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FEATURES OF THE PATHOGEN AND EFFICACY OF DRUG-RESISTANT TUBERCULOSIS TREATMENT

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Abstract

According to the World Health Organization (WHO), nearly 10.6 million new cases of tuberculosis were detected in 2022, indicating an increase of 3.5 % from the reported 10.3 million in 2021. After the COVID-19 pandemic, the incidence of tuberculosis increased by 3.9 % from 2020 to 2022. According to the latest regulatory documents, multidrug-resistant pathogen is diagnosed when any bacteriologic or molecular genetic methods reveal drug resistance of *M. Tuberculosis complex* at least to isoniazid and rifampicin regardless of resistance to other antituberculosis drugs.

With a wide range of virulence genes, the tuberculosis pathogen expresses genes in different phases of infection. Some genes are "switched on" in the early phases and are important for overcoming immune defenses and spreading the pathogen in the host, while others are important for survival in the latent phase. These characteristics of *Mycobacterium tuberculosis* determine the need for correct and adequate selection of therapy. The problem of diagnostics and treatment of drug-resistant tuberculosis remains extremely urgent. Despite the introduction of new tests for rapid determination of drug susceptibility spectrum of Mycobacterium tuberculosis, the problem of timely and adequate prescription of chemotherapy regimen remains. When selecting therapy, the problem of prescribing a combination of antituberculosis drugs with proven efficacy against *M. tuberculosis* remains. The need to assess the patient's comorbid status, which affects the effectiveness of treatment and the occurrence of relapses, remains relevant.

Despite the introduction of new tests for rapid determination of the drug susceptibility spectrum of *Mycobacterium tuberculosis*, the problem of timely and adequate prescription of chemotherapy remains relevant. The problem of prescribing a combination of antituberculosis drugs with proven efficacy against *M. tuberculosis* remains in the selection of therapy. Currently, the introduction of bedaquiline in therapy regimens is important for improving the effectiveness of tuberculosis treatment. In addition, studies are underway to shorten the duration of therapy for MDR-TB and XDR-TB, which is particularly important for maintaining patient adherence to treatment.

Key words: bedaquiline, drug-resistant tuberculosis, efficacy of treatment, MDR, tuberculosis, XDR.

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ОСОБЕННОСТИ ВОЗБУДИТЕЛЯ И ЭФФЕКТИВНОСТЬ ЛЕЧЕНИЯ ЛЕКАРСТВЕННО-УСТОЙЧИВОГО ТУБЕРКУЛЕЗА

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Резюме

По данным Всемирной организации здравоохранения (ВОЗ), в 2022 году было выявлено около 10,6 млн новых случаев заболевания туберкулезом, что на 3,5 % больше, чем в 2021 году, когда было зарегистрировано 10,3 млн. После пандемии COVID-19 заболеваемость туберкулезом выросла на 3,9 % с 2020 по 2022 годы. Согласно последним нормативным документам, диагноз «возбудитель с множественной лекарственной устойчивостью» ставится в том случае, если любые бактериологические или молекулярно-генетические методы выявляют лекарственную устойчивость комплекса *M. Tuberculosis* как минимум к изониазиду и рифампицину, независимо от устойчивости к другим противотуберкулезным препаратам.

Обладая широким набором генов вирулентности, возбудитель туберкулеза экспрессирует гены на разных стадиях инфекции. Одни гены «включаются» на ранних стадиях и важны для преодоления иммунной защиты и распространения возбудителя в организме хозяина, другие важны для выживания в латентной фазе. Эти особенности микобактерий туберкулеза определяют необходимость правильного и адекватного подбора терапии. Проблема диагностики и лечения лекарственно-устойчивого туберкулеза остается чрезвычайно актуальной.

