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TUBERCULOSIS: PREVALENCE, RISK FACTORS, AND FIRST-LINE DRUG RESISTANCE

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Summary

Introduction: In Kazakhstan, according to the National Center of Phthisiopulmonology, there has been a decrease in tuberculosis (TB) incidence, though the issue remains significant. TB is more common among socially vulnerable groups, including the homeless, prisoners, migrants, and individuals with weakened immune systems. The average TB incidence rate in the country is around 55 cases per 100,000 people, which is higher than the Central Asia average.

Aim of the literature review is to analyze TB prevalence worldwide and in Kazakhstan, with attention to key sociodemographic data, risk factors, and multidrug-resistant forms.

Search Strategy: After identifying primary keywords and synonyms, a literature search was conducted in English (PubMed, Google Scholar, Embase) and Russian databases (Cyberleninka, eLibrary), covering the past seven years for relevance. Selected publications underwent citation analysis, and abstracts were screened for relevance. Studies meeting inclusion criteria were then retrieved in full for detailed review. *Inclusion criteria:* studies pertinent to the topic, in English or Russian, published since 2017, including primary/secondary research, systematic reviews, meta-analyses, clinical guidelines, monographs, and conference abstracts.

Results and Conclusion: According to the World Health Organization (WHO), over 10 million new active TB cases are recorded annually. In Kazakhstan, the TB incidence rate in 2022 was 78 cases per 100,000 population. Although TB incidence has been decreasing in the country, the disease burden remains significant, particularly within specific regions and population groups. In 2019, Kyzylorda Region reported the highest incidence at 115 per 100,000, while the lowest rate, 55 per 100,000, was observed in Karaganda Region and its surrounding areas. These disparities may be due to differences in income, living conditions, population age, and comorbidities. A critical issue also remains the prevalence of multidrug-resistant TB (MDR-TB): approximately 25% of new cases and nearly 50% of previously treated patients are resistant to first-line medications. The government of Kazakhstan is actively working to combat TB, achieving significant progress in reducing prevalence and improving treatment outcomes.

Keywords: *tuberculosis, epidemiology, risk factors, drug resistance, Kazakhstan.*

Резюме

ТУБЕРКУЛЕЗ: РАСПРОСТРАНЕННОСТЬ, ФАКТОРЫ РИСКА И УСТОЙЧИВОСТЬ К ПРЕПАРАТАМ ПЕРВОЙ ЛИНИИ

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Введение: В Казахстане (РК), по данным Национального центра фтизиопульмонологии, отмечается снижение заболеваемости туберкулезом (ТБ), однако проблема сохраняет актуальность. Заболевание чаще встречается среди социально уязвимых групп населения — бездомных, заключенных, мигрантов и людей с ослабленным иммунитетом. Средний показатель заболеваемости по Республике составляет около 55 случаев на 100 000 населения, что выше среднего показателя по Центральной Азии.

Цель обзора литературы: изучить распространенность туберкулеза в мире и Республике Касахстан, с учетом основных социально-демографических данных, факторов риска, и мультирезистентных форм.

Стратегия поиска: После определения основных ключевых слов и синонимов был проведен поиск литературы в англоязычных (PubMed, Google Scholar, Embase) и русскоязычных базах данных (Cyberleninka, eLibrary), охватывающий последние семь лет. Выбранные публикации прошли анализ цитирования, а абстракты были проверены на релевантность. Исследования, соответствующие критериям включения, были извлечены в полном объеме для подробного обзора. Критерии включения: исследования, соответствующие теме, на английском или русском языке, опубликованные с 2017 года, включая первичные/вторичные исследования, систематические обзоры, метаанализы, клинические руководства, монографии и тезисы конференций.

