Review

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Lung microbiota in tuberculosis — practical significance (literature review)

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Abstract. Tuberculosis remains one of the leading causes of death from infectious diseases worldwide. To date, some progress has been made in the fight against this serious disease, but problems such as the multidrug resistance of *Mycobacterium tuberculosis* and tuberculosis/HIV coinfection are of serious concern. A significant discovery was the discovery of microbiota in the distal parts of the respiratory tract — respiratory bronchioles and alveoli, which, as it turned out, plays an important role in maintaining local immunity and protecting against pathogens. It has been established that in healthy people this locus is dominated by commensals, for example *Prevotella*, whereas in tuberculosis dysbiosis develops: species diversity decreases and the number of opportunistic microorganisms (*Streptococcus, Neisseria*) increases. This specific microbiota profile can serve as a diagnostic and prognostic marker, helping to detect the disease at an early stage and predict the risk of developing drug resistance of *Mycobacterium tuberculosis*. At the same time, tuberculosis therapy restores the normal composition of the lung microbiota, but at the same time promotes the growth of antibiotic resistance among opportunistic bacteria. A promising area is the management of the lung microbiota. The development of inhaled probiotics opens up new opportunities for tuberculosis prevention and improved treatment effectiveness, especially in complex cases of multidrug resistance of *Mycobacterium tuberculosis*. Thus, the study of the lung microbiota marks the transition to personalized approaches in the fight against tuberculosis.

Keywords: tuberculosis, lung microbiota, bronchoalveolar lavage, pathobionts, tuberculosis therapy, 16S ribosomal RNA gene sequencing, shotgun complete genome sequencing, new generation metagenomic sequencing, inhaled probiotics, horizontal gene transfer

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Микробиота легких при туберкулезе — практическое значение (обзор литературы)

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Резюме. Туберкулез остается одной из ведущих причин смертности от инфекционных заболеваний во всем мире. На сегодняшний день достигнут определенный прогресс в борьбе с этим тяжелым заболеванием, но такие проблемы, как множественная лекарственная устойчивость микобактерий туберкулеза и коинфекции туберкулез/ВИЧ, вызывают серьезную обеспокоенность. Значимым открытием стало обнаружение микробиоты в дистальных отделах дыхательного тракта — респираторных бронхиолах и альвеолах, которая, как выяснилось, играет важную роль в поддержании местного иммунитета и защите от патогенов. У здоровых людей в этом локусе доминируют комменсалы, например *Prevotella*, тогда как при туберкулезе развивается дисбиоз: снижается видовое разнообразие и увеличивается численность условно-патогенных микроорганизмов (*Streptococcus, Neisseria*). Этот специфический профиль микробиоты может служить диагностическим и прогностическим маркером, помогая выявлять болезнь на ранней стадии и прогнозировать риск развития лекарственной устойчивости микобактерий туберкулеза. Противотуберкулезная терапия при этом восстанавливает нормальный состав микробиоты легких, но одновременно способствует росту антибиотикорезистентности среди условно-патогенных бактерий. Перспективным направлением является управление микробиотой легких. Разработка ингаляционных пробиотиков открывает новые возможности для профилактики туберкулеза и повышения эффективности лечения, особенно в сложных случаях множественной лекарственной устойчивости микобактерий туберкулеза. Таким образом, изучение микробиоты легких знаменует переход к персонализированным подходам в борьбе с туберкулезом.

Ключевые слова: туберкулез, микробиота легких, бронхоальвеолярный лаваж, патобионты, противотуберкулезная терапия, секвенирование гена 16S рибосомальной РНК, секвенирование полного генома методом дробовика, метагеномное секвенирование нового поколения, ингаляционные пробиотики, горизонтальный перенос генов

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Despite significant progress made by the global community in the fight against tuberculosis (TB), the disease remains a pressing concern. It is still a source of anxiety for scientists, clinicians, and public health officials.

According to the 2024 Global Tuberculosis Report published by the World Health Organization (WHO), in 2023 TB once again became the leading cause of death among all infectious diseases, displacing COVID-19 (CoronaVIrus Disease 2019), which had dominated in the previous three years [1]. The COVID-19 pandemic severely damaged the health care systems of many countries and became one of several factors preventing humanity from achieving the WHO's 2025 TB elimination targets [2].

Thanks to significant efforts by the Russian healthcare system, Russia joined the ranks of 13 countries that managed to reduce TB deaths by 50% or more between 2015 and 2023. In 2021, the WHO removed Russia from the list of countries with a high TB burden. However, our country still remains on the so-called Global TB Watchlist [1, 3]. This is primarily due to problems with TB caused by multidrug-resistant (MDR-TB) strains of the *Mycobacterium tuberculosis* complex (MTB) and co-infection caused by MTB and the human immunodeficiency virus (TB/HIV) in the Russian Federation [3, 4].

Currently, the Russian Federation is also seeing a sustained positive trend in the TB epidemic among children [5], but sporadic cases of late-stage TB diagnosis in this population group mean that physicians of all specialties must remain vigilant regarding this infection.

Thus, measures for the prevention, diagnosis, and treatment of TB require constant improvement. Since TB is the result of a complex interaction between MTB and the host's immune system [6], which is significantly modulated by the pulmonary microbiota [7], a detailed study of the latter is of particular relevance.

NORMAL LUNG MICROBIOTA

Previously, the respiratory bronchioles and alveoli were considered completely sterile [8]. However, it is now known that all sections of the respiratory tract in a healthy person, including the lower respiratory tract, are colonized by various commensal microorganisms: bacteria, viruses, fungi [9], and, according to the latest data, even archaea [10] .

