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ORIGINAL ARTICLE

RAPID MOLECULAR TEST FOR TUBERCULOSIS: FROM COLLECTION TO BEGINNING OF THE TREATMENT

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ABSTRACT

Objective: To identify the time elapsed between the collection of material for rapid molecular testing and the start of treatment for tuberculosis in units that forwarded samples for processing in centralizing units.

Method: An analytical epidemiological study carried out in two Basic Health Units in Belém-Pará. Data was collected referring to 296 new laboratory confirmed cases diagnosed from December 2014 to December 2015. In the analysis, the Mann-Whitney's U test, p-value ≤ 0.05, was used for the correlation between variables.

Results: There was no statistically significant difference in the time of release of the test results in the Centralizing Units and the Units that sent exams for processing. As for the start of treatment, there was a difference in time between the centralizing units and the coverage units.

Conclusion: The centralization of the processing of the Rapid Molecular Test does not interfere with the time for diagnosis and treatment of tuberculosis, even with the forwarding of samples between services.

DESCRIPTORS: Tuberculosis; Delayed Diagnoses; Community Health Services Molecular Biology; Time Perception.

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TESTE RÁPIDO MOLECULAR PARA TUBERCULOSE: DA COLETA AO INÍCIO DO TRATAMENTO

RESUMO
Objetivo: identificar o tempo decorrido entre a coleta do material para teste rápido molecular e o início do tratamento para tuberculose em unidades que encaminharam amostras para processamento em Unidades centralizadoras.
Método: estudo epidemiológico analítico desenvolvido em duas Unidades Básicas de Saúde em Belém-Pará. Foram coletados dados referentes a 296 casos novos com confirmação laboratorial, diagnosticados de dezembro de 2014 a dezembro de 2015. Na análise, utilizou-se o Teste U de Mann-Whitney, p-valor ≤ 0,05 para a correlação entre as variáveis.
Resultados: não houve diferença estatisticamente significativa no tempo de liberação dos resultados de exames em Unidades Centralizadoras e Unidades que encaminharam exames para processamento. Quanto ao início do tratamento, houve diferença no tempo entre as unidades centralizadoras e as de abrangência.
Conclusão: a centralização do processamento do Teste Rápido Molecular não interfere no tempo para diagnóstico e tratamento da tuberculose, mesmo com o encaminhamento das amostras entre os serviços.

DESCRITORES: Tuberculose; Diagnóstico Tardio; Serviços de Saúde Comunitária; Biologia Molecular; Percepção do Tempo.

PRUEBA MOLECULAR PARA DETECCIÓN RÁPIDA DE TUBERCULOSIS: DE LA RECOLECCIÓN DEL MATERIAL AL INICIO DEL TRATAMIENTO

RESUMEN:
Objetivo: determinar el tiempo transcurrido desde que se recolecta el material para la prueba molecular rápida hasta que se inicia el tratamiento contra la tuberculosis en unidades que enviaron muestras para su procesamiento en Unidades Centralizadoras.
Método: estudio epidemiológico y analítico desarrollado en dos Unidades Básicas de Salud de Belém-Pará. Se recolectaron datos referentes a 296 casos nuevos con confirmación de laboratorio, diagnosticados entre diciembre de 2014 y diciembre de 2015. En el análisis se utilizó la prueba U de Mann-Whitney, con un valor p≤ 0,05 para la correlación entre las variables.
Resultados: no se registró ninguna diferencia estadísticamente significativa en el tiempo de emisión de los resultados de los exámenes entre las Unidades Centralizadoras y las Unidades que enviaron exámenes para su procesamiento. En relación con el inicio del tratamiento, sí se registró una diferencia de tiempos entre las Unidades Centralizadoras y las Unidades Básicas.
Conclusión: centralizar el procesamiento de la Prueba Molecular para Detección Rápida de la Tuberculosis no interfiere en el tiempo de diagnóstico ni en el tratamiento, incluso considerando el envío de muestras entre servicios.

DESCRIPTORES: Tuberculosis; Diagnóstico Tardío; Servicios de Salud Comunitaria; Biología Molecular; Percepción del Tempo.

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INTRODUCTION

Tuberculosis (TB) is a severe public health problem, as it is one of the most prevalent human infections in the world, due to the high cases of multi-drug resistance and being one of the top ten causes of death worldwide[1]. Data from the latest epidemiological bulletin from the Ministry of Health pointed out that, in the world in 2017, approximately 10 million people developed it and, of these, 1.3 million died[2].