Результаты и заключение: По данным Всемирной Организации Здравоохранения (ВОЗ) ежегодно регистрируется более 10 миллионов новых случаев активного ТБ. В РК уровень заболеваемости ТБ в 2022 году составил 78 случаев на 100 000 населения. Несмотря на снижение заболеваемости туберкулезом в РК, бремя болезни остается существенным, особенно в отдельных регионах и среди определенных групп. По данным 2019 года, наивысший уровень заболеваемости - 115 на 100 000 человек - зарегистрирован в Кызылординской области, а самый низкий - 55 на 100 000 - в Карагандинской области и прилегающих районах. Эти различия могут объясняться доходами, условиями проживания, возрастом населения и тяжестью сопутствующих заболеваний. Критической проблемой также остается распространенность ТБ с множественной лекарственной устойчивостью (МЛУ-ТБ): около 25% новых случаев и почти 50% ранее лечившихся пациентов устойчивы к препаратам первой линии. Правительство РК активно борется с заболеванием, достигнув значительного прогресса в снижении заболеваемости и улучшении показателей лечения.

Ключевые слова: *туберкулез, эпидемиология, факторы риска, лекарственная устойчивость, Республика Казахстан.*

Түйіндеме

ТУБЕРКУЛЕЗ: ТАРАЛУЫ, ҚАУІП ФАКТОРЛАРЫ ЖӘНЕ БІРІНШІ ҚАТАРДАҒЫ ПРЕПАРАТТАРҒА ТӨЗІМДІЛІК

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Кіріспе: Қазақстанда (ҚР) Ұлттық фтизиопульмонология орталығының мәліметтері бойынша туберкулезбен (ТБ) сырқаттанушылықтың төмендеуі байқалады, алайда проблема өзектілігін сақтайды. Ауру халықтың әлеуметтік осал топтары арасында жиі кездеседі-үйсіз адамдар, тұтқындар, мигранттар және иммунитеті төмен адамдар. Республика бойынша сырқаттанушылықтың орташа көрсеткіші 100 000 тұрғынға шаққанда шамамен 55 жағдайды құрайды, бұл Орталық Азия бойынша орташа көрсеткіштен жоғары.

Осы шолудың **мақсаты** - негізгі әлеуметтік-демографиялық деректерді, қауіп факторларын және көп төзімді нысандарды ескере отырып, әлемде және Қазақстан Республикасында туберкулездің таралуын зерделеу.

Іздеу стратегиясы: Негізгі түйінді сөздер мен синонимдер анықталғаннан кейін соңғы жеті жылды қамтитын ағылшын тілді (PubMed, Google Scholar, Embase) және орыс тілді мәліметтер базасында (Cyberleninka, eLibrary) әдебиеттерді іздеу жүргізілді. Таңдалған басылымдар дәйексөзді талдаудан өтті және абстрактілер өзектілігі тексерілді. Қосу критерийлеріне сәйкес келетін зерттеулер егжей-тегжейлі шолу үшін толық көлемде алынды. Қосылу критерийлері: 2017 жылдан бері жарияланған ағылшын немесе орыс тілдеріндегі тақырыпқа сәйкес зерттеулер, соның ішінде бастапқы/қайталама зерттеулер, жүйелі шолулар, мета-талдаулар, клиникалық нұсқаулықтар, монографиялар және конференция тезистері.

Нәтижелер және қорытынды: Дүниежүзілік Денсаулық сақтау ұйымының (ДДҰ) мәліметтері бойынша жыл сайын белсенді туберкулездің 10 миллионнан астам жаңа жағдайы тіркеледі. ҚР-да 2022 жылы ТБ сырқаттанушылық деңгейі 100 000 тұрғынға шаққанда 78 жағдайды құрады. ҚР-да туберкулезбен сырқаттанушылықтың төмендеуіне қарамастан, аурудың ауыртпалығы, әсіресе жекелеген өңірлерде және белгілі бір топтар арасында елеулі болып қала береді. 2019 жылдың деректері бойынша сырқаттанушылықтың ең жоғары деңгейі - 100 000 адамға шаққанда 115 - Қызылорда облысында, ал ең төменгісі - 100 000 адамға шаққанда 55 - Қарағанды облысында және оған іргелес аудандарда тіркелген. Бұл айырмашылықтар табысқа, өмір сүру жағдайына, халықтың жасына және қатар жүретін аурулардың ауырлығына байланысты болуы мүмкін. Көптеген дәріге төзімді туберкулездің таралуы да маңызды мәселе болып қала береді: жаңа жағдайлардың шамамен 25% және бұрын емделген пациенттердің шамамен 50% - ы бірінші қатардағы препараттарға төзімді. ҚР Үкіметі аурумен белсенді күресіп, аурушаңдықты төмендетуде және емдеу көрсеткіштерін жақсартуда айтарлықтай прогреске қол жеткізді.

