Understanding the Impact of Alcohol Use Disorder in the Russian Federations Tuberculosis Patients

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Abstract

Tuberculosis (TB) is an archaic disease caused by *Mycobacterium tuberculosis* (Mtb). The World Health Organization (WHO) established the "End TB Strategy" to reduce the incidence of TB. The Russian Federation is one of the seven high TB burden countries that have reached their 2020 milestone goal to reduce TB incidence and deaths. Even though they are on target, they make up 8% of drug-resistant TB cases in 2019. Harmful and hazardous alcohol consumption is strongly associated with an increased risk of TB. When comparing the Russian Federation to other high TB burden countries, the prevalence of alcohol use disorder (AUD) is significantly higher. Through a literature review, the prevalence, treatment outcomes, and interventions of AUD among Russian TB patients are understood. The Russian Federation has a higher prevalence of alcohol abuse among TB patients and higher rates of TB mortality attributed to AUD. The integrated management of physician delivered alcohol care to TB patients (IMPACT) was a randomized control trial designed to identify how successful pharmacological and psychotherapy treatment is in TB patients with AUD. Unfortunately, the study did not find a significant improvement in treatment adherence. To overcome poor treatment outcomes in Russian TB patients with AUD, appropriate interventions should be identified and implemented in the Russian Federation. Such

interventions would include encouraging Russians to seek treatment for AUD, decreasing stigmatization of alcohol use, and improving access to effective AUD treatment across these populations.

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Preface

I want to thank Dr. Mattila and Dr. De Genna for helping me with the writing process and feedback on my essay. My friends and family were significant support mentally throughout the writing process and my program. I am thankful to the Department of Infectious Disease and Microbiology for allowing me to study infectious diseases with a public health focus.

1.0 Introduction

Tuberculosis (TB) is a deadly infectious disease that has been affecting humans for thousands of years. Specialists found writings that describe a disease like TB in India and China, which dates back to 3300 and 2300 years ago, respectively [2]. Skeletal deformities associated with TB, Pott's disease, were found in Egyptian mummies dating back to 2400 BC and Peruvian mummies before European settlers arrived. Aristotle and Hippocrates started the debate on whether TB was an infectious agent or hereditary. This debate continued until Villeman proved the contagious nature of TB in 1865 through inoculation of rabbits with infected tissues from a cadaver [3]. *Mycobacterium tuberculosis* (Mtb), the bacillus that causes TB, was isolated and stained by Robert Koch and announced on March 24, 1882 [4]. After discovering Mtb, scientists began making great strides in identifying Mtb infections through scientific innovations such as the Tuberculin Skin Test (TST) and the Bacillus Calmette-Guerin (BCG) vaccine, which is widely used to prevent pediatric TB.

Streptomycin was one of the first anti-TB drugs created to effectively treat patients with TB [3]. After a few years, Mtb became resistant to streptomycin and alternative anti-TB drugs. Drug-resistant TB challenges the World Health Organization's (WHO) End TB Strategy [5]. Dubos commented over half a century ago that medical and social factors are essential to address TB patients [3]. Despite all the public health advances in TB prevention, diagnostic, and treatment, TB remains a substantial public health challenge requiring medical and social interventions to reduce TB burden.

1.1 Pathogenesis

Mtb spreads from person to person through aerosol transmission. Interactions between the immune system and Mtb can follow several pathways that result in eliminating the bacteria or disease progression. First, the host immune response can successfully kill off Mtb [6, 7]. The second is where the host does not kill Mtb, and the bacilli can persist and cause active TB or asymptomatic latent TB (LTBI). Finally, LTBI can reactivate and lead to active TB equivalent to the disease seen after primary Mtb infection.

The first immune cells that Mtb encounters are alveolar macrophages. They interact through cell surface receptors and phagocytose the Mtb [7, 8]. At some point, innate immune cells recognize the bacilli through recognition by toll-like receptors and produce cytokines and chemokines that activate and recruit other cells in the vicinity of the infection [7]. At some point, dendritic cells phagocytose Mtb and migrate to the lymph nodes to prime naïve T cells against Mtb. Immune cells at the site of infection produce pro-inflammatory and anti-inflammatory cytokines that help in the host's defense against Mtb [7, 9, 10]. A balance between pro-inflammatory and anti-inflammatory cytokines is essential in granuloma formation. Excess inflammation damages surrounding tissues. If there are too many anti-inflammatory cytokines present, it can cause immunosuppression [9].

Mtb has evolved strategies to evade the host's immune response. After phagocytosis, Mtb prevents fusion of the phagosome, and lysosome will not occur, creating an intracellular niche for bacterial replication. Macrophage and monocyte apoptosis can decrease the viability of Mtb and

kill the bacilli. Mtb has the ability to manipulate immune cells and promote necrosis. This cell death pathway can promote bacterial dissemination without reducing the viability of Mtb.

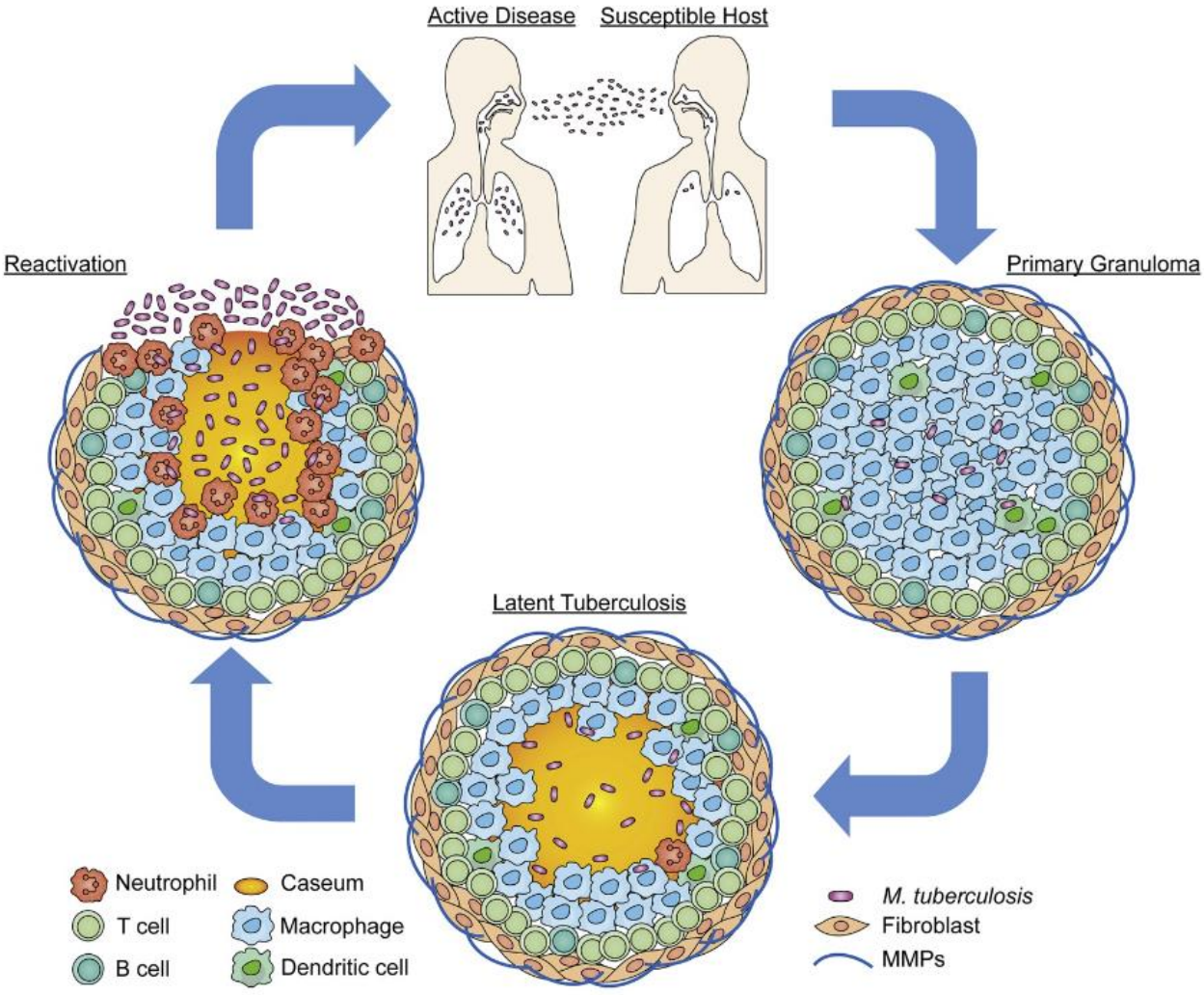


Figure 1 Tuberculosis Granuloma Model

Source : Balcells et al., 2019

The host's innate immune response facilitates the formation of a granuloma [10]. Granulomas are compact structures that consist of immune cells that coordinate to either kill the bacterium or, in cases where coordination is unsuccessful, promote bacterial persistence [11]. The

center of granulomas is a hypoxic environment that prevents Mtb from growing [12]. Cytokines important in granuloma formation include tumor necrosis factor, interferon-γ, and interleukin-12 [10]. If cytokine expression is deficient, then the granulomas become unstable. This allows the Mtb to replicate and disseminate to surrounding cells. When the immune system is compromised by host aging, co-morbidities, or co-infections (especially HIV), immunity in granuloma can weaken, allowing Mtb access to the oxygen and nutrients the bacteria need for replication and eventual dissemination to surrounding cells and other tissues [12, 13].