Несмотря на внедрение новых тестов для быстрого определения спектра лекарственной чувствительности *Mycobacterium tuberculosis*, проблема своевременного и адекватного назначения режима химиотерапии остается актуальной. При подборе терапии сохраняется проблема назначения комбинации противотуберкулезных препаратов с доказанной эффективностью в отношении *M. tuberculosis*. В настоящее время внедрение бедаквилина в схемах терапии имеет значение для повышения эффективности лечения туберкулеза. Кроме того, проводятся исследования по сокращению сроков терапии МЛУ и ШЛУ туберкулеза, что особенно важно для сохранения приверженности пациентов к лечению.

Ключевые слова: бедаквилин, лекарственно-устойчивый туберкулез, МЛУ (множественная лекарственная устойчивость), туберкулез, ШЛУ (широкая лекарственная устойчивость), эффективность лечения.

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Introduction

Tuberculosis infection is one of the major infectious diseases that causes the most frequent deaths worldwide. According to the World Health Organization (WHO), nearly 10.6 million new cases of tuberculosis were detected in 2022, indicating an increase of 3.5 % from the reported 10.3 million in 2021.After the COVID-19 pandemic, the incidence of tuberculosis increased by 3.9 % from 2020 to 2022 [1, 2].

In 2022, in 30 high TB burden countries accounted for 87 % of global TB cases, with eight countries accounting for two-thirds of the total: India (27 %), Indonesia (10 %), China (7.1 %), Philippines (7.0 %), Pakistan (5.7 %), Nigeria (4.5 %), Bangladesh (3.6 %) and Democratic Republic of Congo (3.0 %). In 2022, 55 % of people who developed TB were male, 33 % were female and 12 % were children (aged 0–14 years) [3]. In 2021, the Russian Federation was withdraw from the list of countries with a high burden of tuberculosis, but remained on the list of countries with a high burden of multidrug-resistant tuberculosis (MDR-TB) and tuberculosis with HIV infection [1].

Globally, an estimated 410,000 people (95 % CI: 370,000–450,000) developed multidrug-resistant or rifampicin-resistant tuberculosis (MDR/XDR-TB) of the causative agent in 2022. The number of people with MDR and XDR-TB was diagnosed and treatment was started much lower: 175,650 in 2022, equivalent to about two in five people in need, and still below the pre-pandemic level of 181,533 in 2019 [3].

In 2022, TB treatment was initiated in 7.5 million patients. However, only 70 % of TB patients received treatment [3, 4].

Despite the introduction of new methods of diagnostics and treatment of tuberculosis worldwide, it has not been possible to achieve an increase in the most important indicator — the effectiveness of treatment, which should be about 75–80 %, taking into account the drug sensitivity of the pathogen. The effectiveness of tuberculosis treatment with preserved sensitivity of mycobacteria (60 %) and with multidrug-susceptibility of the pathogen (51 %) continues to be low and does not meet the WHO recommended indicators [1, 3].

The People's Republic of China (PRC) and the Russian Federation (RF) have experience in tuberculosis control with a steady decline in tuberculosis incidence in recent years to 52 and 31 per 100,000 population by 2022, according to statistical analysis. The incidence of drug-resistant tuberculosis remains quite high and it is 2.1 and 21 per 100 thousand population in these countries, respectively. Globally, the overall effectiveness of treatment of first-detected TB is 87 % in 2022. Treatment of multidrug-resistant tuberculosis globally, in Europe and in the Russian Federation remains low with a slight upward trend by 2022 (51 % in the Russian Federation, 51 % in the PRC, 55 % in Europe and 64 % globally) [https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&iso2=%22RU%22&lan=%22RU%22].

According to the latest regulatory documents, multidrug-resistant pathogen is diagnosed when any bacteriologic or molecular genetic methods reveal drug resistance of *M. Tuberculosis complex* at least to isoniazid and rifampicin regardless of resistance to other antituberculosis drugs. At the same time, we can talk about broad drug resistance of the pathogen when drug resistance of *M. tuberculosis complex* to not only isoniazid and rifampicin is detected. Tuberculosis complex not only rifampicin and isoniazid, but also any fluoroquinolone and linezolid or bedaquiline [1, 4].