***Түйінді сөздер**: туберкулез, эпидемиология, қауіп факторлары, дәрілік тұрақтылық, Қазақстан Республикасы.*

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Background

Tuberculosis (TB) is a chronic, socially significant infectious disease of bacterial origin, primarily affecting lung tissue [69]. Despite decades of strategies aimed at controlling the disease, prior to the COVID-19 pandemic, TB remained the leading cause of death worldwide from a single infectious agent [32]. TB has impacted human populations for millennia, leading to substantial mortality and significant losses in population health across generations. By the early 20th century, TB became the predominant infectious disease in many industrialized nations. In the absence of effective treatments, control efforts were limited to supportive care and isolation. This situation persisted until the mid-20th century, when the development of effective anti-TB antibiotics between the 1940s and 1960s dramatically altered the course of the disease [37]. The advent of combination therapies provided reliable treatment, generating optimism among healthcare providers, researchers, and policymakers, who anticipated near-total eradication of TB [56].

Despite these advancements, the emergence of antibiotic resistance has since become a major barrier to TB control worldwide, especially within the European region. By 1993, the rising rates of drug resistance prompted the World Health Organization (WHO) to declare TB a global health emergency [21]. Today, two significant factors exacerbate the global TB trouble: firstly, the increasing antibiotic resistance of *Mycobacterium tuberculosis* (MBT) to first-line

treatments; secondly, the rising number of patients with serious comorbidities, including HIV/AIDS and hepatitis [6, 52].

The Ministry of Health of the Republic of Kazakhstan (RK) has made significant efforts to combat TB, achieving notable reductions in TB prevalence and improvements in treatment outcomes [68]. Nevertheless, the disease burden remains substantial, particularly in specific regions and population groups. This persistence may be linked to factors such as income levels, comorbid conditions, and the effectiveness of screening programs [36]. Collectively, these challenges complicate global TB control efforts, underscoring the need for ongoing innovation in TB management and treatment strategies.

Therefore, the **aim** of this review is to examine the prevalence of TB globally and within Kazakhstan, considering key socio-demographic factors, risk factors, and multidrug-resistant forms.

Search Strategy. Following the identification of the main keywords and their synonyms, a literature search was conducted in English-language databases such as PubMed, Google Scholar, Embase and in Russian-language sources, specifically Cyberleninka and eLibrary. To ensure the most relevant data, the search period covered the past seven years. Once publications were selected, the authors reviewed all bibliographic references both cited within these articles and those citing the selected articles. At the next stage, article abstracts were screened to identify the most relevant studies. After differentiating the collected literature according to inclusion and exclusion criteria, full-text articles were retrieved for a more detailed review. In the final stage, validated sources were included in the study. A brief search strategy is shown in Figure 1.

Inclusion criteria: 1) studies relevant to the review topic, 2) studies in English and Russian, 3) studies published from 2017 onward, 4) all primary and secondary research such as systematic reviews, meta-analyses, clinical guidelines, monographs, and conference abstracts. *Exclusion criteria* included any studies that did not meet the inclusion requirements.