Despite these indexes, it is considered that there has been great progress in its control with the development of programs and goals that have contributed to reducing the occurrence of new cases, as well as their biopsychosocial impacts[2]. As it is a disease that dates back to antiquity and is strongly linked to socioeconomic determinants, diagnosis and effective treatment have become difficult, compromising the ambitious goal of eliminating the disease as a public health problem for the year 2050[3].

According to a report by the Pan American Health Organization, successful results are identified in reducing the mortality rates by 2.5% on average per year, as well as the coefficients of incidence of new cases, which have decreased by 1.4% per year, since 2000[2]. In the regions where there are more social and economic inequalities, these advances are slower. In the Americas, where the largest number of underdeveloped countries is found, around 50 thousand people are unaware that they have the disease, favoring the transmission chain of the *Mycobacterium tuberculosis*, its causing agent[4].

In Brazil, the North region has the highest TB incidence rate among Brazilian regions (44.1/100,000 inhabitants). This data is consistent with the serious situation of the disease in the state of Pará, the fifth state in incidence (40.7/100,000 inhabitants) and its capital, Belém, the fifth capital incidence in Brazil (62.7/100,000 inhabitants). This scenario demands more effective control actions at all stages, contributing to the breakdown of the disease's transmissibility[2].

One of the key points for TB control is early diagnosis, which can be through bacteriological confirmation considering the positive result of two bacilloscopies, or by the detectable Molecular Rapid Test, positive culture and/or a positive bacilloscopy associated with chest radiography that is suggestive for TB[5]. Effective diagnosis helps with timely treatment and, in this sense, new technologies have been incorporated into health services to fill the time gap between these two stages[6].

Among these technologies, the Rapid Molecular Test (RMT) was instituted in order to speed up diagnosis and treatment[6]. RMT-TB is an automated, simple, fast and easy test in the laboratories in which it was incorporated for TB diagnosis and, simultaneously, the verification of resistance to rifampicin[7]. It has 90% sensitivity and 99% specificity, being highly efficient for TB early diagnosis[8].

Thus, as a way to assist in the diagnosis and try to reduce mortality due to pathology, the Ministry of Health acquired 160 RMT-TB equipment, which were distributed among the 92 municipalities that make up the Rapid Test Network for Tuberculosis (RTN-TB)[9]. The implementation of this test in Brazil took place in July 2014, after approval by the National Commission for the Incorporation of Health Technologies for its use in the Unified Health System (*Sistema Único de Saúde*, SUS)[1].

In the state of Pará, the municipalities of Belém and Ananindeua were selected to participate in the RTN-TB in 2014. In Belém, the laboratories of two Municipal Health Units centralized the equipment for processing the samples and act as a reference for carrying out this diagnostic test of the Units in their coverage area.

The RMT is extremely useful in the State of Pará due to its geographic dimensions and the existence of populations that live around the rivers that bathe the state and that, because they live, mostly, of subsistence agriculture, they have few resources to cover

transport for the city regularly. In addition, setting up a laboratory for sputum culture, in accordance with the levels of biosafety required by law, would be costly in these places, which justifies the use of the test in the State and its choice to join the Network.

In this context, it is imperative to understand that control actions should be a priority in primary care[10], showing that it is relevant to know the time that has elapsed since the collection of material for the diagnostic examination until the beginning of treatment, since, from that, it is possible to list improvements aimed at optimizing that time and, consequently, reducing the number of infected people.

In this sense, this study aimed to identify the time elapsed between the collection of material for RMT and the beginning of treatment for TB in units that forwarded samples for processing in Centralizing Units, establishing the following hypotheses:

H1: Centralizing the processing of the RMT exam increases the time for diagnosing and treating tuberculosis;

H0: Centralizing the processing of the RMT exam does not increase the time for diagnosing and treating tuberculosis.

METHOD

An analytical epidemiological study developed in two Basic Health Units located in the city of Belém, here called Centralizing Units A and B, which attend to spontaneous demand and referring patients with suspected TB for diagnosis and treatment, on an outpatient basis. They have a laboratory service including smear microscopy and RMT scan for TB. It is highlighted that, in the state of Pará, the RMT was implemented exclusively in these two Units, meeting criteria pre-established by the Ministry of Health.