Consumption and phthisis are earlier names for TB that refer to the severe wasting of individuals with TB. The main symptoms of active pulmonary TB disease are fever, night sweats, weight loss, fatigue, and cough [5, 14]. These symptoms begin to set in slowly and make it difficult for patients to identify a problem. This results in a delay in the patient's effort in seeking diagnosis or treatment until several weeks after the onset of symptoms. For individuals with extrapulmonary TB, the diagnosis can be elusive. Based on the tissues that Mtb infects, patients can experience different symptoms. The most common forms of extrapulmonary TB are lymphatic, meningitis, and skeletal. Patients with extrapulmonary TB have a 10-50% chance of having pulmonary TB [15]. A patient with lymphatic TB may have pulmonary TB symptoms, except they will not cough [16]. Meningitis TB causes inflammation to the meninges and causes symptoms like other bacterial meningitis infections. Patients with skeletal TB experience pain and inflammation at the site of infection while Mtb destroys the bone.

1.2 Prevention

In 1921, Albert Calmette and Camille Guérin introduced the *Mycobacterium bovis* Calmette- Guérin (BCG) vaccine [17], which is based on an attenuated strain of *M. bovis*. More than 14 strains of BCG are distributed throughout the world and offer variable levels of protection against TB [18]. The BCG vaccine is up to 80 % effective in preventing TB in some cases, but the duration of safety and overall protective effects are highly variable [19]. Considering this, the WHO recommends vaccination of infants with the BCG vaccine in high incidence countries [20]. Several countries provide revaccination in citizens after infancy, although the WHO recommends only one dose of the BCG vaccine [21]. Revaccination in adults is effective in reducing the incidence of pulmonary TB [20]. Due to the BCG vaccine's variable protection, several new TB vaccines are being developed. They are in various stages of testing, in some cases with promising results [20].

1.3 Screening and Diagnostics

Early detection of TB is essential for controlling the spread of TB. The TST and Interferon-gamma release assays (IGRAs) can identify an individual with Mtb exposure [22, 23]. TST is injected intradermally into an individual's arm with purified protein derivatives (PPD). If the person has a mycobacterial infection, TST will elicit type IV delayed hypersensitivity [22]. When an individual has a positive TST, a chest x-ray (CXR) can allow a physician to see if there are lesions in the lung. If there is no lesion present in the CXR, then the TST results are considered a false positive. TST has low sensitivity, and false positives are common among people who have

been vaccinated with BCG or are immunocompromised. The TST's sensitivity is further compromised if an individual is vaccinated with the BCG vaccine more than once [21]. IGRAs assess the release of IFN-γ in blood drawn from an individual. IGRAs overcome the TST's cross-reactivity with BCG to reduce the number of false positives when screening TB. Due to the cost of IGRAs, TST is more favorable for use when screening for TB in high burden areas.

When an individual is symptomatic, they complete a questionnaire and receive a CXR to screen them for the risk of active pulmonary TB. If the results are positive for active TB, then they are referred to a specialist. Sputum smear microscopy, mycobacterial culture, and nucleic acid amplification tests (NAATs) are tests used to identify the presence of Mtb. Low-income countries favor sputum smear microscopy since it the least expensive out of the three and does not require a biosafety level 3 (BSL3) laboratory [24, 25]. Cultures and NAATs both require a BSL3 laboratory to be conducted but have a higher sensitivity than smear microscopy. The WHO recommends using Xpert MTB/RIF, a NAAT method that can produce results in about 2 hours [26]. Other tests the WHO recommends are Xpert Ultra and Truenat assays. Diagnosing extrapulmonary TB is more challenging since Mtb must be cultured from the site of infection. Extra-pulmonary TB is a paucibacillary disease that affects the sensitivity of diagnostic tests [15]. Biopsies and body fluids are collected to identify the presence of Mtb. Xpert MTB/RIF is helpful for testing for extrapulmonary TB and can be tested in children [24, 26]

Drug susceptibility testing (DST) is used to determine if a TB patient is resistant to anti-TB drugs [24, 27]. There are three drug-resistant TB known as rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB) [27, 28]. RR-TB is when the TB is resistant to rifampicin. A TB case is classified as MDR-TB when the strain is resistant to rifampicin and isoniazid [27, 29, 30]. XDR-TB is when the TB strain is resistant to

any of the fluoroquinolone drugs and at least one injectable second-line drug. Drug-resistant TB is acquired through chaotic drug treatment or direct transmission [27, 31].

There are two main routes researchers can go with DST, phenotypic and genotypic testing using culture and NAATs methods [24]. Culture methods such a solid agar or liquid are used for phenotypic DST [24]. If Mtb can persist in the presence of certain anti-TB drugs, then Mtb is considered resistant to them. It may take weeks or up to a couple of months to receive the results from the culture-based methods. This is not effective for treating patients with potential MDR-TB or XDR-TB [29, 31]. Genotypic testing is more sensitive for detecting which drugs the patient is resistant to [24]. Xpert MTB/RIF and line probe assays (LPAs) are more effective at detecting rifampicin resistance and second-line drug resistance, respectively [24].

1.4 Treatment

When an individual is diagnosed with active TB, they are enrolled in treatment to prevent the progression of the disease. The WHO classified all anti-TB drugs into six groups [27, 32]. The groups are classified according to efficacy and toxicity. Group 1 consists of all first-line drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol. Rifampicin is the most effective anti-TB drug currently available for treatment. The other groups are all classified as second-line drugs. These drugs are more toxic than first-line drugs and are not effective at clearing Mtb [32]. Group 2 consists of the fluoroquinolones: high dose levofloxacin, gatifloxacin, and moxifloxacin. Group 3 consists of the newer drugs, including bedaquililine, delamanid, and linezolid. Group 4 is made up of injectable agents. The main injectable anti-TB drugs are amikacin, kanamycin, streptomycin, and capreomycin. Since group 4 anti-TB drugs are injectables, patients would have to travel to the

hospital for routine treatment. Group 5 consists of ethionamide/prothionamide, clofazimine, imipenem, and meropenem. The final group, Group 6, is made up of amoxicillin/clavulanate, cycloserine, and para-aminosalicylic acid, and clarithromycin.

Screening for TB identifies primarily LTBI, which means Mtb is non-replicating, and the patient has no clinical manifestations of the disease [33]. A patient infected with LTBI has about a 10-15% chance of progressing to active TB throughout their life. When an individual is diagnosed with LTBI, they undergo treatment to sterilize the lung environment of Mtb bacilli. The WHO guidelines for treating patients with LTBI include a 6- or 9-month regimen of isoniazid, 3-4 months of rifampicin, or 3-month weekly rifapentine plus isoniazid [34]. The 6- and 9-month isoniazid treatment plan is slightly more hepatoxic and longer than the other two treatment options; patients may not adhere to the regimen as well [34].

Newly diagnosed TB patients with drug-sensitive TB start on first-line anti-TB drugs. With newly diagnosed TB patients, a combination of all four is taken for the first two months of treatment. This is followed up by taking just isoniazid and rifampicin for the next 4-6 months [35]. The first two months of treatment are the intensive phase for TB treatment. The length of treatment for TB is long because Mtb is a slow-growing pathogen that occupies different granuloma microenvironments, which results in varying levels of drug penetrance across microenvironments. Consequently, it will take more time to sterilize the lung environment thoroughly. Oral medication is an effective method for administrating medications since patients do not have to travel to the hospital for treatment every day. Patients must have a sputum smear test done during their regimen to ensure they respond appropriately to the drugs [36]. Suppose the patient still has a positive sputum smear test at the end of their treatment regimen. In that case, they will receive a DST to identify potentially specific drug resistance. Once the sputum smear test is negative, patients will

undergo another round of treatment with second-line medications if they fail their first round. Extra-pulmonary TB treatment regimen guidelines are the same as for pulmonary TB [15]. Patients with meningitis and skeletal TB receive treatment for 9-12 months.