It is believed that the microbiota of the lower respiratory tract (LRT) is exclusively transient. Nevertheless, its composition in conditionally healthy individuals remains relatively constant due to a dynamic equilibrium between the influx of microorganisms, the upper respiratory tract (URT) and the host's immune response [11, 12]. Researchers have figuratively named this model "Yin and Yang" [13], as the optimal qualitative and quantitative composition of the microbiota (eubiosis) arises from the dynamic interplay of various forces.

It should be noted that the URT system consists of the nasal cavity, nasopharynx, and oropharynx, while the LRT includes the larynx, trachea, bronchi, bronchioles, and alveoli [14].

The LRT microbiota in a healthy individual is primarily composed of phyla such as *Pseudomonadota* (Proteobacteria), *Bacillota* (Firmicutes), and *Bacteroidota* (Bacteroides), which together account for about 90% of the bacteria inhabiting this area [15] At the genus level, the following taxa predominate: *Veillonella*, *Prevotella*, *Sphingomonas*, *Pseudomonas*, *Acinetobacter, Fusobacterium, Megasphaera, Staphylococcus, and Streptococcus [16].*

It is important to note that the microbiota of the LRT has been studied mainly by molecular genetic methods. Traditional culture-based methods almost never yield results [17]. Detection of DNA fragments does not allow us to determine whether they originate from a living or a dead bacterial cell. Therefore, it is extremely difficult to establish which microorganisms are resident and which are transient in the LRT.

The nasal cavity is colonized by *Corynebacterium, Propionibacterium, Staphylococcus spp., Moraxella, Pseudomonadota (Proteobacteria),* and *Fusobacterium [14]. Corynebacterium* and *Staphylococcus* dominate the nasopharynx [18]. The oropharynx is inhabited by *Streptococcus, Haemophilus, Neisseria, Prevotella, Veillonella,* and *Leptotrichia* [14].

The microbiota of the URT is richer than in the LRT in both quantitative and qualitative terms. However, their composition largely correlates due to the direct connection between these two sites [19]. In addition, the upper respiratory tract represents an ecological niche for important pathobionts: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus (S. aureus)*. These are symbiotic microorganisms, however, they can cause disease under certain conditions [20].

Viruses found in the respiratory tract include families such as *Picornaviridae, Paramyxoviridae, Orthomyxoviridae, Coronaviridae, Adenoviridae, Parvoviridae, Herpesviridae, Anelloviridae, Papillo-*

maviridae, Polyomaviridae, and numerous bacteriophages [21].

Fungi are predominantly represented by the genera *Aspergillus, Cladosporium, Eurotium, Penicillium,* and several others [22].

Archaea in the respiratory tract include such types as *Euryarchaeota (e.g., Methanobrevibacter smithii* as a result of microaspiration from the gastrointestinal tract), *Thaumarchaeota* (representatives of the skin and upper respiratory tract microbiota) and *Woesearchaeota*, which are specific to the lower respiratory tract. Their role in a healthy organism and in pathological conditions has not yet been sufficiently studied [23].

Some representatives of the normal human respiratory tract microbiota are shown in the diagram (Fig. 1).

The beneficial role of the respiratory tract microbiota is extremely diverse. In particular, it ensures the formation of a balanced immune response, preventing the development of excessive inflammation when exposed to harmless antigens [24] . It also inhibits the proliferation of pathogenic microorganisms by competing with them [25]; enhances antiviral immunity [26]; prevents the development of lung cancer [27]; and, through the production of various bioactive substances, participates in forming the “gut-lung axis” [28].

A disruption in the qualitative and quantitative composition of the respiratory tract microbiota, or dysbiosis, can lead to impairment of the aforementioned protective functions and declined resistance to both specific [29] and nonspecific respiratory infections [24, 30].

Factors leading to respiratory tract dysbiosis include smoking, air pollution, immunodeficiency states (including HIV/AIDS), infectious and non-infectious respiratory diseases, the use of antibacterial drugs, medical interventions (mechanical ventilation, bronchoscopy, etc.), as well as an imbalance in the gut microbiota and diseases of other organs and systems [11, 31, 32]. Figure 2 illustrates the functions of the lung microbiota as well as factors leading to its imbalance.