Data from 517 cases were collected in both Units, and 221 were excluded because they presented incomplete data or because they were identified, in consultation with the SINAN, as a different way of entering a new case or people residing in other municipalities. Thus, 296 new cases with laboratory confirmation from December 2014 to December 2015 were included in the study in secondary sources (record books).

The produced data concern the exams that were collected and processed in the Centralizing Units A and B, which are the ones that perform the exams, and those sent from the respective units in the coverage area of these Centralizing Units, identified here as Units A1 and B1. The researchers were divided into two groups to collect data in each Unit: one group collected the data referring to the samples of patients from the Centralizing Units and the other, the samples that came from the Units in the coverage area of these Units (A1 and B1).

The Respiratory Symptomatic Books were consulted to obtain the date of ordering the exams and the date of receipt of the results, the Laboratory Record Book and laboratory protocol to obtain the date/time of receipt of the sample, in addition to the Record Book of the RMT, a registration instrument created by the Centralizing Units to control the exams performed in this modality. In order to obtain the starting date for the treatment of the cases of the Centralizing Units, the Tuberculosis Case Book was checked, and of the Units that forwarded the samples, this information was obtained directly from the National System of Notifiable Diseases (*Sistema Nacional de Agravos de Notificação*, SINAN).

The team of researchers was composed of five nurses, two professors and one master's student of the Postgraduate Program in Nursing at the State University of Pará (*Universidade do Estado do Pará*, UEPA), and two from the Coordination of the Tuberculosis Control Program of the State Department of Public Health. Four students from the Undergraduate

Nursing Course at the UEPA also participated.

The collected data were recorded in a Microsoft Excel electronic spreadsheet elaborated by the researchers, which contained all the variables considered for the research and, later, transferred to SPSS, version 17. For analysis, a correlation was made between the variables, in order to identify the time elapsed between the laboratory diagnosis with the RMT and the beginning of treatment. For this purpose, the Mann-Whitney's U test, p-value ≤ 0.05, was used.

The study was approved by the Research Ethics Committee of the Nursing Course at the State University of Pará, under opinion No. 1,084,210.

RESULTS

Data relating to 296 patients were analyzed, of which 70 collected and accomplished tests at Centralizing Unit A and 49 at Centralizing Unit B. Of the units in the coverage area, 177 tests were sent, 145 records from area A1, and 32 from B1.

The comparative analysis of the time elapsed between the examination result and the start of treatment, considering the Centralizing Units and the Units in the coverage area, showed that the time intervals for the release of the examination result and for the start of treatment in the Units that sent the exams to the Centralizing Units did not show a statistically significant difference (p value ≥ 0.05). However, when analyzing the time between the result of the exam and the start of treatment in patients who underwent exams directly at the Centralizing Units, it was observed that there is a statistical difference for the time to start treatment at the Centralizing Units (A and B) (Table 1).

Table 1 - Mann-Withney's U test result regarding the time elapsed from the results of the exams and the beginning of treatment in the Health Units in the coverage area that forwarded samples to Centralizing Units A and B. Belém, PA, Brazil, 2016

Unit	Type	U	p-value
Centralizing Unit A	Exam Result	3025	0.180
	Start of Treatment	3343.5	0.000
Centralizing Unit B	Exam Result	1089	0.134
	Start of Treatment	409.5	0.019

Comparing the time to release the results of exams for Units in the coverage area that sent samples (A1) to be processed in Centralizing Unit A, with the time to release the results of the exams that were collected and processed in the Unit itself, it was observed (Figure 1) that the patients from Health Units in the coverage area (A1) received the exam result in a mean time of 0.5 days, that is, in a similar time when compared to the patients treated at Centralizing Unit A.

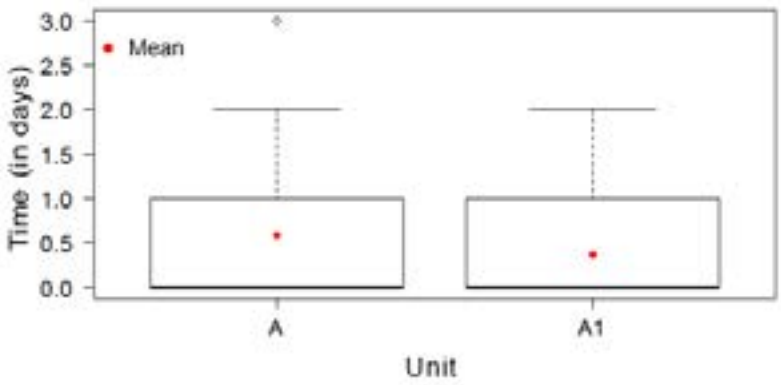

Figure 1 - Time taken to deliver exam results from the Units in the A1 coverage area with the exams collected and processed at Centralizing Unit A. Belém, PA, Brazil, 2016