Characteristics of *Mycobacterium tuberculosis*

One hypothesis based on the current genomes of *Mycobacterium tuberculosis complex* (MTBC) suggests that the closest common ancestor of *Mycobacterium tuberculosis* (MBT) migrated from Africa around 70,000 BCE [5].

However, studies of ancient genomes have determined earlier dates of less than 6,000 years. Mycobacterium tuberculosis was isolated from the calcified lymph node of the Bishop of Lund, who was a famous theologian of the 17th century. The genotype of Mycobacterium tuberculosis was also reconstructed, covering 141 genomes. Prior to this, the latest cases of bone and joint tuberculosis were found from the Neolithic era and date back to 4000 BC, and the first cases of pulmonary tuberculosis were identified in Egypt (3500–2650 BC) [6].

According to the phylogenetic classification based on the similarity of 16S rRNA genes, *M. tuberculosis* belongs to the kingdom Bacteria, type *Actinobacteria*, class *Actinobacteridae*, subclass *Actinomycetales*, order *Firmicutes*, suborder *Corynebacterineae*, family *Mycobacteriaceae*, genus *Mycobacterium* [7].

The genus *Mycobacterium comprises* more than 170 species, including harmless saprophytes, conditionally pathogenic nontuberculous mycobacteria (NTMB) — causative agents of mycobacteriosis, and pathogenic-causative agents of human and animal diseases. Microorganisms of the genus *Mycobacterium* are characterized by a complex composition of the cell wall, which has extremely low permeability. The presence of long chains of α-alkyl, β-hydroxy fatty acids determines such a taxonomically important feature as acid resistance, which provides the ability to perceive differential staining by the Cyl-Nielsen (CN) method [8].

Mycobacterium tuberculosis complex is represented by several closely related species*: M. tuberculosis, M. canettii and M. africanum* are the causative agents of human tuberculosis*; M. bovis* is the main causative agent of bovine and human tuberculosis (attenuated BCG strain is used for immunization*); M. microti, M. caprae, M. pinnipedii (*and recently discovered species *M. mungi, M. orygis, and M. suricattae) c*ause tuberculosis in animals and very rarely in humans [9]. It should be noted that genetic families of *Mycobacterium tuberculosis*, named Haarlem, Africa, and Filipino, have been identified in various regions of the world. These families probably arose as a result of adaptation of mycobacterial strains to specific host populations or environmental conditions [10].

Studying the genetic polymorphism of mycobacteria is important for understanding their evolutionary history, their distribution in different regions of the world, and for developing more effective methods for diagnosing and treating diseases caused by these microorganisms. In addition, these studies may shed light on the mechanisms of pathogenesis and virulence of different strains of mycobacteria, which opens up new opportunities for combating these dangerous infections.

The biodiversity of properties and phenotypic manifestations of *Mycobacterium tuberculosis* (MBT) is largely determined by its genome contained in a single ring chromosome. The genomes of M. tuberculosis complex representatives are characterized by a high degree of conservatism, demonstrating DNA homology at the level of 85–100 %. At the same time, the DNA of other species of the genus Mycobacterium is homologous to the genome of *M. tuberculosis* only by 5–29 %, which indicates significant evolutionary differences [11, 12].

The genome of *M. tuberculosis* is characterized by its smaller size compared to the genomes of other mycobacteria. The classical human tuberculosis pathogen, *M. tuberculosis*, has a larger number of genes than *M. africanum* and *M. bovis*, which have lost some genetic material in the process of evolutionary divergence [13].

In 1998, the nucleotide sequence of the chromosome of the H37Rv strain of M. tuberculosis, the reference "classical" strain for research, was fully deciphered. The chromosome is a toroidal structure containing over 4000 protein-coding genes and 60 genes encoding functional RNA components. The genome contains a unique ribosomal RNA operon, 10Sa RNA involved in the degradation of proteins with atypical matrix RNA, 45 transport RNAs (tRNAs), and about 100 genes encoding lipoproteins.