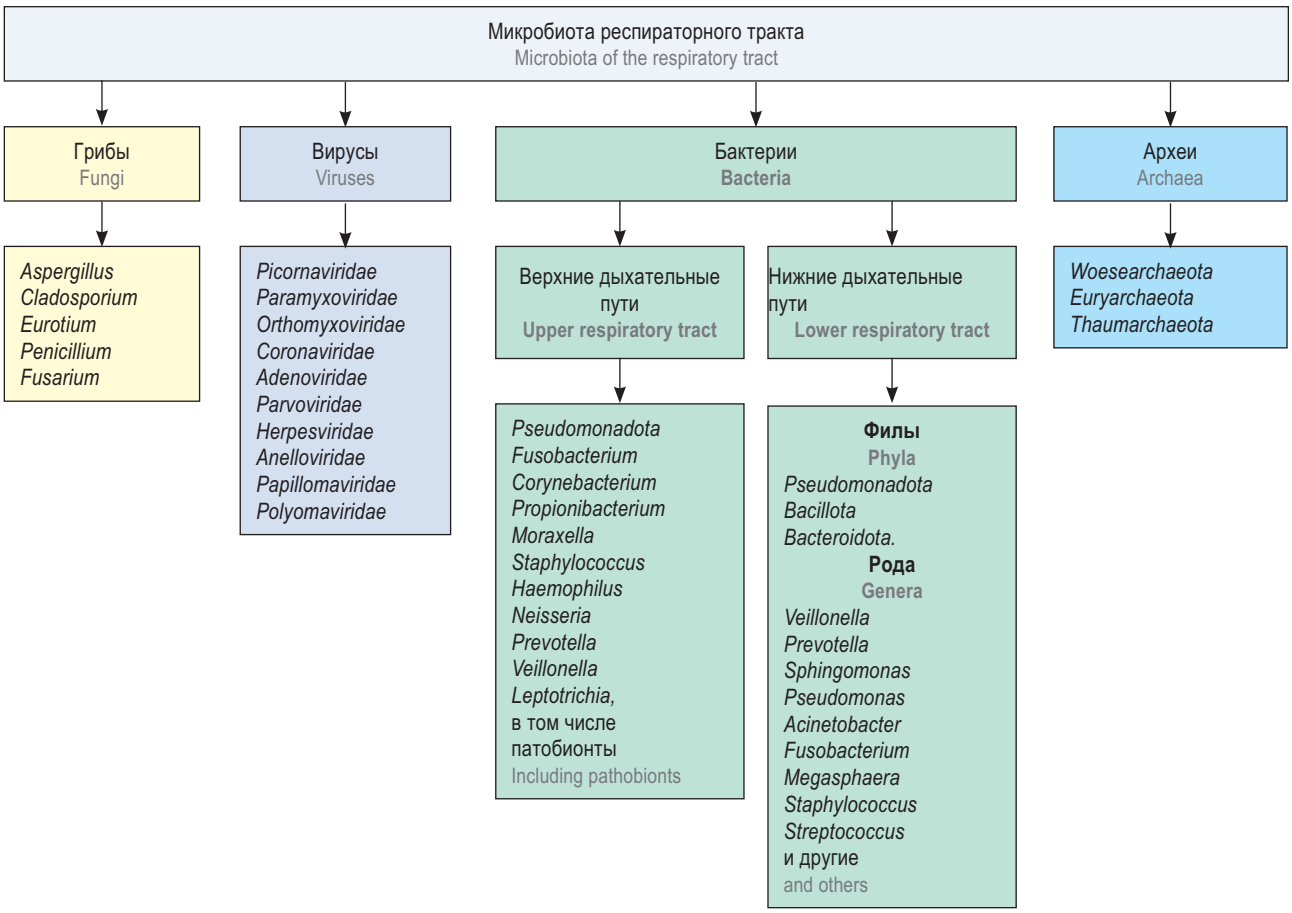


Fig. 1. **Microbiota of the respiratory tract (the figure is prepared by the authors of this article)**

Рис. 1. Микробиота респираторного тракта (рисунок авторов данной статьи)

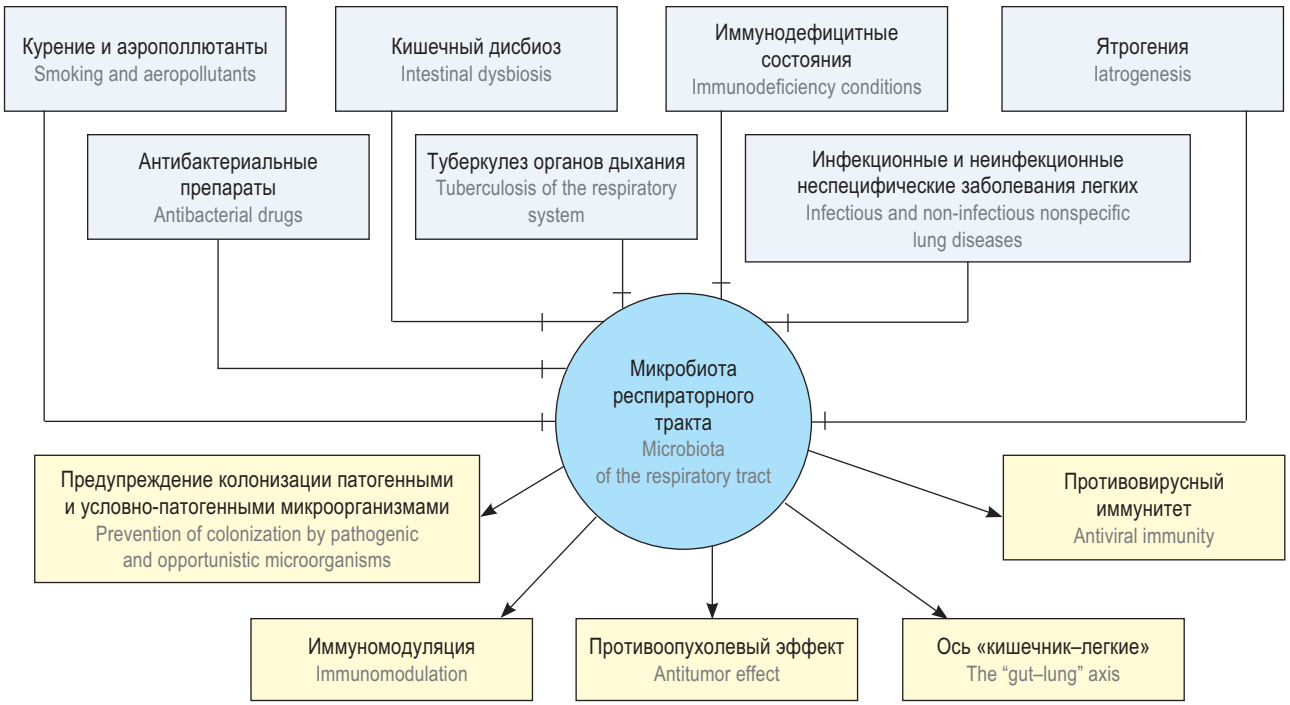


Fig. 2. **The functions of the lung microbiota and the factors leading to its imbalance (the figure is prepared by the authors of this article)**

Рис. 2. Функции микробиоты легких и факторы, приводящие к ее дисбалансу (рисунок авторов данной статьи)

