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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
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]
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 of cost-effectiveness and -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. Incremental indicators ICER and ICUR give the possibility to estimate the ratio of the cost increase to the efficiency gains. In other words, this Pharmacoeconomics allows to estimate the additional costs of budget funds for each additional unit of effectiveness. Receiving incremental parameters are compared with a threshold willingness to pay (WGP), 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 is used only with some indicators of the utility (QALY), in some cases LYS 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).

### METHODOLOGY

- **Cost of illness:**
  - Cost of medical care for TB patients;
  - Cost of medical care for Tuberculosis patients with HIV/AIDS;
  - Cost of medical care for Tuberculosis patients with HIV/AIDS complications.

### PharmacoEconomical analysis of the modes of therapy and pharmacoeconomical 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 (XDR) 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. 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 (XDR) 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. 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 (XDR) 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. 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 (XDR) 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. 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 (XDR) 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. 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 (XDR) 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.
In the future, this will allow to use more effective treatment regimens of patients, certain modes, it becomes possible to assess the impact of adjustment of clinical on the actual effectiveness and statistical data on the number of patients treated in opportunities for improvement of TB treatment. At first, taking into account data Conduct of pharmacoeconomics studies of use of different modes bring several and the associated increase in the cost of treatment. [1] 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 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 and 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.

References: