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- ФАРМАКОЭКОНОМИКА ТУБЕРКУЛЕЗА: МЕТОДОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ПРОВЕДЕНИЯ ИССЛЕДОВАНИЙ
- ФИНАНСИРОВАНИЕ СИСТЕМЫ ЗДРАВООХРАНЕНИЯ НА РЕГИОНАЛЬНОМ УРОВНЕ. ВЗАИМОСВЯЗЬ КАЧЕСТВЕННЫХ И КОЛИЧЕСТВЕННЫХ ПОКАЗАТЕЛЕЙ С ВЕЛИЧИНОЙ ФИНАНСИРОВАНИЯ ЗДРАВООХРАНЕНИЯ

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PHARMACOECONOMICS OF TUBERCULOSIS: THE METHODOLOGICAL ASPECTS OF STUDIES

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Abstract

Main aspects and possible directions of pharmacoeconomic and clinical economic studies on tuberculosis are covered. The main directions of the described possibilities of pharmacoeconomics are the analysis of both individual health technologies (drugs and diagnostic tests), modes of therapy, and assessment of changes in clinical guidelines and standards of treatment of TB patients. Described changing epidemic affect the structure of the disease, the innovative antituberculosis drugs and new practice in the treatment of patients affect on the effectiveness of the treatment and its cost. Features of the methodology of pharmacoeconomic analysis in tuberculosis are paid attention to in this article.

Key words: pharmacoeconomic studies, pharmacoeconomics, methodology of pharmacoeconomic studies, tuberculosis, phthisiology, innovative antituberculosis drugs, choice of effectiveness criteria in tuberculosis study, tuberculosis treatment cost analysis.

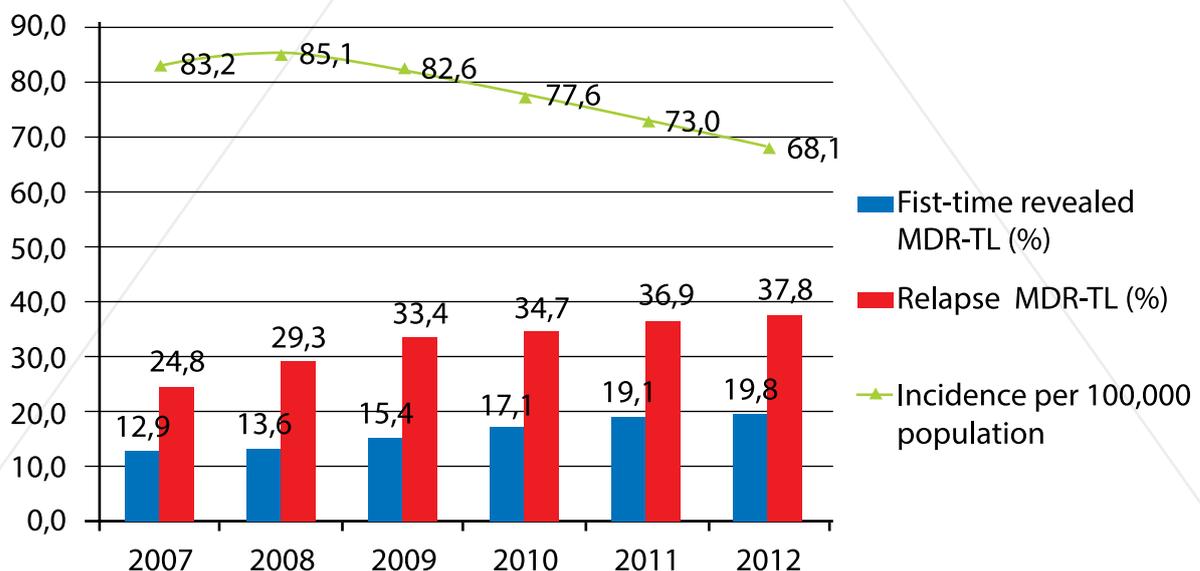
Introduction

The new drug antituberculosis drugs and diagnostic tests are currently and actively introduced, health professionals offer new clinical guidelines for the management

of patients with tuberculosis, as well as improving the system of drug supply. It is necessary to consider many aspects in the treatment of a specific disease for rational decision-making during introduction new medical technologies and assess the adequacy of the use of health services: the effectiveness of selected modes of therapy, diagnostic capabilities, financial and organizational capacities of the health system at all levels.