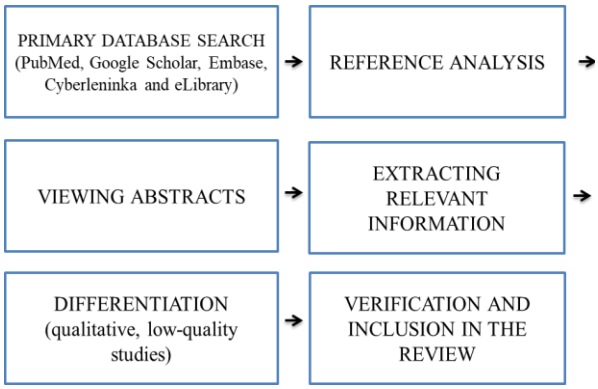

Figure 1. Search strategy.

The main part

Epidemiological dimensions of tuberculosis worldwide and in the Republic of Kazakhstan

According to the WHO, 2.5 billion people worldwide are infected with MBT [50]. TB incidence continues to rise annually, resulting in millions of deaths, including those due to co-infections [58]. In 2014, WHO launched an ambitious plan to eliminate TB as a public health threat by 2035, outlining four key principles necessary for its implementation [10]. To achieve these goals, an annual reduction in incidence of 10% and mortality of 6% is required. However, in 2022, TB was diagnosed in 7.5 million individuals— the highest figure recorded since global monitoring began in 1995. Experts estimate that the net reduction in TB mortality for 2022 was only 19%, far below the planned 75% reduction by 2025. The cumulative incidence decreased by just 8.7%, significantly below the targeted 50% reduction by 2025. Treatment was received by only 84% of the 40 million individuals who were eligible, and preventive treatment reached merely 52% of the 30 million recommended for it [11]. Part of this increase in cases can be attributed to the impact of the COVID-19 pandemic and the conditions of isolation [32].

A decline in TB incidence is primarily observed in high-income countries such as the United States and Canada, where case numbers are fewer than 10 per 100,000 populations. By comparison, high incidence rates are seen in low- and middle-income countries, including nations in Africa, as well as India and Indonesia [35]. According to the latest WHO Global Report, countries with the highest TB burden include India (0.26), Indonesia (0.085), China (0.084), the Philippines (0.06), and Pakistan (0.057). The remaining countries with a high TB burden account for 21% of cases worldwide [11].

Despite being the largest economy in Central Asia, Kazakhstan was classified as a middle-income country at the start of the new century [12]. In 2016, Kazakhstan held the eighth position worldwide for new and recurrent TB cases. It is also listed among the 30 countries with a high burden of multidrug-resistant TB (MDR-TB) specifically to rifampicin, with an overall incidence of 22 cases per 100,000 individuals. Although TB incidence and mortality rates in Kazakhstan have decreased over the last decade, MDR-TB levels remain notably high. MDR-TB accounted for 44% of cases among individuals who had previously received therapy and 27% of newly diagnosed cases by 2019 [24]. However, it is important to note that Kazakhstan has made great strides in the fight against the illness. For example, according to recent data, the mortality rate of pulmonary tuberculosis in Kazakhstan has dropped from 7.4 to 1.5 deaths per 100,000, and the incidence has declined by more than half over the last 20 years, from 171 per 100,000 in 2000 to 78 per 100,000 in 2022. The treatment effectiveness for TB patients in Kazakhstan has reached one of the highest levels globally, with a treatment success rate of 85.9% for newly diagnosed patients with drug-sensitive TB and 80.2% for those with drug resistance in 2021 [68].

To gain a more detailed understanding of the epidemiological situation regarding TB in the country, it is essential to examine incidence rates in specific regions. According to *Aringazina A.M. et al.* (2021), the highest TB incidence rate in 2019 was recorded in the Kyzylorda region at 115.0 per 100,000, while the lowest was 55.0 in Karaganda and neighboring areas. High incidence rates were also observed in the Aktobe and North Kazakhstan regions, with rates of 81.1 and 88.9 per 100,000,

respectively. In East Kazakhstan (now Abay region), the TB prevalence was 69.3 per 100,000. Although these rates were significantly lower than those in the previously mentioned regions, they still exceeded the national average [1]. This disparity in incidence rates across the country may be linked to differences in socio-economic conditions, diagnostic capabilities, access to healthcare services, and the quality of preventive programs.

