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Availability and economic feasibility (retrospective cohort study) of the implementation of rapid diagnostic methods for tuberculosis Xpert MTB / RIF in Kazakhstan.

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ABSTRACT

This article is about Xpert MTB / RIF as the most effective and fastest method of diagnosis, which confirms tuberculosis and rifampicin resistance within 2 hours. The effectiveness of this method has been proved by various studies conducted in a number of countries. It was established in Kazakhstan that the time for giving adequate chemotherapy for anti-TB drugs (PTC) of the first line was 3 days, and the prescription of anti-TB drugs for the second line was 7 days, based on the results of a prospective cohort study evaluating the implementation of Xpert MTB / RIF. This is a significant advantage over traditional methods of diagnosing tuberculosis. Molecular genetic rapid diagnostic method Xpert MTB / RIF is the most specific and sensitive method of diagnosis of pulmonary tuberculosis, in contrast to traditional smear microscopy. According to a systematic survey of 18 studies conducted in different countries of the world, the sensitivity of the method is 88%, the specificity of the method is 98% [6]. In connection with the proven effectiveness of the method, there is widespread implementation and expansion of the use of this method in the country.

Keywords: Xpert MTB / RIF, tuberculosis, rifampicin resistance, Kazakhstan, diagnosing.

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INTRODUCTION

According to the World Health Organization, there are approximately 10.4 million tuberculosis patients worldwide, 5.9 million (56%) of whom are male patients and 3.5 million (34%) are women, as well as 1.2 million (11%) are HIV-associated tuberculosis patients. In addition, 1.4 million people died of tuberculosis. The new global WHO strategy "End TB" was developed in 2016. One of the foundations of this strategy was "development of integrated patient-oriented medical care and prevention of tuberculosis." The first basis of the component is the earlier detection of tuberculosis, its drug susceptibility, the conduct of systematic screening among contacts and risk groups [1]. This suggests that early and timely detection of tuberculosis and drug resistance is the main and priority direction of the development of National TB programs around the world.

Kazakhstan is among the 20 countries in terms of incidence of tuberculosis and multidrug-resistant tuberculosis (MDR-TB). Primary MDR TB in Kazakhstan is 25%; and the acquired is 43% [1-2]. Previously, the identification of drug-resistant tuberculosis in Kazakhstan is a priority area for the development of the National TB Service Program.

WHO recommended the molecular genetic testing of Xpert MTB / RIF for the early detection of tuberculosis and drug resistance of MBT [5]. The number of cartridges used increased from 550,000 in 2011 to 6.2 million in 2015. In 2015, 48 countries with a high burden of tuberculosis adapted diagnostic algorithms that approved the use of Xpert MTB / RIF as the first diagnostic test used in people with suspected on tuberculosis. These countries account for 10% of the total number of tuberculosis cases in 2015 [1].

Following the recommendations of the WHO, the National TB Program of Kazakhstan decided to use and implement Xpert MTB / RIF in 2012 to improve detection and management of MDR-TB [3]. Now all 16 regions of the republic are equipped with Xpert MTB / RIF. Molecular genetic test Xpert MTB / RIF is carried out by all people with suspected tuberculosis, especially with negative smear microscopy. The national management of Xpert MTB / RIF says that this rapid diagnostic method is applied to all people with suspected TB; people living with HIV at risk of developing TB; persons with a risk of developing MDR-TB; children with suspected development of TB; people with extra-pulmonary tuberculosis when using specific samples [1].

In accordance with the Order of the Ministry of Healthcare of the Republic of Kazakhstan No. 19 of August 22, 2014 "On approval of the Instruction on the organization and implementation of preventive measures for tuberculosis," the use of Xpert MTB / RIF is a mandatory and priority method for diagnosing tuberculosis [4].