In addition, the changing epidemiological patterns of the disease is an important factor [1,2]. The analysis of statistical data on tuberculosis for the period from 2005 to 2012 showed that there is a reduction in the incidence of tuberculosis c 83,8 to 68,1 per 100 thousand population, the prevalence of up to 178,7 per 100 thousand population and mortality rate to 12,5 per 100 thousand population, however, these indicators are far from those in developed countries (USA, Canada, Western Europe). However, against the background of stabilization or reduction of other epidemiological indicators, the proportion of patients with multidrug resistant tuberculosis continues to grow (from 9,5% to 19,8% for the analyzed period of time) that brings high epidemic risk due to low efficiency, long duration of treatment, as well as the high cost of treatment of patients with multiple and extensively drug-resistant diseases (Figure 1). [3,5,6,8]

Figure 1. Statistical data of tuberculosis and changes in the epidemiological situation of tuberculosis with multiple and extensively drug-resistance.





In such circumstances, the decisions on the implementation of those or other medical technologies should include comprehensive and evidence-based assessment. In this way, the pharmacoeconomics are able to give evidence-informed decisions in the field of tuberculosis, as it is the science that studies in comparative terms the relationship between cost and efficiency, safety and quality of life when alternative treatment is. Broad methodological apparatus of pharmacoeconomics includes analysis of the methods applied at all levels of the health system and is able to take into account the specifics of the treatment of patients with tuberculosis.

At the present day, Laboratory of pharmacoeconomic studies of I.M. Sechenov First Moscow State Medical University conducted 6 pharmacoeconomic studies on the tuberculosis. The main directions of pharmacoeconomic studies in the field of tuberculosis at the present time are:

- Analysis of the implementation of new drugs;
- Analysis of the implementation of diagnostic tests;
- Analysis of the application of the chemotherapy regimens used in certain groups of patients;
- Cost of illness;

Pharmacoeconomic research on the tuberculosis have their aspects related to the considered nosology and approaches, standards of its treatment. This article will be discussed in more details, the main directions of pharmacoeconomic studies in tuberculosis and related aspects of the research will be covered.

Analysis of the implementation of new drugs and diagnostic tests

Foreign and domestic pharmaceutical companies are actively working on the drugs with new molecules in the composition or which is effective combinations of previously known drugs. Health professionals include innovative drugs in the regimen of tuberculosis instead of losing its efficacy, or in addition to them. Currently, considering such drugs for inclusion in the regimen of tuberculosis, the health professionals need comprehensive assessment and scientific basis for their implementation in clinical practice. Evaluation of the introduction of new medical technologies should include their analysis from the point of view of their efficiency and costs associated with them. The analysis of the use of such drugs in different chemotherapy regimens for tuberculosis patients is possible by using methods of analysis «cost-effectiveness» and «cost-utility». These methods allow us to estimate the ratio of the efficiency or quality of life and treatment costs, as well as consider the safety of the considered schemes of treatment. Thus, comparison of several alternatives of treatment is possible to choose the one with the cost of which will be minimal per unit of effectiveness.

For example, some of the new combined anti-TB drugs have comparable or greater effectiveness than the same set of monodrugs, but often have a lower cost of treatment and provide greater patient compliance, which makes the application more cost-effective for the healthcare system. In actual practice of pharmacoeconomic studies the specialists are often not limited with a simple comparison of «cost-effectiveness» ratio for the analyzed medical technologies. Innovative medical technologies are not only more effective, but as a rule, considerably more expensive, and they require more profound pharmacoeconomic analysis using incremental indicators and budget impact analysis. The situation with the presently implemented anti-TB drugs is the same: after years of «stagnation» of innovation in tuberculosis in recent years (2011-2013) in the pharmaceutical market the new molecules with considerable effectiveness against pathogens of tuberculosis appear and require the expenditure of significant additional funds.

Incremental indicators ICER and ICUR give the possibility to estimate the ratio of the cost increase to the efficiency gains. In other words, this pharmacoeconomic method allows to estimate the additional costs of budget funds for each additional unit of effectiveness. Received incremental parameters are compared with a threshold willingness to pay (GWP), which equals according to the WHO guidelines 3 x GDP per capita.

It should be noted that the comparison with a threshold of willingness-to-pay-resorted is used only with some indicators of the utility (QALY), in some cases LYG) are used. Thus, the assessment of possibility of introduction of new more expensive anti-TB drugs directly to the economic conditions of the specific country in which you plan to use these drugs is conducted.