Some aspects of the pathogenesis of tuberculosis

MBT, the causative agent of TB, is a unique and resilient bacterium characterized by several distinct features [4]. This aerobic, non-spore-forming, and non-motile organism is shaped as slightly curved or straight rods, with dimensions ranging from 0.2-0.6 μm in width to 1-10 μm in length. Its colony morphology is variable and can differ significantly among *Mycobacterium* species, showing a spectrum from rough to smooth textures and a range of pigmentation. Some colonies remain nonpigmented, while others produce carotenoid pigments, giving them a yellowish hue [41]. A defining feature of MBT is its cell wall composition, which includes N-acetyl muramic acid and is exceptionally rich in mycolic acids-complex lipids with long hydrocarbon chains (70-90 carbon atoms). This high mycolic acid content gives MBT its "acid-fast" characteristic, allowing it to resist decolorization by acid-alcohol and enabling it to retain specific dyes used in diagnostic staining. MBT also possesses a DNA structure with a high guanine-cytosine (G + C) content, ranging between 61-71 mol %, which contributes to its stability and unique genetic profile. Its generation time is notably slow, varying from 20 to 36 hours, which explains the lengthy treatment durations required for TB, as the slow growth rate challenges rapid eradication of the bacteria [33, 53, 60].

A critical factor in tuberculosis infection is MBT's ability to invade alveolar macrophages, which are essential components of the immune system's nonspecific defense. However, infection requires more than just the bacterium's presence, as two protective mechanisms help prevent contamination. The first is the bacterial load: not all TB patients produce a sufficient amount of MBT to initiate infection. The second is the quality of lung surfactant, a surface-active compound that can disrupt the bacterium's lipophilic cell wall, aiding macrophages in engulfing and removing the bacterium from the body [17, 29]. Another element that increases infection risk is the duration of exposure to TB patients, as repeated contact raises the likelihood of contracting the disease. If the immune system functions well, surfactant levels and composition are adequate, and exposure to an infected person is brief, phagocytosis will occur—allowing macrophages to ingest, digest, and ultimately clear the bacterium from the lungs [15, 48].

If the immune defense mechanisms are compromised, MBT can enter the macrophage intact, producing an Early Secretory Antigenic Target (ESAT-6), which prevents the formation of a phagolysosome and thus blocks the lysis of the bacterium. This adaptive mechanism enables MBT to freely escape into the cytoplasm and multiply extensively. Inside the macrophage, MBT divides for about 24 hours, eventually causing the cell to die and become an extracellular parasite once again [3].

While residing within the macrophage, MBT releases anti-inflammatory cytokines and interleukins, drawing T-lymphocytes to the infection site. However, the attraction of T-lymphocytes and other immune cells, leading to an inflammatory response, only occurs after the bacterium has repeatedly cycled through entering, dividing within, and exiting the macrophage. This repeated cycle allows macrophages to produce sufficient concentrations of interleukins and cytokines to attract T-lymphocytes and activate other immune cells [2, 47]. During inflammation, blood and lymphatic capillaries in the alveoli dilate, allowing more immune cells to enter; however, this also provides a pathway for MBT to invade the lymph nodes, potentially triggering lymphadenitis. Lymphatic dendritic cells then activate CD4+ T-lymphocytes, which differentiate into Th1 and Th2 subtypes, with Th1 cells primarily responsible for producing gamma-interferon to activate infected macrophages, halting the spread of MBT [46, 59].