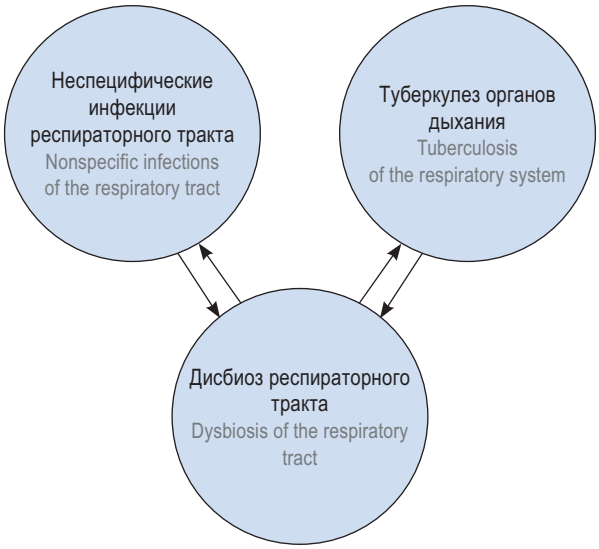


Fig. 3. **A schematic diagram of the relationship between dysbiosis, pulmonary tuberculosis and nonspecific infection (the figure is prepared by the authors of this article)**

Рис. 3. Принципиальная схема взаимосвязи дисбиоза респираторного тракта, туберкулеза легких и неспецифической инфекции (рисунок авторов данной статьи)

Thus, a bidirectional relationship or vicious cycle is formed. Both TB and nonspecific lung infections can lead to local dysbiosis, which increases susceptibility to these diseases [33]. Fig. 3 presents a schematic diagram of the relationship between respiratory tract dysbiosis, pulmonary TB, and nonspecific infection.

Tuberculosis Impact on Lung Microbiome

In 2022, Chinese researchers conducted a large-scale study examining the lung microbiome profile in patients with TB [34]. Bronchoalveolar lavage fluid samples were collected to study the lung microbiota, which is more informative than sputum analysis, as sputum collection inevitably introduces microorganisms from the nasopharynx and oral cavity into sample [15]. The qualitative and quantitative composition of the microbiota was determined using metagenomic next-generation sequencing (mNGS).

Samples obtained from healthy individuals in the control group contained higher levels of *Prevotella melaninogenica (P. melaninogenica)* and *Ralstonia pickettii (R. pickettii)*, while samples from patients with untreated TB contained *S. aureus* and *Neisseria* spp. [34]. These results are partially consistent with data from a 2019 meta-analysis, according to which Streptococcus and Neisseria were more common in TB patients (35.01 and 27.1% of the total, respectively), while *Prevotella* was more common in healthy individuals from the control group (36.9%) [35]. The same study reported that *Veillonella*, *Rothia, Leuconostoc,* and

Lactobacillus were detected only in TB patients and found in 7, 8, 4, 3, 2, and 1.8% of patients, respectively. In addition, the genera *Gammaproteobacteria, Haemophilus,* and *Actinobacillus* were found only in healthy individuals from the control group [35]. Differences in the composition of the lung microbiota at the genus level between TB patients and healthy individuals from the control group are shown in Fig. 4 [34].

It is worth noting that the proportion of MBT in TB patients, according to some data, accounts for only about 0.06% of the total number of all bacteria detected in sputum analysis [36].

Whether TB or respiratory tract dysbiosis is the primary factor remains uncertain. However, MBT appear to significantly influence the lung microenvironment, thereby promoting proliferation of certain microorganisms and suppressing others [34].

Additionally, according to the literature, the microbiota identified in TB patients' sputum via 16S rRNA gene sequencing may vary significantly at the genus level depending on resistance or susceptibility of MTB to various drugs (Fig. 5) [36]. Thus, it has been established that *Delftia* can serve as a potential diagnostic marker for identifying patients with TB caused by MTB resistant to rifampicin; *Kingella* and *Chlamydophila* — to isoniazid; and Bordetella — to rifampicin and isoniazid (in patients with MDR to the pathogen) [36].

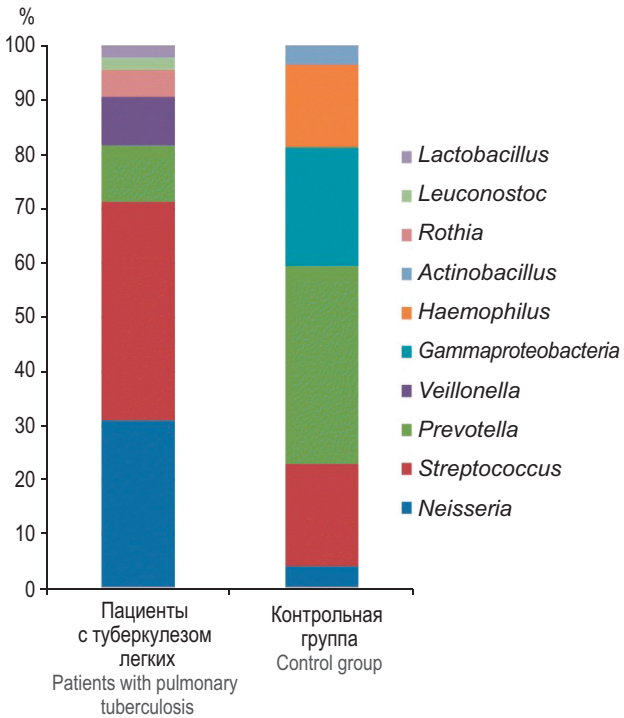


Fig. 4. The composition of the lung microbiota at the genus level in patients with tuberculosis and in healthy people (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/e984/6347808/ff898c63225f/12879_2019_3712_Fig3_HTML.jpg)