Based on the WHO's recommendations, patients with drug-resistant TB can undergo a short-course treatment if eligible for 9-12 months, but most treatment regimens are 18-24 months long [27, 30, 34]. The WHO established a drug classification in 2016 specified for drug-resistant TB patients [32, 37]. There are four anti-TB drug categories, A-D. In group A are the fluoroquinolones, group B are the injectable medications, and group C consists of other major second-line drugs. There are three subgroups in group D: D1, D2, and D3. All the D subgroups consist of anti-TB additional medications, but D1 has two first-line anti-TB drugs, pyrazinamide, and ethambutol. The grouping of these drugs is functional when doctors create a treatment regimen for a patient that has a drug-resistant strain. Even though the classification was designed initially for RR-TB, doctors can use it for MDR- and XDR-TB. The WHO recommends that the patients are on four effective drugs against Mtb for the first six months and then at least three medications for the rest of the treatment course [36]. A patient with drug-resistant TB should have at least one drug from group A and group B in their drug cocktail. A DST is helpful for clinicians when determining which drugs would best treat a patient with drug-resistant TB.

The length of the treatment regimen and toxicity of anti-TB drugs make it difficult to treat patients without interruptions. Interruptions may involve a patient having to stop treatment due to side effects or failure to adhere to a treatment regimen. The reduction in adherence can be due to patients believing that they are cured, thus discontinuing their treatment, or patients may decide to stop taking their medications. Side-effects from anti-TB drugs include hepatoxicity, gastrointestinal distress, nephrotoxicity, hypothyroidism, neurotoxicity, and ototoxicity [27, 34].

About 15% of patients with drug-susceptible TB experience side-effects that cause them to discontinue their treatment [38]. About 86% of MDR-TB patients experience adverse side effects from anti-TB drugs [39]. Patients should be monitored for side effects during treatment to ensure treatment is stopped immediately when symptoms of toxicity become apparent.

The cure rate for MDR-TB is 60-80%, and XDR-TB's cure rates are even lower [31, 40]. These cure rates are only that high when socioeconomic interventions are incorporated into treatment. One of the main concerns that healthcare providers face with MDR- and XDR-TB patients is ethical treatment. Patients with drug-resistant TB can transmit their drug-resistant bacteria to other people. If a patient fails to complete treatment for XDR-TB, the median timeframe for death is 19.8 months [31]. Due to the risk of ongoing transmission, these TB patients are closely observed and provided supplies to prevent the potential spread of drug-resistant strains.

2.0 Global Tuberculosis

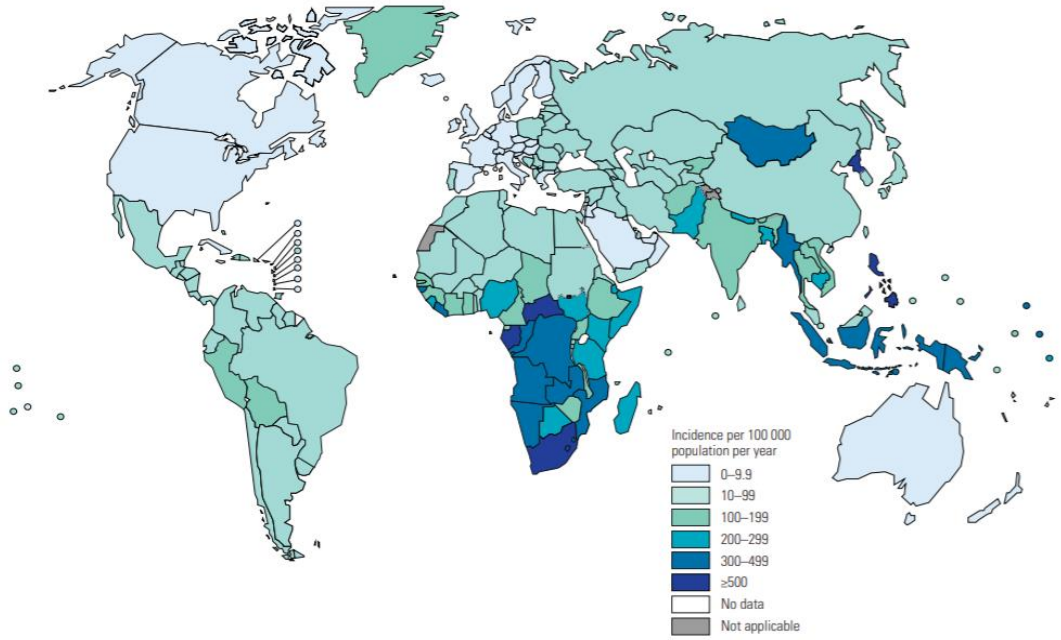


Figure 2 Incidence of Tuberculosis in 2019

WHO, 2020

In 2019, there were around 10 million new cases and about 1.4 million deaths from TB. Of these 10 million cases, about 90% of them were in adults [5]. According to the WHO, TB was one of the top 10 leading causes of death worldwide in 2019. Of the approximate 10 million TB cases, about 465,000 were MDR-TB. Globally, MDR/RR-TB makes up 3.3% of all TB cases in 2019. About 18% of MDR/RR-TB were previously treated for TB cases. The regions with the highest burden of MDR-TB and XDR-TB are China, India, and the Russian Federation [5, 41]. TB is treatable, but individuals diagnosed with MDR-TB have a mortality of 40%, while XDR-TB is 60% [5].

2.1 End Tuberculosis Strategy

In 2015, the WHO established the 'End TB Strategy' initiative to end the global TB epidemic. An indicator the WHO is using is a 95% reduction of global TB burden and deaths by 2035 compared to 2015 [5]. TB must be efficiently diagnosed, treated, and discussed with patients for prevention purposes to accomplish this goal. The WHO began implementing a new TB control strategy called “Directly Observed Treatment, short-course (DOTS)” in the early 1990s. DOTS focuses on five elements: sustained political and financial commitment, diagnosis of TB through practical sputum smear microscopy, a standardized short-course monitored TB treatment, ample supply of anti-TB drugs, and a standardized method for recording and reporting TB cases [29]. This strategy revolves around treating infectious TB patients with a shorter treatment regimen. In the year 2000, WHO implemented DOTS-plus was built off DOTS concepts, with the addition of quality second-line anti-TB drugs provisions [29].

2.2 Determinants of Tuberculosis

Determinants of TB can increase an individual's risk of exposure, treatment-seeking, reactivation of Mtb, adherence, and relapse. Identifying high-risk populations will allow for the development of a targeted intervention. The main determinants of TB involve host characteristics, health system socioeconomic status, and behavioral risk factors associated with TB. These determinants can be split into endogenous and exogenous factors.

Host characteristics are endogenous factors that influence the progression of TB [42]. Adult men make up 56% of TB cases confirmed in 2019. In comparison, adult women make up 32%, and children make up 12% of TB cases in 2019 [5]. Co-morbidities such as diabetes mellitus increase a host's risk of progressing to active TB. In 2019, diabetes mellitus increased an individual's risk of TB by 1.5 fold and attributed to 0.35 million cases of TB, 3.1%, in 2019 [5].

About 0.76 million TB cases were associated with the human immunodeficiency virus (HIV) in 2019, which correlates to 7.7% of TB infections attributed to HIV co-infection [5]. HIV is an infectious agent that attacks the immune system. About 38 million people are living with HIV as of 2019 [43]. HIV left untreated can progress to acquired immunodeficiency syndrome (AIDS), which is the most advanced stage of HIV infection. HIV is spread through bodily fluids such as blood, semen, vaginal fluids, and breast milk [43]. Sharing needles and unprotected sex are risk factors for HIV. A patient with HIV must start on antiretroviral treatment (ART), which inhibits the replication of HIV, immediately after diagnosis [44]. By inhibiting HIV replication, the patient can live longer and healthier while decreasing the risk of transmission to others [44]. If HIV is left untreated, then the patient is vulnerable to potentially fatal infections such as TB. TB is one of the leading causes of death in HIV individuals since 1 in 3 HIV-infected patients die from TB [43].