The formation of a granuloma in tuberculosis represents a complex, organized immune response to contain MBT and prevent its dissemination. Upon inhalation, MBT primarily infects alveolar macrophages in the lungs. Although macrophages attempt to neutralize the bacteria by engulfing them into phagosomes, MBT has evolved mechanisms to evade destruction, such as preventing the fusion of phagosomes with lysosomes, which would otherwise expose the bacteria to destructive enzymes. This survival strategy allows the bacteria to replicate within the macrophages, triggering a more intense immune response [22]. As infected macrophages release chemokines and cytokines, additional immune cells are recruited to the infection site, including monocytes, neutrophils, and T-lymphocytes. CD4+ T-helper cells play a crucial role, particularly the Th1 subtype, which produces interferon-gamma (IFN-γ) upon activation [44]. IFN-γ acts as a potent activator of macrophages, enabling them to mount a stronger defense by releasing reactive oxygen and nitrogen species. These activated macrophages then differentiate into specialized forms, such as epithelioid cells and multinucleated giant cells, which cluster around the bacteria, forming the initial structure of the granuloma [43].

Over time, fibroblasts and additional immune cells encase this cluster, creating a multilayered barrier that helps contain the bacteria within the granuloma. As the granuloma matures, the central core can undergo caseous necrosis-a form of cell death that creates a cheese-like, necrotic area due to immune cell accumulation and bacterial activity [23]. This caseous core is thought to be a toxic environment, with low oxygen and acidic conditions that inhibit bacterial growth; however, MBT can enter a dormant state here, surviving for years in this latent form. The outer layers of the granuloma are rich in immune cells, providing a dynamic interface where immune surveillance is high [40, 44]. This structure not only limits bacterial spread but also serves as a potential reservoir for future infection. If the host's immune system becomes compromised, such as through malnutrition, immunosuppressive drugs, or HIV infection, the granuloma's structure may deteriorate [19, 62]. This breakdown releases dormant bacteria, allowing them to reactivate, multiply, and spread, leading to active tuberculosis and increasing the risk of transmission. Thus, the granuloma in tuberculosis is both a containment

mechanism and a double-edged sword, capable of sequestering bacteria in a dormant state while posing a latent risk of reactivation [20]. This ability of MBT to persist in granulomas is a key factor in its chronic nature and poses significant challenges for eradication and long-term immunity.

Socio-Demographic Characteristics and Risk Factors of Tuberculosis

The main objective of TB control initiatives in high-burden nations is to reduce infection transmission and promote early detection in order to ensure successful treatment and lower mortality [10]. The progression of TB typically involves two phases. In most cases, the immune system contains the bacteria within tubercles. However, about 5% of infections progress rapidly within two years. Additionally, around 10% of individuals with latent TB may experience reactivation, which can occur soon after infection or later due to dormant bacilli or reinfection [18]. Approximately 20% of individuals carrying MBT may develop active TB with bacterial shedding. Those at highest risk are individuals with HIV/AIDS-associated conditions, in which immune function is significantly compromised [28].

Effective TB control requires consideration of both the disease itself and the risk of contracting active TB following an infection [5]. TB infection likelihood is influenced by external factors, including the source's infectiousness, proximity to the infected person, and social behaviors like smoking and indoor air quality. High social stress and overcrowding significantly increase transmission risk [16]. Additionally, prolonged exposure to infected individuals, such as in healthcare settings with long wait times and delayed diagnoses, further elevates the risk of TB infection [30].

The majority of the triggers that accelerate the progression from infection to acute illness are host-related and endogenous. Conditions that impact the immune response, especially those that lower immunity and increase the risk of disease development are the most important of these [49]. Comorbidities like diabetes mellitus, HIV, and hepatitis can worsen the progression of the primary disease [60].

When all risk factors are closely examined, the most critical ones are the source's infectiousness and the proximity of contact with the subject [13]. It is well established that bacillary concentration in sputum positively correlates with the infectiousness of TB patients. *Espinal et al.* (2000), in a prospective study in the Dominican Republic, assessed the impact of HIV on MTB infectiousness among 803 household contacts of 174 TB patients. They found that contacts of patients with higher sputum smear grades had significantly higher odds of a positive TST, with an odds ratio of 1.98 for 1–10 bacilli per field and 5.88 for >10 bacilli per field. Close (household) contact with TB patients elevates the risk of MTB infection and primary active TB development [31]. *Morrison et al.* (2008), in a systematic review of 41 studies, found that the overall TB case rate was 4.5% (CI = 4.3–4.8) among individuals who had contact with infected persons [63].