Рис. 4. Состав микробиоты легких на уровне рода у пациентов с туберкулезом и у здоровых людей (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/e984/6347808/ff898c63225f/12879_2019_3712_Fig3_HTML.jpg)

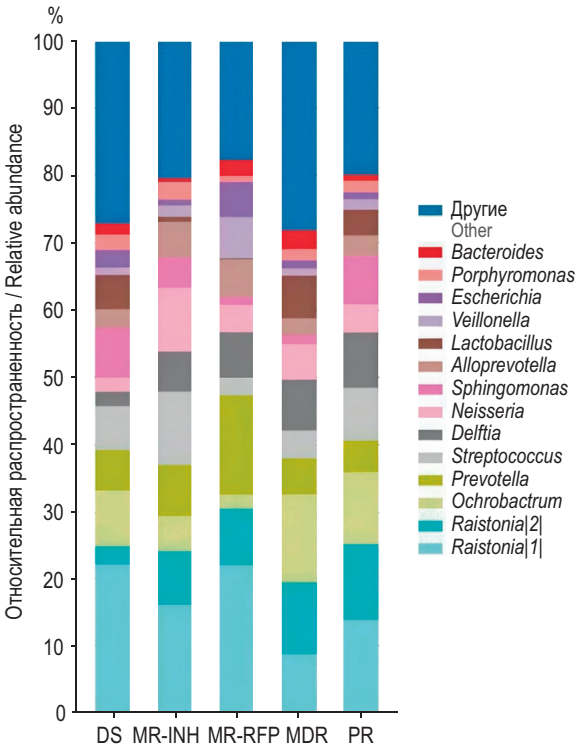


Fig. 5. Composition of the upper respiratory tract microbiota at the genus level in patients with tuberculosis caused by Mycobacterium tuberculosis with different sensitivity profiles to anti-tuberculosis drugs. Relative abundance — prevalence of microorganisms of different species; DS — drug-sensitive tuberculosis; MR-INH — monoresistance isoniazid; MR-RFP — monoresistance rifampicin; MDR — multidrug resistance; PR — polyresistance (this is resistance to two first-line anti-tuberculosis drugs and more, while maintaining sensitivity to at least isoniazid and rifampicin simultaneously) (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/ca0b/8040397/f0e6c4a78ba9/ijmsv18p1935g003.jpg)

Рис. 5. Состав микробиоты верхних дыхательных путей на уровне рода у пациентов с туберкулезом, вызванным микобактериями туберкулеза с различными профилями чувствительности к противотуберкулезным препаратам. Относительная распространенность — распространенность микроорганизмов разных видов; DS — лекарственно-чувствительный туберкулез; MR-INH — монорезистентность к изониазиду; MR-RFP — монорезистентность к рифампицину; MDR — множественная лекарственная устойчивость; PR — полирезистентность (это устойчивость к двум противотуберкулезным препаратам первого ряда и более при сохранении чувствительности как минимум к изониазиду и рифампицину одновременно) (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/ca0b/8040397/f0e6c4a78ba9/ijmsv18p1935g003.jpg)

ANTITUBERCULOSIS THERAPY AND LUNG MICROBIOME

The lung microbiome is significantly influenced by antituberculosis therapy (ATT) [34, 37]. All patients included in the study had drug-sensitive TB and received treatment according to the following regimen: 2 months of HRZE (isoniazid, rifampicin, pyrazinamide, and ethambutol) and 4 months of HR (isoniazid and rifampicin). The microbial composition of healthy individuals, TB patients receiving ATT during the study, and patients who had recently completed a course of chemotherapy (clinically cured with bacteriological confirmation) was similar. However, there was a marked difference in the taxonomic profile of the microbiota among those patients with pulmonary TB who were not receiving treatment during the study. It was noted that the opportunistic pathogen *S. aureus* was significantly more prevalent in the group of patients with untreated TB, while the relative abundance of *R. pickettii and P. melaninogenica,* conversely, was much lower [34]. It has been reported that *R. pickettii* is capable of converting ethionamide into its active form, and a decrease in its abundance in patients with TB may negatively affect treatment outcomes [38]. According to some data, bacteria of the genus *Prevotella* play a positive role in maintaining lung function and controlling inflammation. Accordingly, a decrease in the abundance of *P. melaninogenica* may be associated with impaired lung function and an excessive inflammatory response [39].

Overall, microbial diversity in patients with untreated TB was significantly lower than in other groups. Thus, ATT rapidly restored normal microbial composition in this study, contrary to expectations [34]. Apparently, this is due to the strong local effect of MBT on the microecology of the lower respiratory tract. There are studies both confirming [40] and refuting this observation [37].

At the same time, ATT undoubtedly has negative consequences as well. Of the four drugs prescribed to patients in the study, rifampicin is a broad-spectrum antibiotic and may lead to the development of antibiotic resistance, including in opportunistic pathogens [34]. Other broad-spectrum antibiotics used in various TB treatment regimens include rifabutin and rifapentine; fluoroquinolones (levofloxacin, moxifloxacin, sparfloxacin); aminoglycosides (kanamycin, amikacin, capreomycin); carbapenems (the combination drug imipenem + cilastatin and meropenem); and the semi-synthetic penicillin antibiotic in combination with a beta-lactamase inhibitor—amoxicillin + clavulanic acid [3]. It has been demonstrated that ATT increases