About 71% of TB patients receive full coverage for their treatment worldwide [5]. Treating patients for drug-susceptible TB costs about $860/person [5]. The cost increases to about $5,659/ person if the patient has MDR-TB [5]. TB patients face catastrophic costs due to paying out of pocket for TB treatment, transportation to TB clinics, missing work, and job loss [5]. Countries without universal healthcare coverage for TB patients are likely to see patients defaulting since they cannot afford treatment [42].

Socioeconomic status and living conditions impact an individual's exposure to Mtb, the progression of TB, and adherence. In 2019, 2.2 million cases of TB were attributed to undernourishment[5]. This is a significant point to consider because poverty is commonly associated with an increased risk of TB. Undernourished individuals are 3.2 times more likely to develop active TB. Those who progress to active disease that lack education on TB are less likely to self-diagnose themselves or adhere to their treatment regimen. Unemployment and homelessness are associated with an increased risk for exposure and progression of Mtb infection. Indoor air pollution from wood-burning stoves impairs an individual's immune system. It increases their risk of susceptibility to illness and progression of the disease [42]. Overcrowding has a strong association with an increased risk of exposure to Mtb [42]. Examples of overcrowding are prisons and social gatherings.

Behavioral risks include alcohol consumption and smoking. Both are unhealthy behaviors that can lead to an addictive disorder and an increased risk of TB. With 2.35 billion people consuming alcohol each year and 1.3 billion using tobacco, both raise a significant public health concern [45]. Alcohol consumption and smoking can lead to health side-effects such as liver cirrhosis and chronic obstructive pulmonary disease (COPD), respectively. It was estimated that 0.72 million TB cases were related to Alcohol Use Disorder (AUD), and 0.70 million cases were related to smoking [5]. Individuals are 3.3 and 1.6 times more likely to develop TB if they have AUD or smoke, respectively [5]. Individuals can be at a higher risk for adverse effects, poor outcomes, and relapse if smoking and alcohol consumption are not addressed before or during TB treatment.

3.0 Alcohol Use Disorder

Alcohol is a psychoactive substance that can be considered toxic and deadly when abused [46]. Alcohol consumption contributes to premature deaths worldwide and is one of the leading behavioral causes of death [47]. Wine, beer, and spirits are different forms of alcohol. Beer typically contains about 5% alcohol, wine has 12% alcohol, and spirits are 40% alcohol [48]. A standard drink equates to 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of spirits. The National Institute on Alcohol Abuse and Alcoholism (NIAA) recommends males to consume no more than 14 drinks and females to consume no more than seven drinks a week [49]. The standard drink contains 14 grams of pure alcohol. The WHO estimated that 2.35 billion people, 15 years and older, consumed alcohol over the past 12 months in 2016. About 3 million deaths per year are related to alcohol consumption [45]. In 2016, about 8.6% of men and 1.7% of women had an AUD [45]. A person with AUD does not have the ability to stop or control their alcohol consumption even if it may negatively impact their health and others around them [45].

3.1 Side-Effects

Over 200 diseases and injuries worldwide are related to harmful and hazardous alcohol consumption [50]. Based on the amount of alcohol consumed and drinking patterns, chronic or acute outcomes may occur [51]. Heavy alcohol consumption in males is considered to be four or more drinks. For females, three or more drinks in two hours are classified as binge drinking. Binge drinking is when the blood alcohol content (BAC) of 0.08% in two hours [45]. To achieve a BAC

of 0.08% in two hours, men must consume four or more drinks, and a female must consume three or more drinks. Alcohol overdose occurs when BAC is around 0.35% [45]. Heavy alcohol consumption can negatively impact a person biologically, socioeconomically, and others around them [50].

Alcohol consumption affects an individual's health by impairing the immune system, organ damage, and nutritional deficiency [47, 52, 53]. Chronic alcohol consumption is associated with an increase in pro-inflammatory cytokines, which downstream promotes inflammation in the lungs, bowels, brain, pancreas, and liver [54]. Acute alcohol exposure increases IL-10 cytokine, but chronic alcohol exposure inhibits anti-inflammatory cytokine production to counteract inflammation [54]. Alcohol consumption is often associated with cirrhosis of the liver and gastrointestinal distress due to inflammation [47, 54]. Inflammation of the gastrointestinal inhibits the body's ability to absorb necessary nutrients and results in nutritional deficiencies.

Those suffering from AUD are more likely to experience social exclusion, stigmas, and psychiatric problems [51]. AUD is associated with job loss, homelessness, and loss of social network [52, 53]. Heavy alcohol consumption is related to increased incarceration rates and stigmatization [52]. Psychiatric problems that can arise from heavy alcohol consumption are depression, anxiety disorders, personality disorders, mania, and suicide [47]. Individuals with AUD that live in poverty are at risk for exposure to infectious agents due to poor hygiene and overcrowding [52].

Individuals that consume frequent and voluminous quantities of alcohol have decreased cerebral blood flow, which affects memory and disrupts their ability to abstain from alcohol short-term. They may also experience impairment of cognitive function, inhibiting their ability to process speech and emotional signals. Once a person reaches a BAC of 0.05%, their driving is

impaired [45]. Aggressive behavior occurs when their BAC is about 0.075%. Driving impairment and aggressive behavior can lead to road injuries and violence that affect the person and others. Alcohol consumption is associated with risky sexual behaviors such as unprotected sex, partner selection, and sexual violence [45]. These behaviors can increase the likelihood of a person contracting HIV, which increases their chances of contracting TB.

3.2 Screening and Diagnostics

The Alcohol Use Disorder Identification Test (AUDIT) is a test that allows healthcare providers to screen individuals for harmful alcohol use [55]. AUDIT questions can be broken into three primary measurements: consumption, dependence, and consequences [55]. The test has ten questions where each answer has a score from zero to four. Table 1 is an example of the AUDIT questionnaire with a unit guide on top. The user adds up the scores on all ten questions to determine if they have concerning alcohol use. A total score of eight or greater indicates harmful and hazardous alcohol use [56]. When an individual receives a score of eight or higher, they are referred to a specialist for diagnostic testing.

The Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) both define human disorders and what criteria must be met to diagnosis a patient with that disorder [51, 57]. The DSM is published by the American Psychiatric Association, and the WHO publishes the ICD. In the DSM-IV, alcohol dependence and alcohol abuse were two separate diagnoses. ICD-10 uses alcohol dependence syndrome as the primary alcohol diagnosis based on the definition of alcohol diagnosis in the DSM-IV [57]. The ICD-11, released in 2019, still uses alcohol dependence as its main classification for alcohol disorders but

included hazardous use of alcohol as another classification [57]. The DSM-5, released in 2013, encompasses the alcohol diagnosis from ICD-10, ICD-11, and DSM-IV into one category: AUD [57]. The definition of AUD is "a problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least 2 of the criteria occurring within 12 months" [57]. There 11 criteria used to diagnose AUD are listed in Appendix Figure 1.

Table 1 Example of AUDIT Questionnaire

Source: Alcohol IBA Blog [1]

AUDIT ALCOHOL SCREENING TOOL

1 unit is typically:

UNIT GUIDE

Half-pint of regular beer, lager or cider; 1 small glass of low ABV wine (9%); 1 single measure of spirits (25ml)

The following drinks have more than one unit:

A pint of regular beer, lager or cider, a pint of strong /premium beer, lager or cider, 440ml regular can cider/lager, 440ml "super" lager, 175ml glass of wine (12%)

Questions	Scoring system					Your score
	0	1	2	3	4	
How often do you have a drink containing alcohol?	Never	Monthly or less	2 - 4 times per month	2 - 3 times per week	4+ times per week	
How many units of alcohol do you drink on a typical day when you are drinking?	1 -2	3 - 4	5 - 6	7 - 9	10+	
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you failed to do what was normally expected from you because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
Have you or somebody else been injured as a result of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?	No		Yes, but not in the last year		Yes, during the last year	

Scoring: 0 – 7 Lower risk, 8 – 15 Increasing risk, 16 – 19 Higher risk, 20+ Possible dependence