Relevance of the study

In accordance with the Comprehensive TB Control Plan for 2014-2020 and the new strategy of integrated tuberculosis control in the Republic of Kazakhstan, improving the availability of modern effective technologies for diagnosis and treatment of TB and M / XDR TB is a priority in the development of the country's TB service [7]. However, it should be noted that earlier detection and diagnosis of tuberculosis, incl. tuberculosis with drug resistance, in the republic has its strengths and weaknesses. Along with the widespread introduction of molecular-genetic express methods for diagnosing tuberculosis, there has been a significant reduction in the availability of these tests to the population [8]. This is due to a significant decrease in investments in TB activities by international donors [8].

In this connection, the maintenance and servicing of this apparatus is a burden for the medical anti-tuberculosis institutions and regional health departments of the country.

In the "Updated recommendations of the WHO application of Xpert MTB / RIF" from 2014, it is said that further research into the medical effectiveness of this method is inexpedient and unreasonable. According to WHO strategic development, research should focus on evaluating the cost-effectiveness and cost analysis of Xpert MTB / RIF in different country-specific programming environments [9].

This study was planned to further expand the study of innovative methods for the rapid diagnosis of tuberculosis. The authors are interested in the financial accessibility of the Xpert MTB / RIF express method for Kazakhstan in the current economic conditions. The article assesses the provision of access to the method among the population and assesses the financial aspects of the application of Xpert MTB / RIF in Kazakhstan.

MATERIALS AND METHODS

The materials from the National Register of the patient with tuberculosis of the Ministry of Health of the Republic of Kazakhstan were used for the work. The data were copied from the registration forms of TB 03 / y (a register of patients with tuberculosis of a certain district or region). The duration of the study was 3 years (2013-2015).

53799 patients of the 1st and 2nd category were registered in the database from 2013 to 2015. 21 947 patients using the molecular-genetic express method for the detection of tuberculosis Xpert MTB / RIF were selected by a continuous method. The data on the sex, age, type and category of the patient, the localization of the process, the results of the examination, the outcome of the disease were collected.

Statistical processing was carried out on the SPSS Statistics version 17. All patients who were subjected to Xpert MTB / RIF analyzes during the study period were selected from the register forms TB 03 by a continuous method.

All patients underwent standard tests, according to the algorithms for diagnosing tuberculosis in the republic. Xpert MTB / RIF is performed with a positive result of a sputum smear microscopy on an MBT when it is not possible to use the HAIN test. If the sputum smear microscopy is negative on patients with suspected tuberculosis, Xpert MTB / RIF is mandatory. Simultaneously, the pathological material is sown on a dense medium of Levenshtein-Jensen, and liquid media of the automated system Bactec MGIT-960. Diagnostics of Xpert MTB / RIF is performed in both extrapulmonary and pulmonary forms of tuberculosis [3].

The availability of the method was studied by regions of the republic. The percentage of patients diagnosed with the Xpert MTB / RIF express method among registered patients in various areas was calculated.

The economic benefit from the application of the Xpert MTB / RIF express method was calculated based on the average cost of traditional and accelerated diagnostic methods. The average costs consisted of direct and not direct costs for diagnosis. The cost for 1 diagnostic test was calculated in national currency - tenge, then it was transferred to USD, at the rate of 1 USD = 330 tenge (as of October 25, 2016).

RESULTS

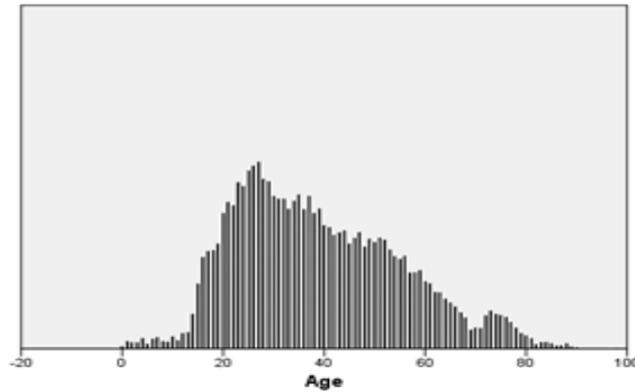
The results of the study were as follows. The distribution of patients by year is presented in Table 1.