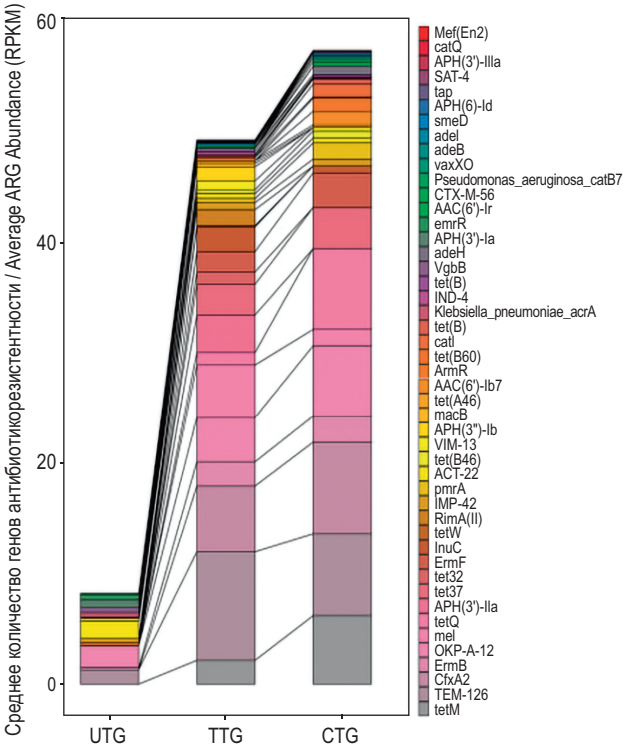


Fig. 6. **The abundance of different lung microbiota resistance genes in different observation groups. Average ARG Abundance — average number of antibiotic resistance genes; UTG — the untreated pulmonary TB group; TTG — the treated pulmonary TB group; CTG — the cured pulmonary TB group (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/3411/8865484/d7e5b5637cde/spectrum.01901-21-f005.jpg)**

Рис. 6. Количество различных генов резистентности микробиоты легких в разных группах наблюдения. UTG — пациенты с туберкулезом, не получавшие лечения; TTG — пациенты с туберкулезом в процессе лечения; CTG — пациенты, излеченные от туберкулеза легких в недавнем прошлом (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/3411/8865484/d7e5b5637cde/spectrum.01901-21-f005.jpg)

the diversity and number of genes responsible for antimicrobial resistance across an entire microbial community. This raises concerns regarding the potential development of nonspecific respiratory infections in patients caused by antibiotic-resistant strains of pathobionts during or after ATT. A histogram showing the number of different resistance genes in the pulmonary microbiota across different observation groups is presented in Fig. 6 [34].

It should be noted that nonspecific lung infections complicating the course of TB are often caused not by the patient's own pathobionts, but by hospital-acquired strains of microorganisms circulating within hospitals with antibiotic resistance profiles specific to them [41]. This is particularly relevant during prolonged

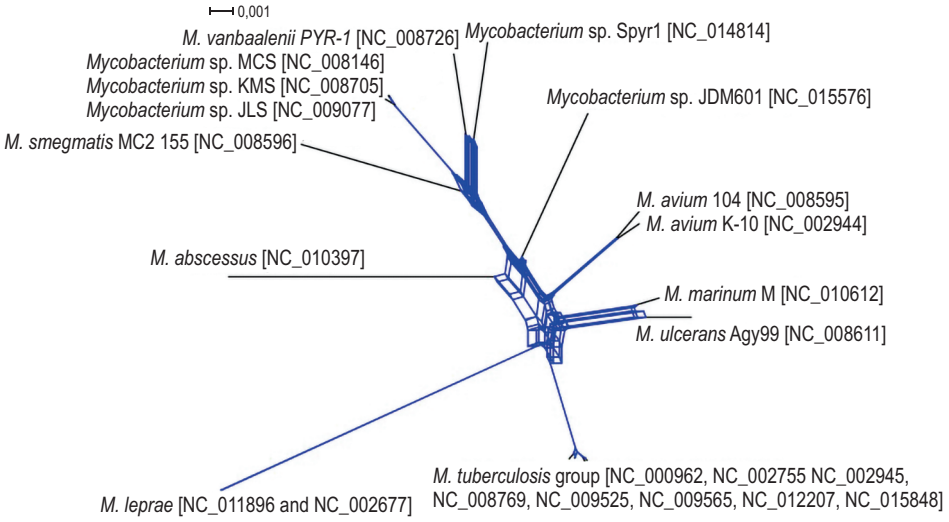


Fig. 7. **A reticulate network showing the events of the exchange of conserved genes between different Mycobacteria (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/d4f0/4331801/b230cfc44751/1471-2148-15-S1-S2-4.jpg)**

Рис. 7. Сетчатая структура, демонстрирующая события обмена консервативными генами между различными микобактериями (https://cdn.ncbi.nlm.nih.gov/pmc/blobs/d4f0/4331801/b230cfc44751/1471-2148-15-S1-S2-4.jpg)

hospitalization of patients with tuberculosis, as well as during their stay in intensive care units, especially when mechanical ventilation is used, which is not uncommon among patients with TB/HIV coinfection, whose immune systems are, moreover, severely compromised [42–44].

In addition, horizontal gene transfer must be mentioned in this context. This process occurs when a microorganism transfers genetic material to another microorganism that is not its descendant via various mobile genetic elements (plasmids, transposons, integrons) [45]. Thanks to this mechanism, resistance determinants can rapidly spread among pathogens causing nosocomial infections, including those belonging to the so-called ESKAPE group, which poses a significant problem for both individual hospitals and healthcare systems worldwide [46].

However, it is encouraging that horizontal gene transfer is not possible between *M. tuberculosis* and pathogens of nonspecific infections. Currently, the evolution of *M. tuberculosis*, including the acquisition of drug resistance, is entirely driven by spontaneous mutations, genomic recombination, gene duplication, and selective pressure [47]. Nevertheless, pathogenicity clusters have been identified in the *M. tuberculosis* genome. They may have been acquired by the microorganism from external sources during its phylogeny and account for its high virulence. Furthermore, other mycobacteria, such as *Mycobacterium avium* and *Mycobacterium marinum*, are currently actively exchanging mobile genetic elements both with each other and with taxonomically distant microorganisms. Thus, we cannot exclude the possibility that, sooner or later in the future, conditionally pathogenic mycobacteria will evolve from pathogens of predominantly opportunistic infections into pathogens that are no less dangerous than MTB [47]. It is particularly important to take this fact into account given the increasing frequency of mycobacterial infections not only among individuals with HIV infection but also among the immunocompetent population [48]. Figure 7 presents a network diagram illustrating the exchange of conserved genes among various mycobacteria [47].