Different criteria of effectiveness of the TB patients treatment are used in pharmacoeconomic studies on tuberculosis. The following end-points are the most important: life years gained (LYG), quality adjusted life years (QALY), disability adjusted life years, (DALY). However, the information search among pharmacoeconomic and clinical studies On tuberculosis shows that the endpoints assessment in tuberculosis is rare. The most used among these indicators is the DALY and in most other cases, there are only data on clinical indicators such as: smear conversion, improvement in radiographic progression (closing cavities of decay).

However, according to the Federal clinical guidelines for the diagnosis and treatment of patients with respiratory TB (23 January 2014) and the Ministry of health of the Russian Federation No. 109 «On improving TB control in the Russian Federation» dated 21 March 2003, the mentioned clinical indicators are the most important criteria for an effective treatment of TB patients.

Held during pharmacoeconomic research cost analysis for new anti-TB drugs and diagnostic tests also has its own characteristics related to nosology.

Cost analysis of new anti-TB drugs has its own peculiarities connected with the disease. Treatment of tuberculosis is carried out in 5 standard modes of therapy (I, IIA, IIB, III, IV), also individualized therapy regimens are used, the purpose of which is connected with the test results of drug susceptibility of the patient.

Each of the modes requires intensive phase of treatment (2 to 10 months in a hospital and of treatment continuation (4 to 16 months as an outpatient or day hospital) and includes several drugs. In this regard, methodologically correct will be accounting of all the costs of drugs that are included in the concrete investigated mode of therapy and all phases of therapy. Despite low cost of adverse events compensation in the total cost of treating of one case of tuberculosis with different modes of therapy, the share of this category in the overall cost can range from 0.25% (V mode) up to 5% in some cases, treatment for mode I, which also requires to take into account these costs. Thus, the evaluation of the application of new anti-TB drugs isolated from the evaluation of the whole scheme of pharmacotherapy in general (or assessment of the individual phases of therapy without taking into account the full cost of treatment) makes no sense and leads to significant errors in the results of pharmacoeconomic studies. In practice, the decisive factor in the cost estimate for the new therapy can be a total savings of both direct and indirect costs. For example, in the situation when an innovative product is added to the standard treatment regimen for patients, direct costs should increase, however, the medical technology can significantly reduce the duration of the intensive phase of therapy, thereby reducing direct costs (costs while in the hospital) and indirect costs (associated with decreasing term disability and time of disability).

It should be noted that pharmacoeconomic analysis of innovative drugs and diagnostic tests can be performed on stages before the release of the drug in the pharmaceutical market («pre-launch»). At this stage, using the data obtained from clinical studies on efficacy and safety, pharmacoeconomics gives the possibility of defining the objective price on the drug and subgroups of patients for whom the benefits of supplementation will be the greatest. [9, 10] Research on the stage «to launch» is important for new drugs intended for specific groups of patients (for example, drugs only for patients with multiple drug resistance pathogen) or for introduction on the market of diagnostic tests. In the case of screening testing technologies, intended group of potential recipients of services may include hundreds of thousands or millions of people. State purchase of more sensitive and specific diagnostic tests in such quantities can assume the high financial costs and the change of procurement patterns that must be estimated in advance. To assess the competitiveness of such technologies on the «pre-market» stage can be determined pharmacoeconomic reasonable rates and budget impact analysis, which will allow you to calculate the amount of budgetary savings or extra costs.

Thus, pharmacoeconomic studies aimed at the evaluation of specific drugs or diagnostic tests that allow choosing the most cost-effective medical technologies within a well-defined group of patients, thereby improving the quality of care and reducing costs to the state for treatment of patients

Pharmacoeconomic analysis of the modes of therapy and pharmacoepidemiological aspects

The new federal guidelines for the diagnosis and treatment of TB patients and the gradual introduction of molecular genetic methods for testing drug resistance change current orders assigning modes of therapy, their composition and duration. Thus, in practice the treatment of extensively drug-resistant (EDR) tuberculosis a new V mode of therapy is introduced and with the introduction of molecular-genetic methods application IIB regimen becomes «questionable» and the change of the timing of hospital stay with MDR and XDR tuberculosis.

