Managing Tuberculosis in Refugee Populations

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Abstract

Tuberculosis (TB) is an airborne-transmitted infectious disease, responsible for more global deaths than HIV. Multidrug-resistant strains are developing, which heightens the need for swift eradication. Current data states that 71.4% of all TB cases in the United States occur in foreign-born individuals, so populations traveling from TB endemic areas are a key target population for prevention strategies. Various screening procedures exist, but no successful standard is in place. Beyond prevention and treatment strategies, adaptations to cultural communication differences are integral to successful medical interventions. This synthesis of TB pathophysiology, treatments, risk factors, and cultural considerations is intended for use in implementing effective disease-mitigation processes among refugee populations.

Managing Tuberculosis in Refugee Populations

The United States Department of Homeland security defines a refugee as "a person who has left their national country and is either unable or unwilling to return to their home country due to well-founded fear of persecution due to status of race, religion, nationality, social membership, or political action/opinion".[1] Neither this paper nor the references used limit the definition of "refugee" to only those with a particular legal status of immigration. Some sources used in this work studied "refugees" as a specific population demographic, however, it is not currently possible to independently validate the status of the participants used in the studies. The assumption is made throughout this work that use of the term "refugee" aligns with The United States Department of Homeland Security's definition.

Tuberculosis (TB) is the leading cause of death by infectious disease among adults globally, causing over 4,000 deaths per day worldwide.[2,3] The World Health Organization reports that between 2018 and 2022, 40 million people were treated for TB, including 1.5 million individuals with drug-resistant TB.[4] Up to 13 million individuals in the United States are currently reported to have latent TB infections, which could progress to active infections.[3] Since the advent of multidrug-resistant strains, eradication of this disease has become an urgent priority. As resistant strains increase, so do deaths on account of this disease. The heaviest burden of active TB cases occurs in India, China, Indonesia, South Africa, Nigeria, the Philippines, Pakistan, and Bangladesh.[3] While the United States does not appear on this list, individuals from these and similar countries enter the United States through various immigration pathways, and transmission is possible from infected individuals entering from high-burden countries to those from low-burden countries. Up to 71.4% of TB cases in the United States

occur in foreign-born individuals.[5] While not all foreign-born individuals come to the United States as refugees, a refugee status increases TB transmission risk. Global deaths due to TB are increasing as of 2022, with steep increases in newly diagnosed cases occurring in the eastern Mediterranean region, Africa, southeast Asia, and the Americas.[4] In the U.S. Office of Immigration Statistics' annual refugees and asylees report, it states that most refugees admitted into the United States from 2011 to 2020 came from Burma, Iraq, Democratic Republic of the Congo, Bhutan, Somalia, Syria, Iran, Ukraine, Eritrea, Cuba, Afghanistan, Sudan, Ethiopia, Burundi, and El Salvador.[6] Refugees pose unique challenges to completion of treatment programs due to communication preferences and religious customs that may not necessarily align with American norms. An effective TB intervention strategy must synthesize developing research in TB treatment, considerations for medical complications, and current information on medical communication with non-Western populations. This paper is a synthesis of some of the current knowledge of the pathophysiology of TB and its associated complications, the options for screening and treatment, and the cultural adjustments necessary for health care contexts. The intent of this work is to provide a summary of current data on TB mitigation procedures, highlighting their interaction with the key cultural differences faced in treating migrant populations. The Afghan refugees that recently entered the United States during the 2021 political coup can serve as a specific example for identifying cultural adjustments needed in mitigation procedures, since Afghanistan contributes significantly to the global TB case burden.[4] The data used in this synthesis was sourced from the Jerry Fallwell Library online database. No specific medical databases were used, but general searches of the library resources were used for obtaining sources. Data was found using keywords "tuberculosis," "drug-resistant," "treatment,"

"complications of tuberculosis," "HIV," and "Afghanistan," followed by multiple specific searches concerning the Bacille Calmette-Guerin (BCG) vaccine and its efficacy. Additional sources were found through the reference lists of articles identified in the keyword searches. Multiple sources on oral communication were obtained as class materials from Liberty University's GLST390: Engaging Oral Communicators course.

Tuberculosis Pathophysiology

TB disease is caused by infection with *Mycobacterium tuberculosis*. *M. tuberculosis* is a non-motile, intracellular, pathogenic bacterium with a mycolic acid coating. This bacterium undergoes cell division every 18-24 hours, making it a slower progressing bacterium. Infections with *M. tuberculosis* can occur in a latent or active form. Active *M. tuberculosis* infections follow a progression of aerosolization, macrophage phagocytosis, phagolysosome blockage and replication, T helper type 1 response, granuloma formation, clinical manifestation, and transmission. The primary infection site is usually the lungs, although other organs such as the skin, nervous system, eyes, lymph nodes, bony joints, genitourinary organs, and abdomen can also be sites of extra-pulmonary infection.[3] Transmission of *M. tuberculosis* begins with an active case of TB. An individual with such an infection will generate infectious particles that will be transmitted through aerosolization produced by coughing, sneezing, shouting, or singing. These particles enter a new host via mucous membranes, breaches of the skin layers, the digestive system, or the respiratory tract. Upon inhalation of these aerosolized particles, the bacilli can reach the alveolar sacs of the lungs, where they will begin to take up residence and begin the next phase of infection, phagocytosis.[3] Within the alveolar sacs of the lungs, the innate immune system will respond to the presence of *M. tuberculosis* through phagocytosis by alveolar