Another significant risk factor for TB is patient age [51]. Children under five and adults over 65 are at higher risk. This may be due to the still-developing immune system in young children, making them vulnerable to severe forms of TB, including extrapulmonary TB, while older adults have weakened immunity due to aging and chronic conditions [61, 66]. Men have twice the susceptibility to TB compared to women, likely influenced by biological factors, lifestyle choices, and occupational hazards. Nevertheless, the risk of tuberculosis infection increases in women during the postpartum and lactation periods [54].

The connection between smoking and TB has long been recognized, but recent research highlights that both active and passive smoking increase TB risk and worsen outcomes [64]. Smoking damages lung tissue, weakens immune defenses, and accelerates the transition from infection to active disease. Smokers are up to four times more likely to die from pulmonary TB than non-smokers. The heat and chemicals in cigarette smoke harm lung cells, making them more susceptible to infection and impairing the effectiveness of TB treatments. Consequently, TB in smokers tends to be more severe and harder to treat, increasing the risk of spread through coughing and breathlessness. In terms of alcohol consumption, a systematic review encompassing three cohort studies and 18 case-control studies found a significantly heightened risk of developing active tuberculosis (OR = 2.94, 95% CI = 1.89-4.59) in individuals who consume over 40 grams of alcohol daily or have alcohol-related disorders. This elevated risk is associated with immune system dysfunction, specifically through the disruption of signaling molecules involved in the production of cytokines [55, 65].

The high rate of tuberculosis in poorer nations can be attributed to factors like indoor air pollution from using solid fuels for cooking and heating during colder seasons. Research indicates that biomass combustion releases a substantial amount of particulate pollutants, including carbon monoxide (CO), nitric oxide, methanal, and polycyclic aromatic compounds. These particles penetrate deep into the alveoli, posing serious risks to respiratory health [34]. Furthermore, Barry and colleagues (2021) discovered that the prevalence of latent tuberculosis infection (LTBI) is greater among people who live in low- and middle-income nations [14].

Socio-demographic factors associated with TB are closely linked to urbanization and migration trends [7]. TB primarily impacts the most disadvantaged groups, including those living in poverty, incarcerated individuals, and the homeless. This is likely attributable to substandard living conditions, insufficient nutrition, coexisting health issues, and substance abuse, especially intravenous drug use. Recent research also points to ethnic factors in TB susceptibility, as certain gene deletions found among Canadian Indigenous populations may predispose them to active TB [42].

The most important immunosuppressive factor for active TB is concomitant HIV infection, which is mostly associated with endogenous risk factors for TB. According to the literature, the highest incidence rates of HIV/AIDS are observed in Southern African countries, where high TB incidence is also recorded. It is estimated that TB incidence may reach 700 cases per 100,000 people annually in regions where HIV prevalence exceeds 20%, while in the United States, it is just 5 cases per 100,000 [67]. Notably, HIV co-infection speeds up the course of TB following first infection or reinfection and increases the chance of latent

TB infection reactivation. Studies in both high- and low-TB-burden countries consistently link rising TB incidence to HIV infection [57].

According to a 2012 study, Kazakhstan's national TB program classified a high percentage of patients (83%–87%) as having no identifiable TB risk factors [25]. However, other research highlights population migration as a significant socio-demographic risk factor for TB spread in Kazakhstan. Low living standards and lack of employment opportunities drive people to migrate to other countries in search of work. Migrants face a higher risk of TB infection, which may be due to a lack of insurance, poor living conditions, and generally lower health indicators. In the Atyrau and Mangystau regions of Kazakhstan, the incidence of MDR-TB is significantly higher than in other regions, a trend that experts attribute to the substantial influx of immigrants. Additionally, if MDR-TB cases are not diagnosed promptly, nosocomial transmission may significantly contribute to TB incidence rates, especially given Kazakhstan's practice of prolonged hospitalization for TB patients [25].