3.3 Treatment

When an individual starts rehabilitation for AUD, they meet with a specialist to make a treatment plan. Therapy talk and medication-assisted treatment are the two main treatment courses [58]. An individual can receive treatment as an outpatient, inpatient, partial hospitalization, or in their residence. Once individual sets up their treatment plan with a specialist, they may undergo detox. In this stage, the individual completely stops consuming alcohol. Patients with AUD that go through detoxification may go through medical distress and require the supervision of a specialist. A patient can begin experiencing withdrawal symptoms as early as 6-12 hours after their last drink [59]. Symptoms range across somatic, emotional, and psychotic [59, 60]. The WHO recommends using benzodiazepines, antipsychotic, and psychoactive medications to treat patients experiencing alcohol withdrawal symptoms [61]. For continued recovery, pharmacological interventions such as acamprosate, disulfiram, naltrexone, or baclofen can prevent alcohol cravings and promote abstinence [59, 62]. About 5 % of patients experience delirium tremens when going through detox [59]. Delirium tremens is a severe symptom of withdrawal that occurs about five days after the onset of withdrawal symptoms. Patients will present as disoriented and have disturbances with memory, attention, language, and visuospatial ability that fluctuate throughout the day. These symptoms are often missed since very few patients exhibit them [60]. Psychosocial interventions for continued recovery include behavioral therapies, twelve-step facilitation, social network, contingency management, psychodynamic therapy, and cognitive-behavioral couple therapy [59, 63]

3.4 Tuberculosis and Alcohol

Alcohol and TB are causally linked, and they are both “diseases of poverty” [52, 64]. The diagnosis of AUD increases an individual’s risk of having TB by threefold [65]. AUD is significantly associated with MDR-TB [66]. In addition, AUD increases the risk of susceptibility and progression of TB through social behaviors, immunosuppression, and treatment adherence.

Social behaviors such as frequenting pubs, bars, and other social drinking venues place individuals at a higher risk for exposure to TB since they congregate settings. Individuals with AUD may frequent those venues more than others. Once an individual is infected with Mtb, they are about three times more likely to progress to active TB than those who do not consume excessive amounts of alcohol or have AUD. Patients with concomitant TB and AUD experience social problems that delay their diagnosis and treatment [52, 53]. These problems include homelessness, lack of a social network, and inadequate health literacy to self-diagnosis themselves with TB.

Heavy alcohol consumption can impair a person’s immune system. Acute and chronic alcohol consumption may lead to poor self-regulation of inflammation and inhibition of alveolar macrophages [52]. Through dysregulation of the immune response, the host is susceptible to microbial infections. This increases the risk of progressing to active TB. Studies have shown that alcohol interacts poorly with anti-TB drugs and interferes with metabolism and absorption [52].

Alcohol is also significantly associated with poor treatment adherence among TB patients [66]. Poor outcomes include a positive-sputum smear test at the end of treatment and require retreatment, interruptions due to adverse side effects, and failure to complete treatment (default) [46]. Individuals suffering from AUD are at a greater risk for relapse and developing MDR-TB [67]. Alcohol consumption during treatment increases the difficulty of managing MDR-TB.

4.0 The Russian Federation

Comparing the Russian Federation with other high TB burden countries, the Russian Federation has a similar prevalence of diabetes mellitus and smoking but a lower prevalence of undernourishment than other high TB burden countries [5]. The Russian Federation has a significantly higher prevalence of AUD compared to other high TB burden countries. In the Russian Federation, about 7.4% of females and 37% of males were diagnosed with AUD (Figure 3). The average prevalence of AUD in the high burden TB countries, excluding the Russian Federation, is 1.1% in females and 7.3% in males. Figure 4 shows a correlation between alcohol sales and TB mortality in the Russian Federation, requiring further investigation. Due to the high prevalence of AUD in the Russian Federation, especially among males, it would be imperative to understand TB and AUD in the country and the potential interaction between both conditions.

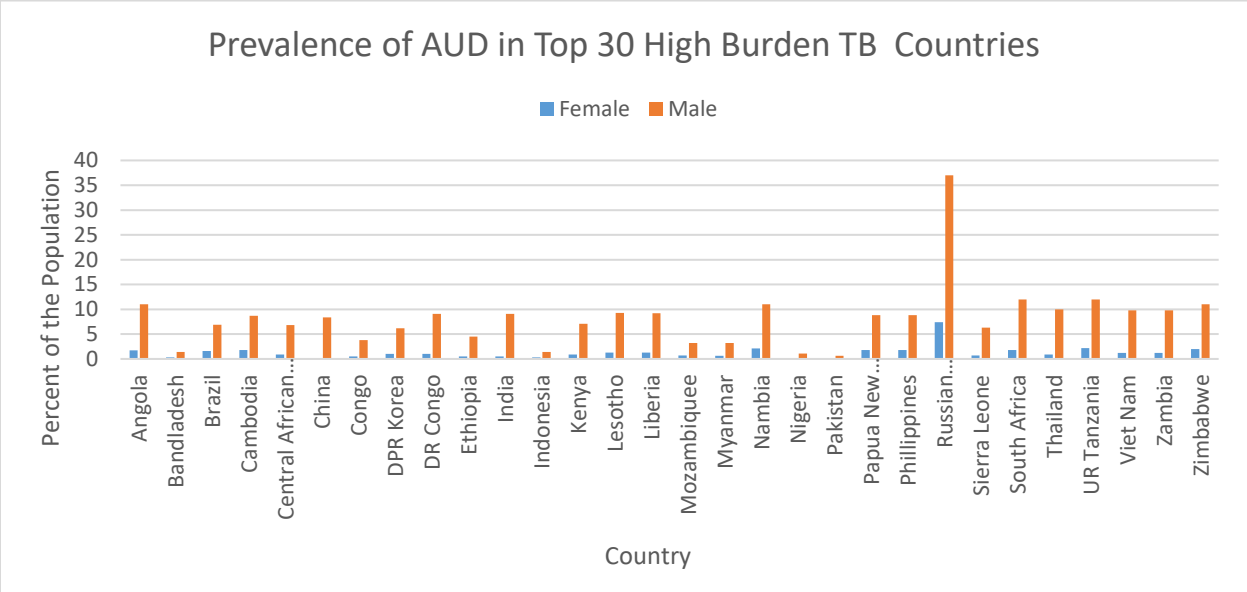


Figure 3 Prevalence of AUD ≥ 15 years in the top 30 High Burden Tuberculosis Countries

Source: WHO, 2020

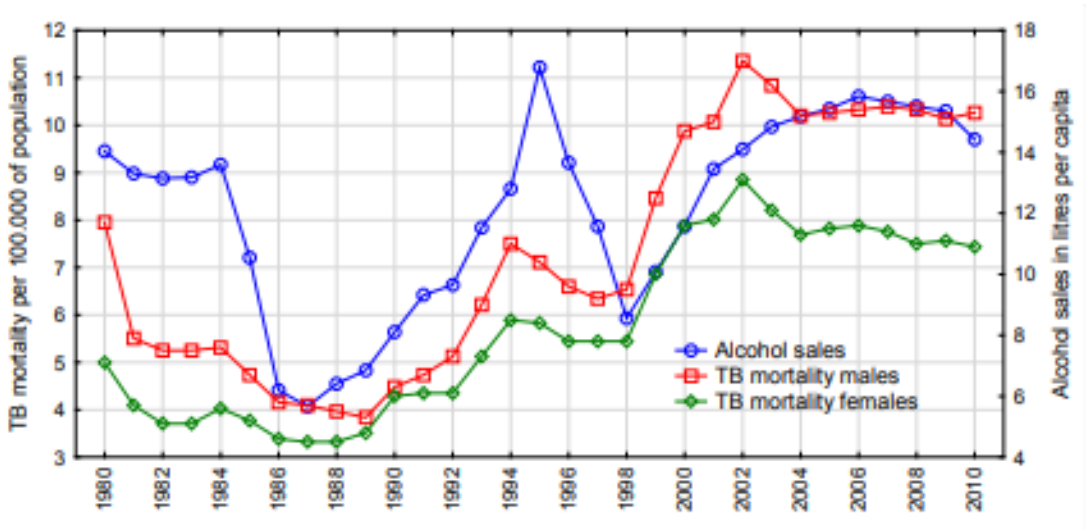


Figure 4 Correlation between alcohol sales and TB mortality by sex in the Russian Federation

Source: Razodovsky, 2014

4.1 Tuberculosis

The Russian Federation is one of the top 30 high burden TB countries [5]. Throughout the 20th century, the Russian Federation revised its TB intervention and steadily decreased in cases until 1990 [68]. After the Union of Soviet Social Republics (USSR) collapsed in Dec. 1991, the Russian Federation scaled back on TB screening and anti-TB drug distribution [68]. Throughout the 1990s, the Russian Federation saw a spike in TB cases. It quickly became one of the highest-burden TB countries. In 2000, the Russian Federation hit its peak TB incidence of about 90 per 100,000. The WHO tried to get the Russian Federation to adopt DOTS in the 1990s but failed [68]. After the WHO revised DOTS in 1999, the Russian Federation began to adopt the system into their TB program in 2000 and now incorporate DOTS-plus for MDR-TB patients [68].