Basing on industry performance indicators of TB control in the Russian Federation (2011-2012) it can be assumed that the described changes in the scope of the Russian Federation will cover a minimum of 10,000 new cases of TB in 2014. The introduction of such large-scale initiatives can significantly change the structure of budget expenditures in tuberculosis. A comprehensive assessment of the consequences of such changes is necessary and the rationale for its implementation from a scientific point of view is one of the stages must be pharmacoeconomic evaluation. In the most comprehensive pharmacoeconomic research in the field of phthisiology the following aspects of treatment of patients with tuberculosis should be reflected: the emergence of remote consequences

and costs on them (frequency of occurrence of drug resistance and the transfer of patients to other modes of therapy, frequency of relapses), epidemic indicators and indicators of system health (prevalence of the disease in the region, the percentage of patients treated by a particular mode of therapy), as well as the possibility of new methods of diagnostics

It was previously described that treatment of patients with various chemotherapy regimens may vary significantly in duration of treatment, and cost. As shows the analysis of the «costs» held in the framework of the «Pharmacoeconomic studies on the use of modes of treatment for TB patients with multiple and extensively drug-resistant» Laboratory of pharmacoeconomic studies of I.M. Sechenov First Moscow State Medical University direct costs per patient by use I and IV therapy regimens are more than 4 times and is currently being installed V regime of chemotherapy for patients with extensively drug-resistant - 9.5 times (Figure 2) [5,7,8, 11] In addition, hospital stay time and indirect costs for different modes of therapy significantly differ.

A comparative analysis of several methods of treatment taking into account many parameters used schemes are possible using simulation. Such multivariate analysis is conducted by building the decision trees and Markov models. Foreign and domestic experts in the field of pharmacoeconomic studies tend to create automatic models-calculators that can automatically calculate and modify the results of the analysis using the input data on the effectiveness and cost of drugs and epidemiological information. Pharmacoeconomic analysis of the treatment of certain patient groups comparing their treatment on different modes of therapy is an interesting direction of research in tuberculosis. According to experts and in connection with the application of new methods of drug susceptibility testing, some of the modes of treatment become less relevant, for example, the use of IIb regimen for patients with high risk of MDR.

Due to changes in the epidemiological patterns of the disease and increase of drug resistance to many commonly used the frequency of drugs prescribing change. Also specialists in dire need to assess the effectiveness of real-life practice in the treatment of patients with I, IV, and V modes of therapy and the assessment of the probability of transition to other modes in the future., the long-term effects of treatment of patients often remain unaccounted in these questions, namely: frequency amplification of drug resistance, transition probabilities for treatment by other modes, speed and frequency of abacillation, recurrence of tuberculosis and the associated increase in the cost of treatment. [1]

Conduct of pharmacoeconomics studies of use of different modes bring several opportunities for improvement of TB treatment. At first, taking into account data on the actual effectiveness and statistical data on the number of patients treated in certain modes, it becomes possible to assess the impact of adjustment of clinical guidelines (with the exception of some modes and the inclusion of the other). In the future, this will allow to use more effective treatment regimens of patients,

thereby reducing the reservoir of infection in the Russian Federation and reducing the tension of the epidemiological situation. Secondly, the evaluation of statistical and epidemiological indicators will allow you to more accurately predict the need for cash and needs the drugs to patients at any level of health (state, region, center).

The treatment coverage and the effectiveness of treatment of patients with MDR and EDR of the pathogen remains one of the reasons for discussions of health professionals Currently in the Russian Federation is not a separate accounting of patients with EDR infection, and the frequency determining EDR estimated at around 9% of all cases of MDR. The proposed EDR treatment of patients V mode of therapy is significantly more expensive than the treatment MDR: total direct costs per patient is about 2.900.000 RUB when treating on V mode and about 1.450.000 RUB - on IV therapy mode. Health professionals also note the lack of effectiveness of treatment and the low life expectancy of patients with EDR, especially in antisocial patients who ignore treatment.