Table 1. Distribution of patients by year of study

| Year | Number | Percent |
|-------|--------|---------|
| 2013 | 3592 | 16,4 |
| 2014 | 9366 | 42,7 |
| 2015 | 8989 | 41,0 |
| Total | 21947 | 100,0 |

The greater part was equally composed of patients from 2014 and 2015 (42.7% and 41%). This is explained by the expansion of the implementation of the method in the last 2 years in the country and the equipping of all regional laboratories with the Xpert MTB / RIF.

Pulmonary localization of tuberculosis was 91.8% (n = 20,138), extrapulmonary tuberculosis was 8.2% (n = 1809). 60.4% (n = 13 261) were men; 39.6% (n = 8681) were women. The average age of the patients was



38.9 ± 16.4 (Figure 1).

Figure 1. The distribution of patients by age

64% (n = 14053) of the patient were registered for the 1st category of treatment. They represented the category "a new case of tuberculosis" regardless of the localization of the process. Repeated cases of tuberculosis (category 2) were 36% (n = 7894). Patients were classified as follows (Table 2):

Table 2. Classification of patients

| Nº | Type of patient | Number | Percent |
|----|--------------------------------|--------|---------|
| 1 | New | 12 943 | 59,0 |
| 2 | Relapse | 3505 | 16,0 |
| 3 | Recurrence of MT (-) | 2816 | 12,8 |
| 4 | Transferred | 1959 | 8,9 |
| 5 | Failure of treatment | 349 | 1,6 |
| 6 | Treatment after a break | 229 | 1,0 |
| 7 | Treatment after a break MT (-) | 94 | 0,4 |
| 8 | Failure to treat MT (-) | 52 | 0,2 |
| | Total | 21947 | 100,0 |

The effect of rapid diagnostic results on outcomes of tuberculosis treatment in this cohort of patients was investigated to assess the effectiveness of the application of Xpert MTB / RIF. The outcomes of the disease patients were grouped into favorable and unfavorable to improve the effectiveness of the analysis. The favorable outcomes included "cured" and "treatment completed". The adverse outcomes included "violation of the regime," "failure of treatment," "transferred to category 4," "died." The outcome of "transferred" was left unchanged. The following results were obtained analyzing the impact of Xpert MTB / RIF on the results of treatment. (Table 3).

Table 3. Influence of Xpert MTB / RIF results on disease outcomes

| Nº | Xpert MTB / RIF Results | Results of treatment | | |
|----|-------------------------|----------------------|-----------------|---------------|
| | | Favorable outcome | Adverse outcome | Transferred |
| 1 | TB+/R indefind | 1,2% (n=147) | 0,9% (n=96) | 1% (n=4) |
| 2 | Invalid result / error | 2,0% (n=254) | 1,1% (n=95) | 1,1% (n=4) |
| 3 | TB- | 50,5% (n=6365) | 33,5% (n=2993) | 49,6% (n=188) |
| 4 | TB+/R- | 45,4% (n=5730) | 42,5% (n=3805) | 44,6% (n=169) |
| 5 | TB+/R+ | 0,9% (n=115) | 22,0% (n=1968) | 3,7% (n=14) |
| | Total | 100% (n=12611) | 100% (n=8957) | 100% (n=379) |

A greater percentage of favorable outcomes 50.5% (n = 6365) was recorded in the absence of detection of tuberculosis in the biomaterial (the result of TB-). The share of unfavorable outcomes was 22.0% (n = 1968) with simultaneous detection of tuberculosis and rifampicin resistance. The data obtained were statistically significant; χ^2 was 2840.9; the degree of freedom was 10, $p < 0,001$. All this suggests that this test is highly reliable and the simultaneous detection of tuberculosis and rifampicin resistance reduces the likelihood of favorable outcomes.

Table 4. Availability of the Xpert MTB / RIF express method

| | Number of patients | % |
|---|--------------------|------|
| Total number of patients in the database | 53799 | 100 |
| Patients surveyed by Xpert MTB / RIF | 21947 | 40,8 |
| Patients surveyed without Xpert MTB / RIF | 31852 | 59,2 |

In general, 53 799 patients passed the database in 3 years. 21 947 patients were able to be examined by the Xpert MTB / RIF express method and this amounted to 40.8% of all registered patients. Approximately 41% of the patients were prescribed timely and adequate antituberculosis treatment in the early stages.