In 2019 the Russian Federation reported a TB incidence of 50 per 100,000 [69]. According to the WHO 2020 TB Report, the Russian Federation reached its 2020 milestone for TB incidence

reduction and mortality. The Russian Federation reduced TB incidence by 19% and TB mortality by 35% between 2015 to 2019 [5]. Although the Russian Federation is declining in TB cases, it is still one of the top 30 high TB burden countries in 2019. Even though the Russian Federation has seen a significant drop in TB incidence, they had a 6% increase in MDR-TB cases from 2010-2019 [5]. The Russian Federation is one of the top three countries for MDR-TB and makes up 8% of the world's MDR-TB cases [5].

The demographic of TB cases in the Russian Federation is 68% male. Russian males ages 35-44 are the highest impact in the Russian Federation [69]. The incidence of HIV-positive TB cases is 12 per 100,000 in the Russian Federation, which is higher than the global incidence of HIV-positive TB cases. The rate of MDR/RR-TB cases is 27 per 100,000 in the Russian Federation, which is more than half of their total TB incidence in 2019. About 71% of MDR/RR-TB cases have been previously treated for TB. The high TB mortality in the Russian Federation is attributed to MDR-TB and XDR-TB. Non-adherence during TB treatment is associated with drug resistance in the Russian Federation [70].

4.2 Alcohol

The 'drinking culture' in the Russian Federation is a social custom [71]. The Russian Federation has one of the highest rates of hazardous drinking globally, highlighted in Figure 5 [45]. As seen in Figure 6, the Russian Federation's peak alcohol consumption was in the early 2000s but has declined to under 10 liters per capita in 2019 [72]. After the collapse of the Soviet Union, the population health in the Russian Federation declined. From 1991 to 1994, the life expectancy in the Russian Federation dropped from 63.4 to 57.4 years in males and 74.2 to 71.1

years in females [73]. The decline in life expectancy is due to a breakdown in the healthcare system. Citizens are experiencing psychological stress from economic and political distress [73]. The fluctuation in life expectancy in the Russian Federation is also firmly attributed to alcohol [74]. From 1991 to 2000, there were about 400,000 to 700,000 premature deaths per year from alcohol consumption [75].

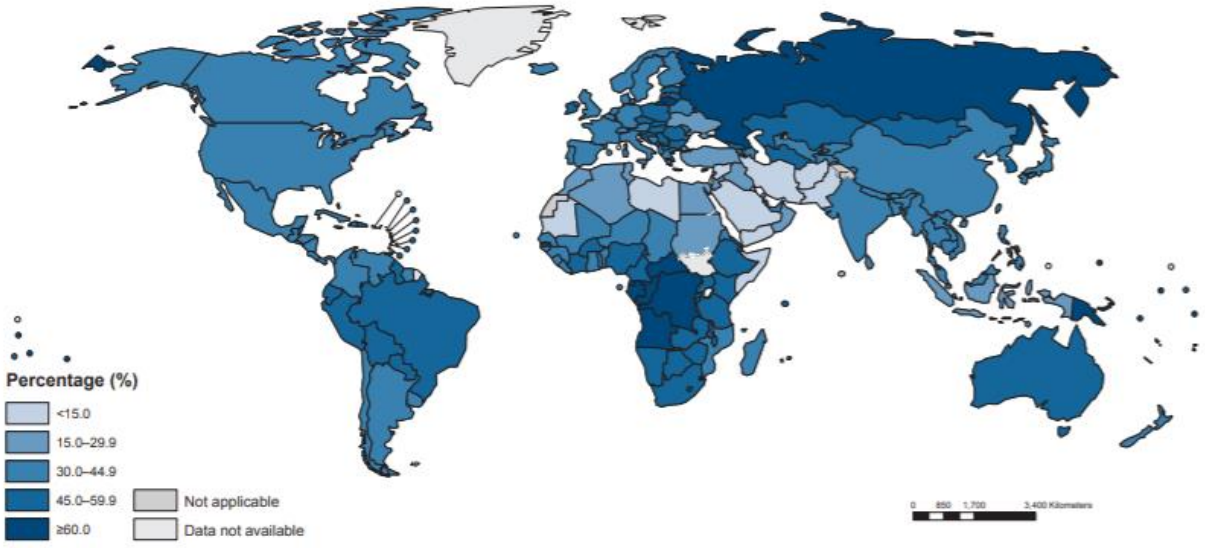


Figure 5 Prevalence of Heavy Episodic Drinking in ≥ 15 years in 2016

Source: WHO, 2018

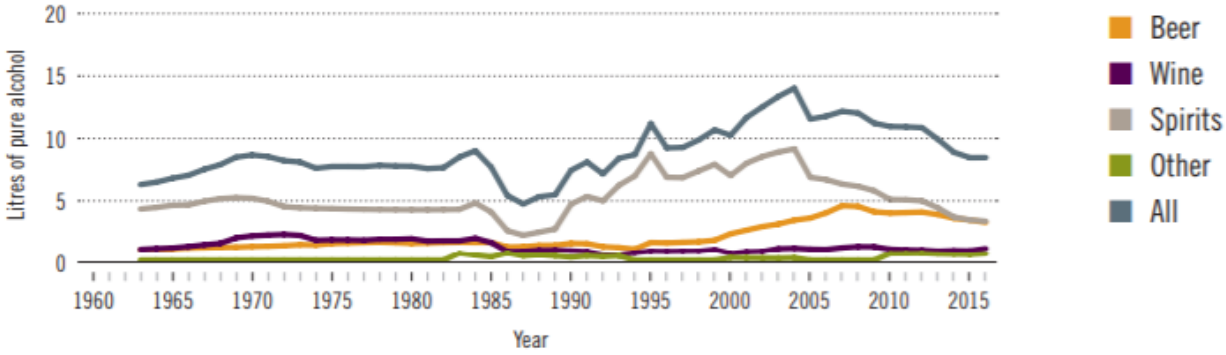


Figure 6 Recorded alcohol consumption in the Russian Federation from 1961 to 2016

Source: WHO, 2018

4.2.1 Alcohol Policies

The Russian Federation recognized that alcohol consumption is a significant health concern in the early 2000s. From 1985-88, Gorbachev's anti-alcohol campaign successfully reduced alcohol consumption, as seen in Figure 6. During the anti-alcohol campaign, deaths related to alcohol dropped from 23 per 100,000 to 9.1 per 100,000 [71]. Not long after Gorbachev's campaign ended, the Soviet Union collapsed while alcohol consumption skyrocketed [76]. The Russian Federation implemented new policies regarding alcohol distribution and production throughout the 2000s to decrease alcohol consumption and stop the production of homemade alcohol [77].

In 2005 and 2006, prices for vodka increased to discourage citizens from buying vodka. It was observed that violent crimes, premature death, and incarceration rates were positively associated with the consumption of spirits [72, 78]. As seen in Figure 3, the Russian Federation successfully decreased the consumption of spirits [75, 79]. The Russian Federation established the Federal Service for Alcohol Market Regulation to reduce alcohol disorders and promote a healthy lifestyle starting in 2010 [72]. The Russian Federation also established 14 tasks to achieve by 2020. One of these tasks included establishing the Unified State Automated Information System (EGAIS) in 2016. EGAIS is an advanced monitoring system for alcohol production and sales [72]. In 2018, the Russian Federation established AUDIT as a standardized screening tool for hazardous and harmful alcohol use [72]. From 2007 to 2018, the Russian Federation has seen a 39.6% decreases in alcohol consumption [80]. This decrease was seen across light to heavy drinkers.