So, the socio-demographic characteristics and risk factors associated with TB emphasize the complexity of this disease. Addressing these factors necessitates a comprehensive approach that improves living conditions, expands healthcare access, and implements targeted interventions for vulnerable populations.

Tuberculosis treatment and multidrug resistance

Effective TB treatment relies on a comprehensive pharmacological approach tailored to the disease stage, type (latent or active), and resistance profile [27]. First-line anti-TB medications remain the cornerstone of treatment due to their high efficacy and relatively low toxicity. The WHO recommends a regimen for active TB that includes four key drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) [9]. Each of these medications works in a different way. For instance, isoniazid (INH) breaks down the membrane of bacteria by targeting the formation of mycolic acid. By interfering with microbial RNA polymerase, which is necessary for basement life in tuberculosis, rifampicin (RIF) prevents RNA production. Pyrazinamide (PZA) affects latent microorganisms inside macrophages and has bactericidal effect in acidic settings. Ethambutol (EMB) targets arabinogalactan to prevent the formation of cell membranes [8].

The initial phase of TB treatment involves administering all first-line drugs and typically lasts between two to four months. This is followed by a maintenance phase, which includes only two anti-TB medications and continues for another four months. It is important to note that such a standard treatment regimen may not be suitable for individuals with MDR and extensively drug-resistant (XDR) TB. These conditions necessitate a longer and more complex treatment plan due to potential resistance to second-line drugs, including levofloxacin and ciprofloxacin [45]. These medications tend to be less effective and more toxic, emphasizing the need for careful management. Second-line treatment primarily includes levofloxacin or moxifloxacin, which inhibit DNA synthesis, followed by clofazimine and linezolid, initially developed for leprosy treatment. Clofazimine's antibacterial properties make it valuable for treating MDR-TB, while linezolid has shown potent bacteriostatic activity, particularly in XDR-TB cases. Additionally, WHO recommends bedaquiline, delamanid, and pretomanid for MDR- and XDR-TB treatment [38]. For example, unlike conventional anti-TB medications, bedaquiline attacks the ATP polymerase of MBT, whereas delamanid disrupts the formation of cell membranes [26]. For best results against MDR-TB or XDR-TB, a six-drug combination is often used, with modifications made depending on drug tolerance testing to guarantee successful therapy.

Currently, global efforts are underway to reduce the standard six-month treatment course for TB using optimized combinations of new and existing drugs. The BPaL regimen (bedaquiline, pretomanid, and linezolid), endorsed by WHO, shortens the treatment duration for XDR-TB to six months, demonstrating promising efficacy and adherence. For both MDR-TB and XDR-TB, an individualized approach is critical. Molecular diagnostics enable rapid identification of resistance profiles, facilitating personalized treatment plans based on the specific resistance profile of the patient [39].

However, it is important to recognize that treating TB, especially drug-resistant forms, poses several challenges. Adhering to lengthy and complex treatment regimens is often difficult, particularly in resource-limited settings, leading to treatment failures and increased resistance. Second-line drugs carry a high risk of toxicity, making monitoring and management of side effects critically important. Risk factors such as poverty, limited access to healthcare, and overcrowded living conditions exacerbate TB transmission and complicate treatment. Therefore, comprehensive strategies that combine pharmacological innovations with effective public health initiatives and patient-centered care are essential. Only through a multifaceted approach can meaningful progress be made in combating and ultimately eliminating tuberculosis.

Conclusion

In summary, TB remains a significant challenge both globally and in Kazakhstan, exacerbated by the emergence of drug-resistant strains that require substantial resources for effective management. A comprehensive strategy that includes optimizing preventive measures, ensuring equitable access to high-quality healthcare, and addressing the social determinants of health is essential for reducing TB incidence and mortality rates. By prioritizing these efforts, it is possible to make meaningful progress in the fight against TB and ultimately improve public health outcomes.

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