Making the same comparison for the start of treatment time, it is observed (Figure 2) that the patients whose exams were sent by the Units in the coverage area A1 to Centralizing Unit A took longer to start treatment when compared to the patients of the Unit itself, and there are some time dispersions in the Centralizing Unit, that is, some patients took more than the mean time to start their treatments.

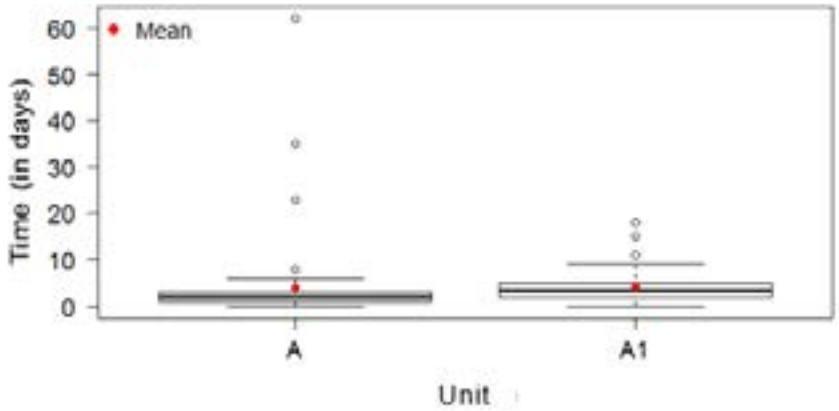

Figure 2 - Treatment start time for patients whose tests were sent from the coverage area (A1) with the treatment start time for patients whose tests were collected and processed in Centralizing Unit A. Belém, Pará, Brazil, 2016

Regarding the time to release the results of exams from the Units in the coverage area (B1) that sent the exams to Centralizing Unit B, it was observed that these results were released in a similar time to the patients seen in Unit B itself (Figure 3).

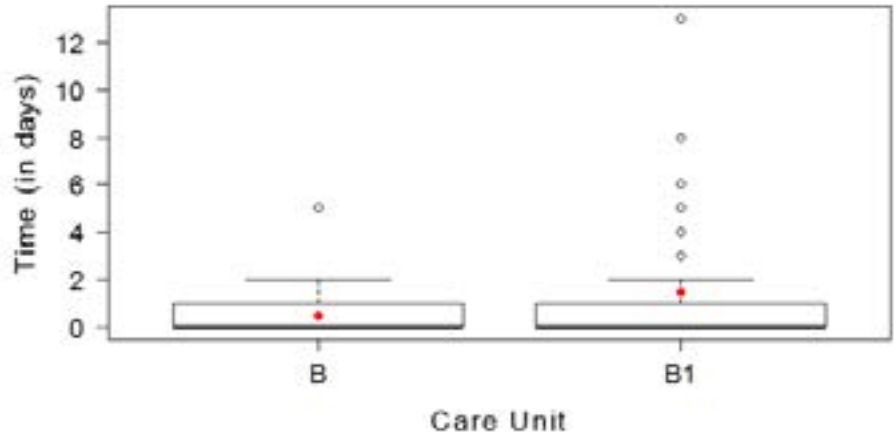

Figure 3 - Time of delivery of test results from the Health Units in the coverage area (B1) and the tests collected and processed at the Centralizing Unit (B). Belém, PA, Brazil, 2016

However, when comparing the time for starting the treatment, it is observed (Figure 4) that the patients treated at Centralizing Unit B took longer to start their treatments, compared to those from Units in the B1 coverage area.

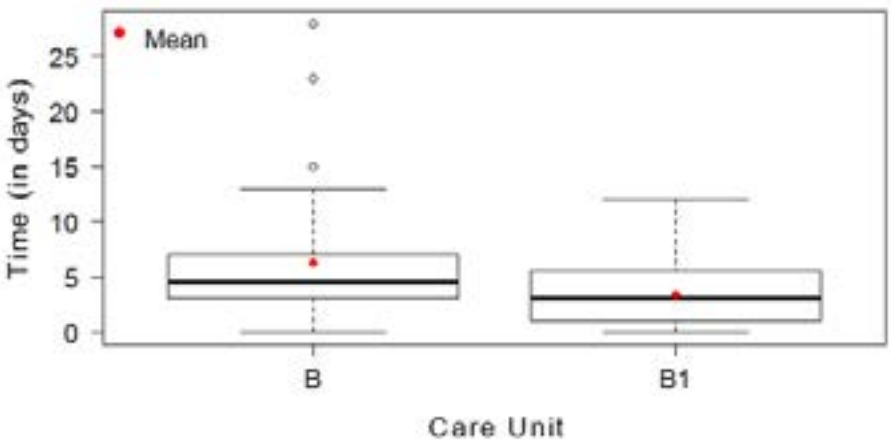

Figure 4 - Treatment start time for the patients with results from the Health Units in the coverage area (B1) and treatment start time for patients whose tests were collected and processed at Centralizing Unit B. Belém, PA, Brazil, 2016

DISCUSSION

The results of this study expressed the time elapsed between the diagnosis and the beginning of TB treatment in two centralizing units with their respective coverage units in Belém, Pará. It was evidenced that there was no statistically significant difference for the time related to releasing test results; however, there was a statistical difference for the time

related to the beginning of the treatment in the Centralizing Units (A and B). That is, the time for diagnosing the disease is similar between the centralizing units and those in their area of coverage; however, for the beginning of treatment, there was a difference in time between the centralizing units and the coverage units.

A study conducted in Durban, South Africa, using the Xpert test in a centralizing laboratory, identified a delay between the time of diagnosis and treatment start, due to the longer processing and inefficient transport of test results to the health services, affecting the clinical status of patients with TB[11].

This demonstrates that, when deploying new technologies for diagnosis, one must take into account the logistics that involves its operation, because, even if the examination is fast processed, if the logistics are not efficient, it ends up not producing the expected impact. The National Health Surveillance Agency recommends the need for a logistics network for the transportation of biological samples, in order to guarantee safety, punctuality and reliability in their transit[12]. Thus, it is worth noting that transport and storage can affect the viability of the samples, resulting in harms and analysis errors[13].

A study carried out with newly diagnosed patients in Uzbekistan found that the mean delay was 27 days to start treatment, being related to self-medication and, in some cases, only to the use of antibiotics that delayed the symptoms of the pathology. Thus, delays in diagnosis and initiation of treatment should be reduced to prevent the spread of TB[14].

It is a fact that, when the health professional suspects and requests tests in a timely manner, the time for diagnosis is significantly reduced. Thus, the success of timely treatment is not only related to the diagnostic method that is being used, but to the sensitivity of the health professional to identify possible respiratory symptoms in the service[15].

The efficacy in controlling TB infection is directly related to the time taken to identify respiratory symptoms, early diagnosis, and timely treatment[16]. Although the ideal time for diagnosing the disease has not been settled in the technical manuals, an essential factor to increase its incidence is the delay in the diagnosis and treatment of cases with bacteriological confirmation, thus maintaining the chain of transmission[17].

It is understood that the study had some limitations because it was carried out, for the most part, with data available in the Basic Units, which did not always have complete records. Even so, its results indicate that the use of the RMT in the public health network is opportune for TB diagnosis, even in conditions of centralized processing for the exams, referring to the need for accomplishing further studies in order to assess the real benefits of this technology for the health care and disease control.

CONCLUSION

It can be said that centralizing the processing of the RMT exam did not interfere with the time for TB diagnosis and treatment, even forwarding the samples between the services, confirming the null hypothesis formulated for this study.

The RMT offer with centralization in strategic Units proved to be timely and able to respond to the needs of prompt diagnosis, regardless of whether the patient is linked to the Unit that performs the test or to the Unit that only collects the material and sends it for processing.

Therefore, it is understood that it is necessary to value the qualification of the work processes, instituting adequate logistics to ensure the transport of the samples with agility and regularity, in order to provide readiness for access to the diagnosis and to provide immediate treatment. It is also important to highlight the importance of the health

teams adding to their daily practices the use of technology, with intranets systems, to allow accessing to the results immediately after their processing, both for the team of the Centralizing Units and for the teams of the Units that have sent the samples.

In addition, it is necessary to better assess the cost-benefit ratio of using this strategy, aligning it to the impacts on TB morbidity and mortality indicators.

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