4.2.2 Treatment for AUD

The Russian Federation has a narcology treatment clinic where patients can receive registered treatment for AUD. Patients can receive unregistered treatment if they pay out-of-pocket through private healthcare providers [72]. The Russian Federation has substance abuse specialists called narcologists responsible for dealing with prevention treatment, diagnosis, AUD, and social care and recovery of drug-dependent patients. They are the primary providers that help patients undergo detox and treatment. While patients go through detox and pharmacological interventions, they are monitored by a psychologist to assess their mental state and provide counseling and psychotherapy throughout their treatment [55]. Russians fear the stigmatizing narcology registry because they can potentially lose their driver's license or job [81]. There were no standardized screening tools for AUD in the Russian Federation until 2015 [72].

5.0 Literature Review

The objective of the literature review is to identify the relationship between AUD and TB among patients living within the Russian Federation. Articles should identify the prevalence of AUD among TB patients, their risk for poor treatment outcomes, and measurements of alcohol consumption. Targeted interventions should be created and implemented to address potential increases in AUD cases, an individual's risk for TB, progression to drug-resistant TB, as well as ineffective treatment outcomes.

5.1 Methods

A search was conducted on *Pubmed* to identify articles that used 'Tuberculosis,' 'Alcohol,' and 'Russia.' Full-text articles that included studies related to AUD, alcohol abuse, dependence, and addiction was also included. These articles were analyzed and identified based on three criteria: the type of study design, data collection methods, and analysis. Articles in a different language, solemnly review articles, or articles that lacked a central focus on the Russian Federation were excluded from this analysis.

5.2 Results

A total of 105 articles were found on *Pubmed*. After excluding articles that did not match the criteria, 21 articles were used for the literature review. The primary study designs were focus

group, retrospective cohort study, prospective cohort study, and randomized control trial. The articles identified data collection through previous medical documentation of alcohol abuse or alcohol dependence by a trained clinician or narcologist or questioned participants. Only five articles used AUDIT for measuring hazardous alcohol use [55, 82-85]. The main types of data analysis used were the Chi-square test, t-test, Fisher's exact test, Kaplan-Meier survival analysis, and odds ratio. The studies can be split into assessing the prevalence of AUDs among Russian TB patients, treatment outcomes, and interventions.

5.2.1 Prevalence

TB physicians in the Russian Federation believe alcoholism is a risk factor for TB [86]. Several studies confirmed high AUD rates among TB patients in the Russian Federation [53, 55, 70, 85, 87, 88]. Researchers identified how many TB patients with current and previous AUDS using previous medical records and self-reporting. AUDIT scores were used to determine the use of alcohol in TB patients. The prevalence of AUD among TB patients in the Russian Federation ranges from 17.2% to 67.7% [87, 88]. One study that compared AUD in male and female TB patients found that 28.3% of females and 70.6% of males had lifetime alcohol abuse or dependence [89]. Females with AUD in the study consumed on average 12 standard drinks a day, and males consumed about 16 standard drinks a day. The average AUDIT scores ranged from 11.5 to 18.3 in Russian TB patients [55, 82, 83, 89]. In these studies, over half the participants had an AUDIT score of eight or higher.

5.2.2 Treatment Outcome

Alcohol is associated with a higher risk for poor treatment outcomes in the Russian Federation [88, 90]. TB patients with a previous history of AUD or a current diagnosis are at an increased risk for defaulting during treatment [91]. Alcohol consumption is associated with an increased risk for interruptions and adverse effects [91-93]. Russian TB patients were three to almost six times more likely to experience disruption during treatment if they have AUD [94]. In an older study, they found alcohol increased the risk of drug-resistant TB eight-fold [70]. Heavy alcohol consumption results in delayed surgery until they can decrease or stop their intake [82]. Alcohol impacts the treatment process and outcome for TB patients in the Russian Federation.

Alcohol contributed to death in TB patients directly or indirectly [95]. Those who consumed alcohol during treatment have a higher mortality rate than those who do not [74, 95-97]. About 35.4 % of all male and 32% of all female TB deaths from 1980-2010 in the Russian Federation could be attributed to alcohol [97]. TB mortality increased when patients consumed 40 grams or more of pure alcohol in one day during treatment [97]. One standard drink of alcohol contains about 14 grams of pure alcohol. Overall, alcohol negatively impacts the survival rate of TB patients in the Russian Federation.

5.2.3 Interventions

TB physicians do not receive sufficient training to diagnose and treat patients with substance abuse and addiction disorders [85]. The narcologists are specialists trained to treat patients for AUD in the Russian Federation. There may be a narcologist working at TB clinics, otherwise, patients must travel to a narcology center for treatment. In 2006 TB physicians, in the

city of Tomosk were trained to use AUDIT to screen TB patients for possible AUD [85]. Researchers found that more TB patients were screened for AUD and successfully referred to a specialist for treatment. The Integrated Management of Physician delivered Alcohol Care to Tuberculosis patients (IMPACT) is a randomized control trial in the Russian Federation that trained TB physicians to treat TB patients with AUD using behavioral and pharmacological interventions. They would provide a combination of oral naltrexone, brief behavioral compliance enhancement therapy (BBCET), or no treatment for AUD. Studies found that brief counseling interventions (BCI) effectively improved their treatment outcome in TB patients with AUD [81, 83, 84]. Found TB patients with AUD treated with naltrexone, BBCET, and BCI in the contemplative stage had better outcomes than those in the pre-contemplative stage. The authors identified that most TB patients in the study were in the pre-contemplative stage of change. In Appendix B, the transtheoretical model of change describes the pre-contemplative stage as individuals that are resistant to changing their current behavior.

6.0 Discussion

The literature review articles identified a wide prevalence of AUD among Russian TB patients. The prevalence of AUD varied by region across the Russian Federation and use of alcohol measurements. Compared to those using the AUDIT scores to measure alcohol use, there was a lower prevalence across studies that relied on current or previous clinician diagnosis of AUD in TB patients and patients self-reporting their alcohol use. Researchers were able to implement AUDIT in the Tomosk TB clinic successfully. However, they were not able to integrate behavioral therapy and medication intervention to improve treatment compliance. According to physicians, they were not accustomed to utilizing behavioral therapy treatment before. The physicians did not believe patients were comfortable with goal setting and discussing problems with alcohol. Limitations of several articles were no standardized alcohol use measurements. Self-reporting alcohol use can be affected by social desirability bias.

Another growing concern in the Russian Federation is the HIV epidemic. In 2018, there were a total of 1 million cases of HIV, and this number has increased by about 10 to 15% each year in the Russian Federation [98]. Risky behaviors include multiple sexual partners, lack of protection, and intravenous drug use. Patients with AUD and TB were 2.5-3 times more likely to have risky behaviors related to HIV [70]. Risky behaviors include multiple sexual partners, lack of protection, and intravenous drug use.

The Russian Federation has been combating the high alcohol consumption rates by implementing new policies restricting alcohol production and sales. The country has seen a decrease in alcohol consumption and AUD diagnosis. However, they have done little to improve the treatment of citizens with AUD. In the Russian Federation, citizens dealing with alcohol use

