosis by fibrobronchoscopy in HIV patients. Chilean Journal of Nursing. 30(1): 46-53.

[13] Tucci P. (2020). Development of tools that contribute to the diagnosis of active *Mycobacterium tuberculosis* infection. [Doctoral thesis] Montevideo: Publications and Scientific Exchange Services, University of the Republic of Uruguay. Available at: https://www.colibri.udelar.edu.uy/jspui/bitstream/20.500.12008/26054/1/uy24-19791.pdf

[14] Moure GR. (2013). Rapid detection of Mycobacterium tuberculosis complex and antituberculosis drug resistance by gene amplification and hybridisation methods. [Doctoral thesis]. Barcelona: Scientific Repository, University of Barcelona, Spain. Available at: http://diposit.ub.edu/dspace/handle/2445/55153

[15] Diz MOM. (2020). Molecular biology techniques in the diagnosis of infectious diseases. NPunto. 3(30): 88-111.

[16] Martínez RMR, Secretário CT, Lemus MD, Mederos CLM, Sardina AM, García LG, et al. (2019). Evaluation of Xpert MTB RIF for tuberculosis diagnosis and detection of rifampicin resistance in vulnerable groups. Neumol Cir Torax. 78(3): 284-289.

[17] DHAMM (Declaración de Helsinki de la AMM). (2013). Ethical Principles for Medical Research Involving Human Subjects. 64th General Assembly, Fortaleza, Brazil, October. World Medical Association, Inc. – All Rights reserved. 9 pp.

[18] López MAY, Ramos JRE. (2017). Evaluation of the sensitivity and specificity of Gene XPERT MTB/RIF in the detection of *Mycobacterium tuberculosis* in pulmonary samples at the Dr. Max Bloch National Reference Laboratory in 2013. [Doctoral thesis]. San Salvador: Scientific Repository, University of El Salvador. Available at: https://ri.ues.edu.sv/id/eprint/16292

[19] Cadavid C, Realpe T, Mejía GI, Zapata E, Hernández M, Robledo J. (2022). Contribution of the use of XPERT MTB/RIF and its cost-effectiveness in the diagnosis of pulmonary tuberculosis and rifampicin resistance: a comparison with non-molecular diagnostic methods. Infectology. 26(2): 121-127.

[20] Martínez RMR, Sardiñas AM, García LG, Mederos CLM, Lemus MD, Echemendía FM. (2018). Impact of XPERT MTB/Rif for the diagnosis of Tuberculosis in Cuba. International Health Convention, CubaHealth. Available at: http://convencionsalud2018.sld.cu/index.php/connvencionsalud/2018/rt/metadata/251/2458#:~:text=El%20Xpert%20MTB%2F%20RIF%20permiti%C3%B3,como%20indicador%20de%20TB%20%E2%80%93%20MDR.

[21] Ruiz MLFJ, Arzuza OL, Guerra SM, Maestre SR. (2020). Resistance profile of *Mycobacterium tuberculosis* to first-line antituberculosis drugs and their combinations. Cuban Journal of Tropical Medicine. 72(2): e525.

[22] Sanabria DEV. (2018). Evaluation of the performance of the Xpert MTB/Rif test for the detection of Tuberculosis in a Public Hospital in Bucaramanga [master's thesis]. Bogotá D.C: Repositorio Científico, Universidad CES-Faculty of Health Sciences of Bogotá, Colombia. Available at: https://repository.urosario.edu.co/handle/10336/18047

[23] Yang J, Shen Y, Wang L, Ju L, Wu X, Wang P, et al. (2021). Efficacy of the Xpert *Mycobacterium tuberculosis*/rifampicin assay for diagnosing sputum-smear negative or sputum-scarce pulmonary tuberculosis in bronchoalveolar lavage fluid. International Journal of Infectious Diseases. 107: 121–126.

[24] Ortiz JJ, Franco-Sotomayor G, Ramos-Ramírez M. (2019). Validation and implementation of GeneXpert MTB/RIF for tuberculosis diagnosis in Ecuador. Kasmera. 47(1): 29-37.

[25] Atehortúa S, Ramírez F, Echeverria LM, Peñata A, Ospina S. (2015). Xpert MTB/RIF test performance assay in respiratory samples at real work settings in a developing country. Biomedica. 35(1): 125-30.

[26] Jima SMJ, Montúfar-Silva MR, Cevallos-Montalvo JP, Sánchez-Andino BM, García-Ríos CA. (2020). Smear microscopy, genexpert MTB/RIF and culture findings in patients with drug-resistant tuberculosis. Pablo Arturo Suárez Hospital. Pol. Con. 5(09): 927-936. Disponible en: http://dx.doi.org/10.23857/pc.v5i9.1740

[27] Medina BAL, Kim-Morales D, Abrego-Fernández JA, Laniado-Laborín R. (2019). Xpert®MTB/RIF for TB diagnosis under programmatic conditions in a highly endemic region in Mexico. Neumol Cir Torax 78(2): 122-125.

[28] Argueta de Gutierrez YL, Contreras de Lazo OL, Escalante Campos EN, Sánchez Reyes RI, Viera Ascencio CE. (2019). Characterization of tuberculosis cases confirmed with Gene XPERT from the Hospital Nacional San Juan de Dios de San Miguel between May 2016 and June 2019 [master thesis]. San Salvador: Scientific Repository, Universidad Dr. José Matías Delgado, Salvador. Available at: https://www.lareferencia.info/vufind/Record/SV_8008f500afe7e91c4ab8d7066df78e78

[29] Zahoor D, Farhana A, Kanth F, Manzoor M. (2018). Evaluation of smear microscopy and geneXpert for the rapid diagnosis of pulmonary and extrapulmonary tuberculosis in a tertiary care hospital in North India: a descriptive prospective study. Int J Res Med Sci. 6(5): 1756-1760.

[30] Montalvo OR, Ramírez BM, Bruno-Huamán A, Damián Mucha M, Vilchez-Bravo S, Quisurco-Cárdenas M. (2020). Geographical distribution and risk factors for multidrug-resistant tuberculosis in central Peru. Rev Fac Med. 68(2). Available at: http://dx.doi.org/10.15446/revfacmed.v68n2.71715.

[31] Heredia MG. (2020). Clinical and epidemiological characteristics and pattern of resistance in patients with drug-resistant pulmonary tuberculosis over 15 years of age treated at Hospital II-2 Tarapoto in the period 2017- 2019 [doctoral thesis]. Tarapoto: Scientific Repository, National University of San Martín. Tarapoto, Peru. Available at: https://repositorio.unsm.edu.pe/handle/11458/3718?show=full

[32] Agredo F, Osorio L. (2020). Coverage and fidelity of the Xpert MTB/RIF™ test in a high burden area of pulmonary tuberculosis in Colombia. Biomedica. 40(4): 626-640.