Table 5. Percentage of coverage by the Xpert MTB / RIF express method in various regions of Kazakhstan, of the total number of registered patients of the 1.2 category

| Region / cities | 2013 | 2014 | 2015 |
|-------------------------|------|------|------|
| Akmola | 37,0 | 49,0 | 83,4 |
| Aktobe | 0,6 | 38,7 | 75,4 |
| Almaty | 10,7 | 43,7 | 55,1 |
| Atyrau | 25,8 | 71,8 | 95,1 |
| East Kazakhstan region | 37,5 | 56,9 | 73,1 |
| Almaty | 19,1 | 31,1 | 38,0 |
| Astana | 26,1 | 63,7 | 55,6 |
| Zhambyl | 14,8 | 72,6 | 69,4 |
| West-Kazakhstan region | 0,9 | 53,5 | 74,1 |
| Karaganda | 15,8 | 53,1 | 66,7 |
| Kostanay | 20,8 | 71,2 | 72,0 |
| Kyzylorda | 1,1 | 39,9 | 64,3 |
| Mangistau | 28,5 | 75,0 | 74,4 |
| Pavlodar | 23,7 | 65,6 | 86,7 |
| North-Kazakhstan region | 0,4 | 57,1 | 85,5 |
| South-Kazakhstan region | 10,3 | 33,1 | 40,5 |
| Kazakhstan Republic | 16,8 | 51,9 | 66,0 |

The coverage of the Xpert MTB / RIF express method in different regions of the country is shown in Table 5. Annually, the percentage of using the Xpert MTB / RIF express method has been increased from 16.8% in 2013 to 66.0% in 2015. At this time, the task of the National TB program is to identify opportunities to find funds and expand the application of the Xpert MTB / RIF express method in the country.

The financial benefits that the government had from the introduction of the molecular-genetic express method Xpert MTB / RIF were calculated in order to justify the economic costs. A comparison of the cost of various methods for diagnosis of tuberculosis, taking into account the definition of drug resistance of MBT, was conducted. The cost included all costs, direct and indirect costs associated with the implementation of these analyzes.

Table 6. Average cost price of diagnostic tests in the Republic of Kazakhstan (in USD)

| No | Name of diagnostic tests | Cost of 1 diagnostic test |
|----|--------------------------------------|---------------------------|
| 1 | Lowenstein Jensen (LJ) Media | 19 USD |
| 2 | The automated system Bactec MGIT-960 | 32 USD |
| 3 | Hain-test | 58 USD |
| 4 | Xpert RIF/MBT | 84 USD |

* According to the National Center for Tuberculosis Problems of the Ministry of Health and the Republic of Kazakhstan

As can be seen from Table 6, the Xpert RIF / MBT express method is the most expensive diagnostic method. According to the calculations of the National Center for Tuberculosis Problems of the Ministry of Health and Social Development of the Republic of Kazakhstan, the cost of the study was 84 US dollars.

The authors calculated the costs of maintaining the patients until an adequate anti-tuberculosis treatment using Xpert MTB / RIF and without the use of Xpert MTB / RIF (Table 7).

Table 7. Costs of maintaining patients before an adequate antituberculous treatment (in USD)