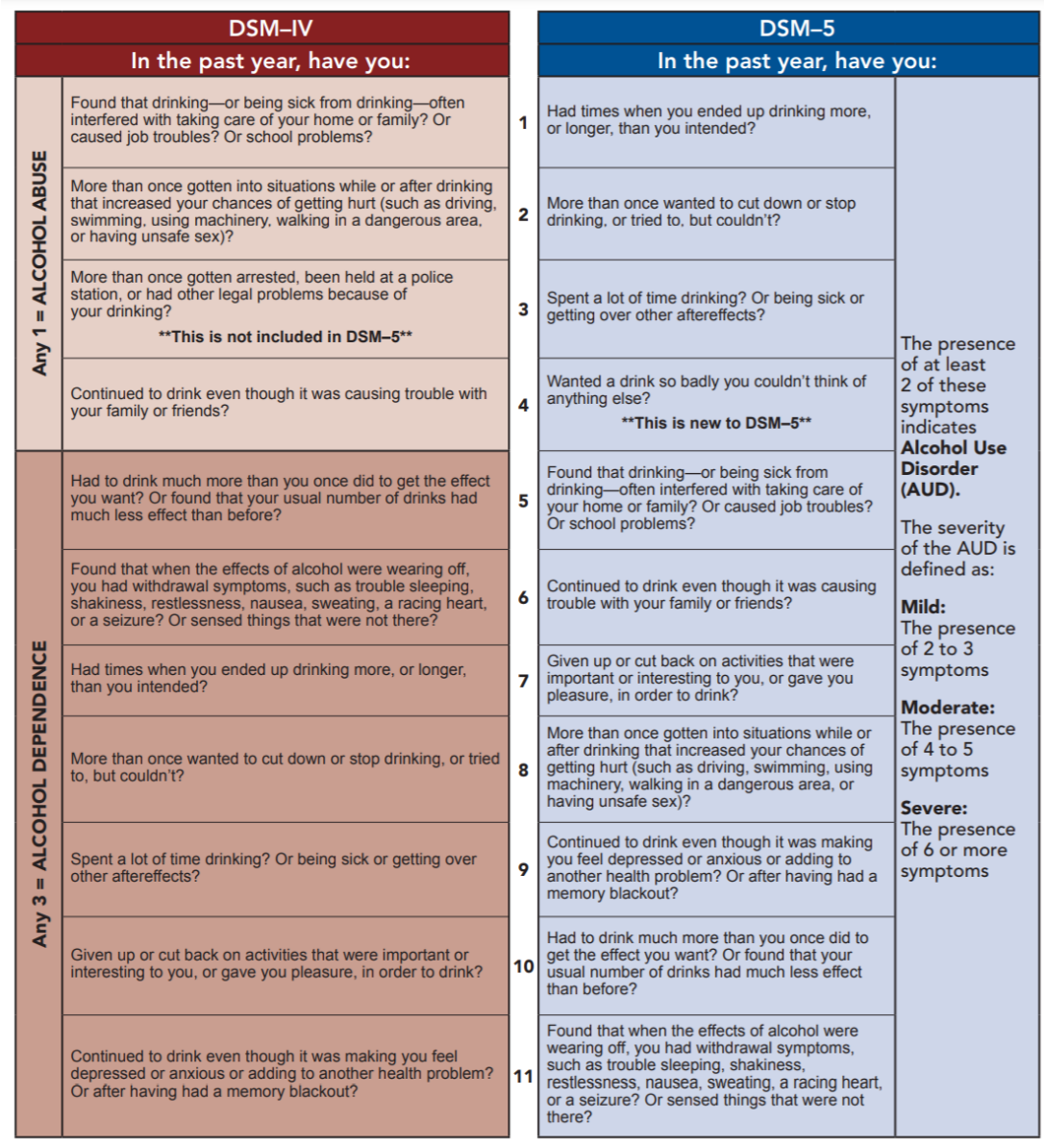
problems are not encouraged to speak up about the issue [81]. Along with the stigmatizing narcology registry, Russian citizens are less likely to seek help for their unhealthy alcohol use. Another barrier faced by individuals with AUD is the lack of outpatient narcology centers in rural areas [99]. Since narcology centers are in cities, Russian citizens in rural areas can find it difficult to commute to a narcology center to receive treatment. Russian citizens should be encouraged to seek out treatment for AUDs. There should be various treatment options available for patients to find the best one that suits them.

7.0 Conclusion

Alcohol is a significant part of the culture in the Russian Federation. Since alcohol is related to several health-side effects and behavioral risks, the Russian Federation has successfully established policies that decreased alcohol consumption since the early 2000s. Patients consuming alcohol during treatment have a higher risk of treatment failure and progressing to MDR-TB. This makes it challenging to contain the drug-resistant epidemic in the Russian Federation. Although the IMPACT study did not yield significant results for improved treatment outcomes, it did highlight that many TB patients are in the pre-contemplative stage. Interventions can be tailored to help individuals in the pre-contemplative stage advance to the contemplation stage to be prepared to take action ultimately.

There should be total anonymity when treating patients for any substance abuse disorder without concerns of the stigmatizing narcology registry. Narcology centers should have clinics located in rural areas to allow more patients to have ease of access to treatment. The Russian Federation should also offer more treatment options besides pharmacological interventions to patients with AUD or other substance abuse issues that are culturally appropriate.

Appendix A Supplemental information for Alcohol Use Diagnosis (AUD) criteria and definitions



Appendix Figure 1 Comparison of DSM-IV and DSM-5 Diagnostic Criteria

Source: NIAA

Appendix Table 1 DSM-IV, DSM-5, ICD-10, and ICD-11 Alcohol Diagnosis Definitions

Source: Saunder et al., 2019

	ICD-11 Alcohol Dependence	ICD-10 Alcohol Dependence Syndrome	DSM-IV Alcohol Dependence	DSM-5 Alcohol Use Disorder	DSM-IV Alcohol Abuse
Stem	**A disorder of regulation of alcohol use** arising from repeated or continuous use of alcohol. The characteristic feature is a **strong internal drive to use alcohol**. The diagnosis requires 2 or more of the 3 central features to be evident over a period of at least 12 months, but the diagnosis may be made if alcohol use is continuous for at least 1 month.	A cluster of physiological, behavioral, and cognitive phenomena in which the use of alcohol takes on a much higher priority for a given individual than other behaviors that once had greater value. Three or more of the following manifestations should have occurred together for at least 1 month or occurred together repeatedly within a 12-month period.	A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by 3 or more of the following occurring at any time in the same 12-month period.	A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least 2 of the following occurring within a 12-month period	A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by one or more of the following occurring within a 12-month period.
1.	**Impaired control** over alcohol use—in terms of the onset, level, circumstances or termination of use, often but not necessarily accompanied by a subjective sensation of urge or craving to use alcohol	A strong desire or sense of compulsion to take alcohol (craving or compulsion)		Craving or a strong desire or urge to use alcohol.	
			There is persistent desire or unsuccessful attempts to cut down or control alcohol use	There is persistent desire or unsuccessful efforts to cut down or control alcohol use.	
		Difficulties in controlling alcohol use in terms of its onset, termination, or levels of use (*loss of control*)	Alcohol is often taken in larger amounts or over a longer period of time than was intended	Alcohol is often taken in larger amounts or over a longer period than was intended.	
2.	Alcohol use becomes an **increasing priority** in life such that its use takes precedence over other interests or enjoyments, daily activities, responsibilities, or health or personal care. Alcohol use takes an increasingly central role in the person's life and relegates other areas of life to the periphery, and it often continues despite the occurrence of problems.	Progressive neglect of alternative pleasures and responsibilities because of alcohol use, or increased amount of time necessary to obtain or take alcohol or to recover from its effects.	Important social, occupational or recreational activities are given up or reduced because of alcohol use	Important social, occupational or recreational activities are given up or reduced because of alcohol use.	
				Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance …)	Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance …)
			A great deal of time is spent in activities necessary to obtain alcohol, use it, or recover from its effects	A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects	
		Persisting with alcohol use despite clear evidence of overtly harmful consequences.	Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.	Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.	
				Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.	Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol (e.g., arguments with spouse about consequences of intoxication, physical fights).
3.	**Physiological features** (indicative of neuroadaptation to alcohol) as manifested by: (i) tolerance, (ii) withdrawal symptoms following cessation or reduction in use of alcohol, or (iii) repeated use of alcohol (or a pharmacologically similar substance) to prevent or alleviate withdrawal symptoms. Withdrawal symptoms must be characteristic for the withdrawal syndrome for alcohol and must not simply reflect a hangover effect	Tolerance: such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses	Tolerance: as defined by either: (i) a need for markedly increased amounts of the alcohol to achieve the desired effects or (ii) markedly diminished effect with continued use of the same amount of the substance	Tolerance is defined by either of the following: (i) a need for markedly increased amounts of alcohol to achieve intoxication or desired effect or (ii) a markedly diminished effect with continued use of the same amount of alcohol	
		A physiological withdrawal state when alcohol use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for alcohol; or use of alcohol (or a closely related substance) with the intention of relieving or avoiding withdrawal symptoms	Withdrawal as manifested by either: (i) the characteristic withdrawal syndrome for alcohol or (ii) alcohol is taken to relieve or avoid withdrawal symptoms	Withdrawal, as manifested by either of the following: (i) the characteristic withdrawal syndrome for alcohol, or (ii) alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms	
				Recurrent alcohol use in situations in which it is physically hazardous	Persistent alcohol use in situations in which it is typically hazardous (e.g., driving an automobile)
					Recurrent alcohol-related legal problems (e.g., arrests for disorderly conduct)

Appendix B Transtheoretical Table

Appendix Table 2 Transtheoretical Stages of Change

Source: Nidecker et al., 2008 [100]

Stage	Definition
Pre-contemplation	Individual is unaware their behavior is problematic. They have no desire to change.
Contemplation	Individual recognizes unhealthy behavior.
Preparation	Individual is ready to take action to change behavior.
Action	Individual is changing their behavior or replacing it with another.
Maintenance	Individual has maintained modified behavior for more than 6 months.

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