Using basic molecular genetic techniques, *M. tuberculosis* typing can be performed to recognize strain differences. This is the basis for the molecular epidemiology of tuberculosis. More than 2,000 different genotypes have been discovered, some of which are widespread, while others are less common or characteristic of a particular region [11]. Thus, the most common genotype is the *Beijing/W* family (the so-called "Beijing strain"), with LAM (Latin American strain) and Haarlem being somewhat less common. The *Beijing* genotype is largely associated with an unfavorable course of tuberculosis,

increased virulence and transmissibility, and more frequent detection of drug resistance to antituberculosis drugs. Thus, in the territory of the North-West of the Russian Federation, the Beijing genotype has been detected in 57 % of cases in recent years. In half of the cases, the isolated Beijing strain showed multidrug resistance (MDR) to TB drugs [12].

With a wide range of virulence genes, the tuberculosis pathogen expresses genes in different phases of infection. Some genes are "switched on" in the early phases and are important for overcoming immune defenses and spreading the pathogen in the host, while others are important for survival in the latent phase.

These characteristics of *Mycobacterium tuberculosis* determine the need for correct and adequate selection of therapy.

Treatment of drug-resistant tuberculosis

In 1943, a real breakthrough in the treatment of tuberculosis was made when scientists A. Vaksman, Shatz, and Buji managed to obtain streptomycin, a powerful antituberculosis antibiotic [4]. It was with the introduction of streptomycin into phthisiatric practice that the first successes in reducing the mortality rate from tuberculosis were achieved. From 1950 to 1969, according to official data, the mortality rate in the USSR decreased by 6.5 times, and in some areas by 10 times (Figure 1) [15].

A new era of tuberculosis control began. Streptomycin was used in clinical prectice and also aminosalicylic acid and isoniazid. Since 1960, courses of anti-TB therapy for a long time (12–24 months) with the use of 2 anti-TB drugs have been used. In the 70s, a new drug, rifampicin, was introduced into practice for the treatment of patients with tuberculosis, which reduced the duration of specific therapy to less than 12 months [15].

In order to increase the effectiveness of specific therapy in 1970–2000, pathogenetic therapy with the use of hormones, immunomodulators, antioxidants and hypoxants began to be developed, which led to a significant decrease in tuberculosis morbidity, which reached the lowest values in the history of Russia [4, 16].

Drug resistance of *Mycobacterium tuberculosis* is one of the main factors limiting the effectiveness of tuberculosis chemotherapy, which requires the development of new antituberculosis drugs (ATDs) for the treatment of tuberculosis patients, including multidrug-resistant tuberculosis (MDR-TB).

One of the new drugs used in the most severe category of patients is bedaquiline, which belongs to the group of diarylquinolines — a new class of antitubercular compounds. Bactericidal action of bedaquiline is caused by specific inhibition of proton pump ATP synthase of mycobacteria (adenosine 5'triphosphate synthase) — an enzyme that plays the main role in the process of cellular respiration of *Mycobacterium tuberculosis*. Suppression of ATP synthesis leads to impaired energy production and, as a result, to microbial cell death [17–20].

In recent years, a large number of preclinical studies have been conducted in search of drugs effective against