| Diagnostic Methods | Result | Number of days of hospitalization before adequate anti-tuberculosis treatment* | Average hospital costs per day (USD)* | Expenses for the maintenance of the patient before adequate anti-tuberculosis treatment (USD) | Average Expenses | Average costs per patient until adequate treatment (USD) | The number of patients who underwent a 3-year base examination (USD) | Total costs for inpatient treatment before the adequate treatment in the country for 3 years (USD) |
|---|--------|--|---------------------------------------|---|------------------|--|--|--|
| Solid media by Lowenstein-Jensen | TB- | 75 days | 36,16 | 2 712,27 | 3 182,40 | 1 609,28 | 31 852 | 51 258 786,6 |
| | TB + | 30-45 days | 36,16 | 1 627,36 | | | | |
| | DST | 28 days | 36,16 | 1 012,58 | | | | |
| Analysis for liquid media of the automated system Bactec MGIT-960 | TB- | 42 days | 36,16 | 1 518,87 | 1 573,12 | | | |
| | TB + | 10-25 days | 36,16 | 904,09 | | | | |
| | DST | 7-10 days | 36,16 | 361,64 | | | | |
| Hain test with determination of drug resistance MBT | | 2 days | 36,16 | 72,33 | | | | |
| Xpert RIF/MBT | | 2 hours | 36,16 | 3,01 | | | 21947 | 66 060,47 |

* According to the National Center for Tuberculosis Problems of the Ministry of Health and the Republic of Kazakhstan

As can be seen from Table 7, the average cost per patient before the application of adequate therapy without the use of Xpert RIF / MBT was 1 609.28 USD. 31,852 patients did not undergo Xpert RIF / MBT screening, in total, 51,258,786.6 USD were spent on the contents of these patients before the appointment of adequate anti-tuberculosis treatment.

For patients examined by Xpert RIF / MBT for inpatient treatment, 66,060.47 USD was spent. The difference and the benefit of the spent sums is obvious. Even with all the high cost of Xpert RIF / MBT express

method, the cost of inpatient maintenance of patients before an adequate antituberculous treatment is much more expensive. Therefore, the use of the Xpert RIF / MBT express method for Kazakhstan's antituberculosis service is financially beneficial.

According to the National Center for Tuberculosis Problems, the Ministry of Health and the Republic of Kazakhstan plans to increase the number of studies per year to 75,000. Based on the calculations (1 study = 84 USD), the planned amount will be spent up to 6,300,000 USD, which is substantially lower than hospital costs research on Xpert RIF / MBT.

DISCUSSION

Kazakhstan stands at the stage of reforming the system of medical care for patients with tuberculosis. Since 2014, the focus of tuberculosis treatment has been shifted from inpatient to outpatient care. The patient-centered TB care approach to patient treatment is beginning to develop in the republic. The Integrated Tuberculosis Control Strategy was developed and approved. The strategy will step-by-step reduce hospital beds and integrate the PHC network with the TB service, and shift emphasis to Directly Controlled Treatment (NCL) in outpatient settings.

Implementation of this strategy is impossible without the development of an early detection system for tuberculosis. This principle is fundamental and necessary for the functioning of the integrated model of tuberculosis control. In this regard, the development of the application of molecular genetic rapid methods Xpert MTB / RIF acquire special significance.

A retrospective analysis for 2013-2015 of application of Xpert MTB / RIF method showed good results in medical aspects. A statistically significant relationship was found between the results of Xpert MTB / RIF and the outcome of the disease. However, the availability of the method was about 41%, although from year to year the application of the method is increasing.

The economic benefits for the state are also obvious. As the study shows, the state had a financial benefit by reducing the stay of patients in the hospital over the past 3 years using the Xpert MTB / RIF express method in Kazakhstan.

However, there is a dependence of the application of this method on the allocated financing. Uninterrupted supply of supplies, the allocation of new resources to expand funding for this area should be established for the full use of the express method Xpert MTB / RIF in Kazakhstan. Also, redistribution of funding from the stationary maintenance of patients for procurement and the smooth operation of the Xpert MTB / RIF express method should be done.

CONCLUSION

The first results revealed a statistically significant relationship between the results of the Xpert MTB / RIF rapid tuberculosis test and the outcome of the disease. Significantly reduced the likelihood of favorable outcomes with the simultaneous detection of tuberculosis and resistance to rifampicin. An increase in the application of the Xpert MTB / RIF express method to 41% was recorded for the analyzed period (2013-2015) in Kazakhstan. The financial benefit from the application of the Xpert MTB / RIF method for Kazakhstan was calculated. The benefit was due to reduced costs for inpatient maintenance of patients.

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