DIAGNOSTIC SIGNIFICANCE OF ASSESSING LUNG MICROBIOME IN ASSOCIATION WITH TUBERCULOSIS

Therefore, assessing the lung microbiome appears to be an important diagnostic tool for pulmonologists and other specialists. Patients with TB have a unique lung microbiome profile, and its determination can help verify TB in early stages, conduct differential diagnosis between TB and lung cancer, as well as other pathologies, and predict the severity of TB, the likelihood of a secondary nonspecific infection, and the development of drug resistance in a specific patient [34–36, 49]. Furthermore, since respiratory tract dysbiosis is one of the risk factors for developing TB, modifying a microbal composition could help to prevent TB [50, 51].

Currently, three main molecular genetic methods are used to study the microbiota. Each of these methods has its own advantages and disadvantages: 16S rRNA gene sequencing [52], whole-genome

Table 1

Comparison of some molecular genetic methods of microbiota research

Таблица 1

Сравнение некоторых молекулярно-генетических методов исследования микробиоты

Характеристика Characteristic	Секвенирование гена 16S рибосомальной РНК 16S ribosomal RNA Gene Sequencing [52]	Секвенирование полного генома методом дробовика Shotgun Whole-Genome Sequencing [53]	Метагеномное секвенирование нового поколения Next-generation metagenomic sequencing (mNGS) [54]
Объект секвенирования Sequencing facility	Один ген (16S рибосомальной РНК) A single gene (16S ribosomal RNA)	Весь геном одной изолированной бактерии The entire genome of a single, isolated bacterium	Вся ДНК/РНК из образца (бактерии, археи, вирусы, грибы) All DNA/RNA from a sample (bacteria, archaea, viruses, fungi)
Принцип метода The principle of the method	Амплификация и секвенирование консервативного гена с вариабельными регионами для идентификации таксонов Amplification and sequencing of a conserved gene with variable regions to identify taxa	Случайная фрагментация всей ДНК бактерии, секвенирование фрагментов и «сборка» полного генома Random fragmentation of the entire bacterial DNA, sequencing fragments and “assembling” the complete genome	Секвенирование всей ДНК/РНК, извлеченной из образца среды, с последующей сборкой и таксономическим/функциональным анализом Sequencing of all DNA/RNA extracted from a medium sample, followed by assembly and taxonomic/functional analysis
Разрешающая способность Resolution capacity	Уровень рода, реже вида Genus-level, rarely species-level	Уровень штамма, возможно определение генов вирулентности и резистентности Strain level, possible determination of virulence and resistance genes	Уровень вида, иногда штамма. Дает представление о функциональном потенциале сообщества Species-level, sometimes strain-level. Functional potential of the community
Количественная оценка Quantitative assessment	Относительная численность микроорганизмов в микробном сообществе (доля в сообществе) Relative abundance (proportion within the community)	Невозможна (метод используют для чистой культуры) Not applicable (the method is used for pure culture)	Относительная и абсолютная численность микроорганизмов (при использовании методов калибровки) Relative and absolute abundance of microorganisms (when using calibration methods)
Основное применение Main application	Оценка таксономического профиля сообщества, альфа- и бета-разнообразия Taxonomic profile of a community, alpha- and beta-diversity	Детальное изучение конкретного микроорганизма: геномика, вирулентность, эволюция Detailed study of a specific microorganism: genomics, virulence, evolution	Полная картина сообщества: таксоны и гены вирулентности, резистентности и т.д. (то есть функциональный потенциал) The full picture of the community: taxa and genes of virulence, resistance, etc. (i.e. functional potential)
Преимущества метода Advantages of the method	Низкая стоимость, стандартизированный метод, наличие больших баз данных Low cost, standardized method, availability of large databases	«Золотой стандарт» для изучения индивидуальных геномов, высокая разрешающая способность The “gold standard” for studying individual genomes, high resolution	Наиболее полная информация без необходимости культивирования The most complete information without the need for cultivation
Недостатки метода Disadvantages of the method	Низкое разрешение, не дает представления о функциональном потенциале сообщества, ПЦР-амплификация вносит искажения, не применяется для изучения вирусов и грибов Low resolution, does not provide an idea of the functional potential of the community, PCR amplification introduces distortions, and is not used to study viruses and fungi	Требует выделения и культивирования чистой культуры (трудоемкость) Requires isolation and cultivation of pure culture (labor intensity)	Высокая стоимость, сложный анализ, требует больших вычислительных мощностей High cost, complex analysis, requires a lot of computing power

Note: PCR — polymerase chain reaction.
Примечание: ПЦР — полимеразная цепная реакция.

The table is prepared by the authors
Таблица составлена авторами

shotgun sequencing [53], and mNGS [54]. A comparison of these methods for sequencing the microbiota's genetic material is presented in Table 1.

All methods have their own unique capabilities and limitations, making them complementary tools in the modern microbiologist's arsenal.