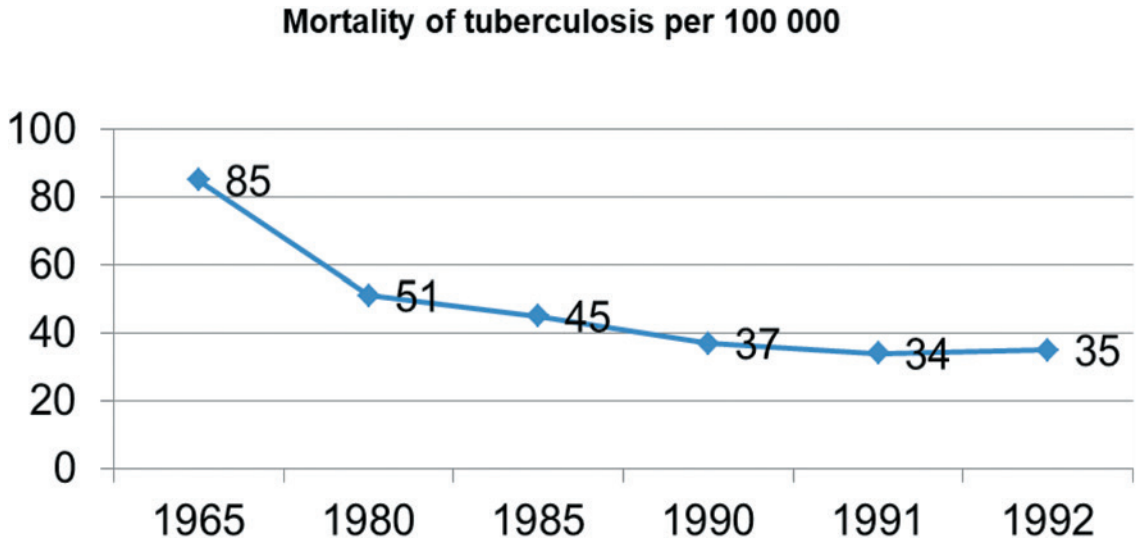

Figure 1. Tuberculosis mortality rate in the USSR in 1965–1992 [4, 15]

Рис. 1. Показатели смертности от туберкулеза на 100 тыс. населения в СССР в 1965–1992 гг. [4, 15]

Table 1. Clinical studies with tuberculosis treatment regimens using anti-tuberculosis drugs

Таблица 1. Исследования новых схем лечения туберкулеза

Title of the study / Название исследования	Experimental groups [the control] / Экспериментальная группа [контрольная группа]	Treatment of tuberculosis / Лечение туберкулеза	Study phase and number of patients included / Фаза клинического исследования	Study completion data / Данные о завершении исследования
HIGHSHORT-RP NCT04694586	2HRHd ZE/2HRHd [2HRZE/4HR]	DST *	II / 40	Suspended recruitment
STEP2C-01 NCT05807399	3RHd HZM600 3RHd HZHdM600 3BDMS1200 [2HRZE/4HR]	DST*	IIb/c/ 360	Recruitment through February 2025
OptiRiMoxTB NCT05575518	4HRHd ZE 4HRHd MZ [2HRZE/4HR]	DST	III/ 414	Recruitment through March 2026
ORIENT NCT05401071	2HP600 MZ/2HP600 M 2HP900 MZ/2HP900 M 2HP1200 MZ/2HP1200 M [2HRZE/4HR]	DST	II/III 2 442	Recruitment through November 2027
Hi-DoRi-3 NCT04485156	1–2HRHd Z/3HRHd [2HRZE/4HR]	DST	III / 926	No set
PORT NCT06057519	2HRHd ZE/4HRHd [2HRZE/4HR]	DST	III / 136	No set
endTB NCT02754765	9BLzMZ 9BLzLxCZ 9BDLzLxZ 9DLzLxCZ 9DMCZ	MDR-TB **	III/ 754	The study is completed research submitted
K21-024 NCT05278988	6–9BDCZ 6BDLzC 9BDLzC	MDR-TB	IV/ 60	Finalization in September 2024
DRAMATIC NCT03828201	16wkBDCLxLz8wk 24wkBDCLxLz8wk 32wkBDCLxLz8wk 40wkBDCLxLz8wk	MDR-TB	IIc/ 220	Finalization in July 2025

Note: * DST — drug-susceptible tuberculosis.

** MDR-TB — multidrug-resistant tuberculosis.

B = bedaquiline, C = clofazimine, D = delamanid, E = ethambutol, H = isoniazid, Lx = levofloxacin, Lz = linezolid, M = moxifloxacin, P = rifapentine, Pa = pretomanid, R = rifampicin, S = sutezolid, Sx = sitafloxacin, SMZ/TMP = sulfamethoxazole/ trimethoprim, Z = pyrazinamide.

Примечания: * ЛЧ — лекарственно-чувствительный туберкулез.