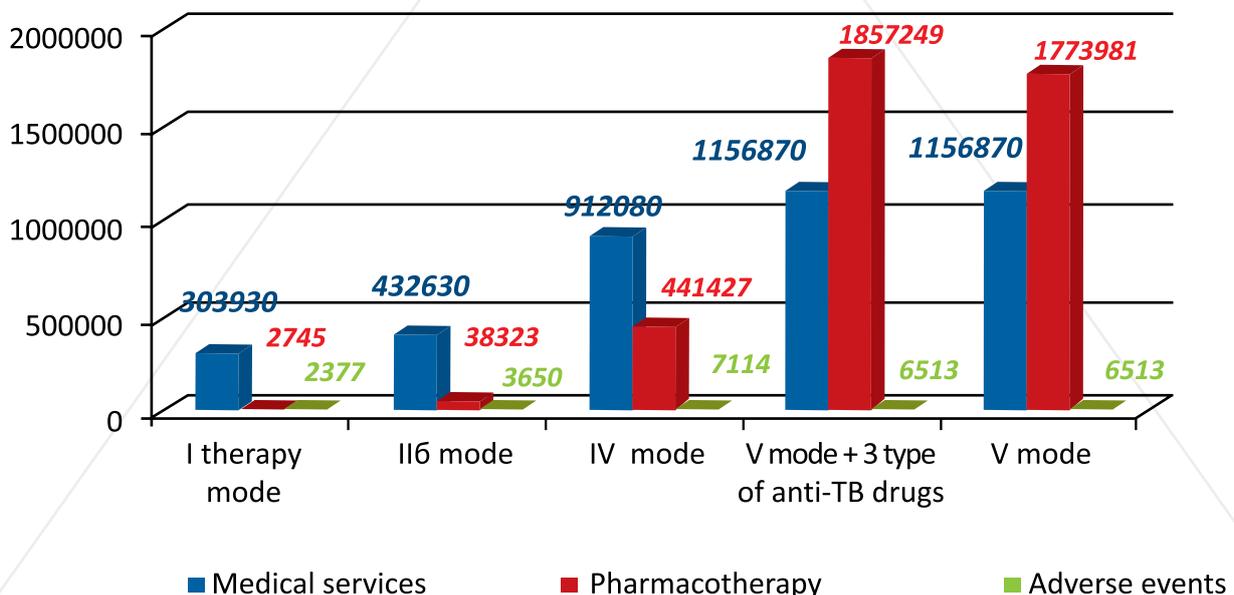
Estimating from the point of view of cost and epidemiology simulated situation with no treatment, it should be noted that when the horizon modeling is about 5 years 60-66% of patients without treatment have the outcome of «death», and during the life these ones are the cause of high indirect costs from the state (about 2.800.000 rubles per one case of lack of treatment), which is a significant amount in comparison with the treatment of such patients. In addition, the low efficiency of some modes of therapy and low coverage of treatment adds to the general «reservoir» of infection with multiple and extensively drug-resistant.

In a situation of growth in the percentage of patients with MDR and EDR infection, high projected cost to the state with insufficient coverage of treatment it is necessary to conduct a full pharmacoeconomic analysis of the application of the IV и V modes of therapy according to new federal guidelines and to conduct modeling of epidemiological situation. Main aspects of pharmacoeconomic study in this case will be:

- Modeling taking into account all possible outcomes («effective treatment», « mode change», «ineffective treatment», «death», «backset», «distant recurrence») within the simulation horizon,
- Search of effectiveness parameters in real clinical practice for each outcomes of the model;
- Full cost accounting among which the principal will be direct (such as medication, medical services, adverse events compensation) and indirect costs (loss of disability, disability);
- Cost-effectiveness analysis of treatment regimens comparison;
- Conduct of budget impact analysis on the scale of each region and the whole country
- Using the statistical, epidemiological data to model the situation in specific regions and in the country as a whole

Finally, the cost of illness analysis in phthisiology will allow us to estimate the

Figure 2. Comparative analysis of cost structure (in rubles) for different modes of treatment of tuberculosis is based on one patient (According to the State registry of limiting selling prices of essential drugs and price list for paid medical services of the FGBU «Central scientific research Institute of RAMS).[7, 11]



total cost of the disease, and to compare the direct and indirect costs of the health system. Such researches allow us to identify the main factors that influence on the cost of treatment of patients with tuberculosis, the ways of improving the organization of provision of medicines. The conclusions made by experts on the basis of this analysis, in addition to epidemiological data, allows to plan and to adjust the budget for health care, the need for medical supplies and medical staff, equipment and occupancy of facilities with TB profile.[9]

Conclusion

Conducting pharmacoeconomic studies on tuberculosis is associated with many difficulties and issues arising from the peculiarities of treatment of tuberculosis. Successful treatment of tuberculosis is not connected with individual factors, but of the whole complex of measures: timely diagnosis, the feed speed of the results of drug susceptibility, the right assignment, composition, and mode of therapy, timing, and compliance of treatment.

However, at the present day, the development of medical technologies in the areas of treatment, prevention and diagnosis of tuberculosis in a period of «Renaissance», which is associated with the emergence of innovation in this area for the first time in the last 40 years. This fact will undoubtedly put before the TB doctors and specialists in the organization of provision of medicines the task of selecting the most optimal medical technologies, finding the least expensive ways to improve the care of patients. Pharmacoeconomics are an integral tool in decision-making.

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