As mentioned above, the upper respiratory tract is colonized by a much greater variety of microorganisms than the lower respiratory tract. Therefore, certain aspects of sampling from the latter deserve special mention. To avoid unwanted contamination, the following techniques are used: rinsing the mouth before the procedure, refraining from aspiration during bronchoscope insertion until it enters the trachea, and the use of protected sampling methods [55]. These methods include protected bronchoalveolar lavage, in which a sterile protected catheter is passed through the working channel of the bronchoscope, after which sterile saline is introduced and aspirated from the distal airways, and protected brush biopsy (protected brush biopsy), which involves keeping the brush within a special sheath before and after obtaining material from the area of interest [55]. Performing these procedures can be associated with significant difficulties and requires specific training for endoscopists. Figure 8 shows a photograph from the endoscope camera depicting bronchoalveolar lavage fluid in the bronchial lumen, which, when properly obtained, should have a foamy look.

When studying the microbiota of the lower respiratory tract, it is essential to examine control samples, namely flushing fluid from a working channel, uninoculated sterile saline solution, and throat swabs, which undergo the same analysis as main samples [56]. Then, using bioinformatics methods, a "subtraction" is performed: the number of counts of all microbial taxa detected in the additional controls is subtracted from the corresponding counts obtained from the main samples, which allows to exclude contaminants from the final analysis [55, 56].

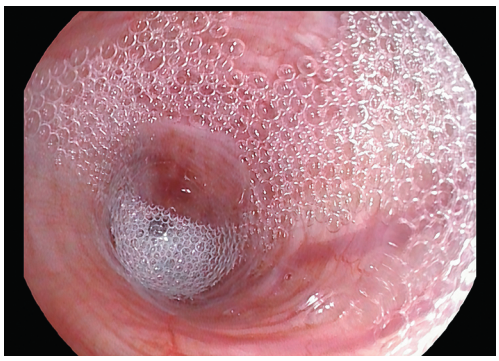


Fig. 8. **A photograph of foamy bronchoalveolar lavage fluid in the bronchial lumen, taken using an endoscope camera (from the personal archive of A.V. Derevyanko)**

Рис. 8. Фотография пенистой бронхоальвеолярной лаважной жидкости в просвете бронха, сделанная при помощи камеры эндоскопа (из личного архива А.В. Деревянко)

INHALED PROBIOTICS IN TREATMENT AND PREVENTION OF LUNG DISEASES

As described above, the normal lung microbiota performs a large number of beneficial functions [24–28]. In this regard, it is proposed to use special probiotics for inhalation to treat and prevent various infectious and non-infectious lung diseases [49, 50].

There are a number of challenges in developing probiotics that can be delivered to the lungs by means of inhalation. Particles with a diameter of 1–5 μm are considered ideal for accumulating in the lungs. Larger particles are cleared retrograde via mucociliary clearance, while smaller ones are cleared with exhaled air [57]. Therefore, to ensure the required particle size, drug delivery systems such as microcapsules, microspheres, liposomes, and niosomes (similar to liposomes but containing synthetic nonionic surfactants) are preferred [51].

Careful selection of a device is also necessary to ensure effective delivery of probiotics into the lungs. Nebulizers with vibrating mesh technology and "soft mist" inhalers (respirators) are best suited for this task [58]. One limitation is that the preparation must be soluble in water or in a mixture of water and ethanol to prevent filter clogging [59]. Another option is the use of dried powdered probiotics via dry powder inhalers. Lactose is used as a carrier in approximately 90% of dry powder inhalers that are currently available on the market. Consequently, the drug under development must remain stable and effective in the presence of lactose [51].

Already today, there are proposals to use an inhaled biotherapeutic preparation based on lactobacilli for treating bronchopulmonary dysplasia in preterm newborns and chronic obstructive pulmonary disease. It has demonstrated its efficacy in various experimental models in vitro and *in vivo* [60]. There are proposals to consider lung microbiota transplantation by analogy with gut microbiota transplantation [61].

Inhaled probiotics will be undoubtedly useful for treating and preventing infectious lung diseases [50, 51], including TB. The use of such preparations is

particularly promising in treating TB caused by drug-resistant mycobacteria or complicated by a nonspecific infection, as well as for the rapid normalization of the lung microbiota in convalescents. This area is highly interesting for future scientific research.

The lung microbiota is a highly active participant in maintaining respiratory homeostasis. By shaping local immunity and providing colonization resistance, it acts as a key factor in defense against respiratory pathogens, including *M. tuberculosis* [24, 25, 33, 34].

As studies have shown, tuberculosis infection has a profound effect on lung microbial communities, leading to characteristic dysbiosis. Specifically, this involves a decrease in biodiversity, a reduction in commensals such as *Prevotella*, and an increase in the abundance of pathobionts [34, 35]. This specific profile has significant diagnostic and prognostic potential and opens up prospects for developing non-invasive methods for detecting TB in cases that are difficult to diagnose, assessing the risk of drug resistance, and predicting disease progression. It is important to note that modern anti-tuberculosis chemotherapy may partly restore normal lung microbiota composition but simultaneously induces the selective growth of antibiotic-resistant strains among opportunistic pathogens [34, 40, 62].

In this regard, modulating the lung microbiota appears to be an extremely promising strategy in combating TB. The development of inhaled probiotics and methods for correcting pulmonary dysbiosis could become a new tool for improving treatment efficacy, especially in cases of drug-resistant TB, as well as for preventing the disease in at-risk populations, including children [50, 51, 60, 61].

Thus, an in-depth study of the microecology of the respiratory tract opens new horizons for phthisiology, heralding a transition to more personalized and effective approaches in the diagnosis, treatment, and prevention of one of the oldest and most socially significant infections in human history.

ADDITIONAL INFORMATION

Author contribution. I.A. Baranov — review concept, writing the final text of the article; N.V. Tivirikin — writing and editing the test, developing infographics; A.V. Derevyanko — editing the text, providing photo materials; D.P. Gladin, M.E. Lozovskaya — management, editing the text; E.S. Zubareva, N.S. Kozlova — writing and editing the text.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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