** МЛУ-ТБ — туберкулез со множественной лекарственной устойчивостью возбудителя.

M. tuberculosis, including those with drug resistance. Data on clofazimine analog — TBI-166, TBI-354 — a 2nd generation nitroimidazole with similar activity to delamanid, CPZEN-45 (caprazamycin) — a nucleoside antibiotic, SQ641 (sapuramycin) — a nucleoside antibiotic were obtained, Spectinamide 1599 is a semi-synthetic streptomycin analog, SEQ-9 (sequanamycin) is a macrolide, Q203 is an imidazopyridine derivative, a new class of drugs, blocks the respiratory cytochrome bc1 complex, TBK-613 — fluoroquinolone, VXc-486 — aminobenzimidazole, BTZ-043 — has a novel mechanism of action (inhibits the formation of the enzyme DprE1 (decaprinylphosphoryl-b-D-ribose-2'epimerase), which disrupts cell wall synthesis and leads to lysis of the bacterium, which have showed certain results that allow further phase II clinical trials [21].

Phase II clinical trials were conducted to determine the efficacy and safety in TB patients with LU MBT

when TBA-354, Q203 (imidazopyridine), Sutezolid (PNU-100480 — oxazolidinone), OPC-67683 (delamanid), TMC207 (bedaquiline, diarylquinoline), AZD5847 (oxazolidinone), PBTZ-169 (benzothiazinone derivative), SQ109 (ethylenediamine — an analog of ethambutol), tedizolid (a representative of oxazolidones), and thioureidoiminomethylpyridinium perchlorate (Tpp) was studied in the Russian Federation [22–26].

A large number of clinical trials are currently underway examining the efficacy and safety of various regimens for the treatment of both drug-sensitive and drug-resistant tuberculosis (Table 1).

As can be seen from the data presented in Table 1, many studies will be completed after 2025. Many clinical trials are not completed for various reasons.

Different approaches to tuberculosis chemotherapy have been developed worldwide [22–26].

The BPaLM (6 Bdq-Pa-Lzd-Mfx) regimen is used to treat patients with MDR-TB in the presence or absence of additional resistance to fluoroquinolones. This six-month all-oral regimen includes the administration of bedaquiline, pretomanid, linezolid, and moxifloxacin. In patients with MDR/XDR-TB and confirmed fluoroquinolone resistance, moxifloxacin can be excluded from this regimen and BPaL can be initiated or continued.

A nine-month all-oral regimen (4-6 Bdq(6 months)-Lfx/Mfx-CfzZ-E-Hh-Eto or Lzd(2 months)/5 Lfx/Mfx-Cfz-Z-E) is used to treat patients with MDR-TB and excluded fluoroquinolone resistance. This nine-month all-oral regimen includes bedaquiline (for six months) in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide, and clofazimine (for four months, with an option to extend to six months if the patient remains sputum smear positive after four months); followed by levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for five months). Ethionamide can be substituted for two months of linezolid.

Longer individualized regimens are used to treat MDR-TB patients who are not indicated or have not benefited from the six- or nine-month regimens described above, whose TB is caused by extensively drug-resistant strains of M. tuberculosis (e.g., extensively drug-resistant tuberculosis (XDR-TB)), or who are intolerant to the main components of the above regimens. Such regimens have a duration of at least 18 months and are individually tailored based on sequentially grouped second-line antituberculosis drugs, taking into account the nature of drug resistance and the patient's medical history. Ethambutol and pyrazinamide (for five months). Ethionamide can be substituted for two months of linezolid.

Conclusion

Currently, the problem of diagnostics and treatment of drug-resistant tuberculosis remains extremely urgent. Despite the introduction of new tests for rapid determination of drug susceptibility spectrum of Mycobacterium tuberculosis, the problem of timely and adequate prescription of chemotherapy regimen remains. When selecting therapy, the problem of prescribing a combination of antituberculosis drugs with proven efficacy against *M. tuberculosis* remains. The need to assess the patient's comorbid status, which affects the effectiveness of treatment and the occurrence of relapses, remains relevant.

Конфликт интересов / Conflict of interest

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