macrophages, monocytes, and dendritic cells. *M. tuberculosis* binds with alveolar macrophages via its mannose receptors, scavenger receptors, complement receptors, Fc receptors, and surfactant protein receptors. Upon binding of the macrophage, Grb2 is recruited and the Rac/Pak/Cdc-42 pathway of *M. tuberculosis* is initiated. The src homology 2 domain and protein tyrosine phosphatase 1 of *M. tuberculosis* limit phagosome and lysosome fusion by limiting the trafficking phospholipid phosphatidylinositol 3-phosphate.[3] This results in the growth of *M. tuberculosis* within the alveolar macrophages, since the usual lysing process has been inhibited. *M. tuberculosis* also has cell wall lipids that inhibit lysosome fusion with the phagosome, prevent acidification, and increase permeability of the phagosome, allowing *M. tuberculosis* to continue growing in its host's immune cells, despite the functioning of an initial innate immune system response.[3] During the T helper type 1 response phase, *M. tuberculosis* bacilli activate toll-like receptors from within the macrophage and release peptidoglycan, DNA, and RNA into the cytosol. These secretions activate an inflammatory response from the host immune system. As more immune cells and macrophages are recruited to the site of infection, the bacilli induce expression of vascular endothelial growth factor (VEGF) from the macrophage into the extracellular space, which promotes angiogenesis and acts as a chemokine to recruit more macrophages and monocytes to the site of infection. This aggregation of immune cells acts as a host cell source for proliferation of the *M. tuberculosis* bacterium.[3] The role of angiogenesis is not fully understood in TB disease. It is known that this vasculature can act as a direct pathway for further *M. tuberculosis* infection and also allow the immune system to attack the bacterium directly. During the granuloma phase, *M. tuberculosis* will continue to replicate by way of asymmetric cell division, resulting in a fast-growing daughter cell and a slow-growing daughter

cell, which differ in their growth rate and antibiotic resistance. Replicated cells emerge from the alveolar space into the lung parenchyma, where the immune system will surround it with monocytes and immune cells. Here, replication of the bacteria will eventually result in apoptosis of the macrophage cells and lung inflammation. The immune cell concentration in the parenchyma is called a granuloma or tuberculoma and can occasionally be seen on an x-ray as a calcified spot within the lungs.[3] From the granuloma state, the body will attempt to eliminate the *M. tuberculosis* cells and prevent growth and spread from the concentrated site. CD4+ T-cells play a primary role in the cell-mediated immune response to this bacterium, as well as the recruitment of natural killer cells, and subsequent secretion of interferons.[3] IFNɣ, released from the T_H1 response will result in the production of nitric oxide by the macrophage and induction of autophagy.[3] TNFα is released by the activated macrophages and results in caseation of differentiated monocytes and other immune cells around the granuloma in a continual feedback chain.[3] This encasement creates a hypoxic environment, where the aerobic bacteria *M. tuberculosis* is restricted.[3] During this stage it is still possible for the bacteria to escape complete encasement. Further angiogenesis and the nutrient source of the protective barrier itself may allow the bacteria to survive.[3] If the immune response is successful in encapsulating the bacteria and its infected macrophages, the *M. tuberculosis* infection may be eliminated and resolved. However, if the bacteria are successful in angiogenesis, the infection may eventually proliferate itself into further tissues, such as the pulmonary lymph nodes, producing a dangerous systemic active infection.

TB disease has multiple clinical presentations that correspond to different stages of infection: primary TB, latent TB, and secondary TB.[3] The initial infection of an individual with

M. tuberculosis is categorized as primary TB.[3] Primary infection is a result of the immune system's inability to control *M. tuberculosis* growth and proliferation.[3] If a granuloma is successfully formed by the immune system, cutting off the bacteria from further angiogenesis or active survival, a primary infection is avoided. However, this does not mean the pathogen is fully eliminated from the body; a latent infection may still occur. Throughout this latent stage, the bacteria can create protective biofilms within their necrotic tissue encapsulation as a last defense against the body's immune response.[3] Following any form of immunosuppression in the human host following the formation of a latent granuloma, whether due to drug-induced immunosuppression or other infection, *M. tuberculosis* bacterium can reactivate and produce an active secondary infection, progressing into pulmonary disease.[3] In this case, the reactivation of *M. tuberculosis* will produce cough, hemolysis, weight loss, night sweats, and fever. Extra-pulmonary disease can also follow bacterial reactivation. This occurs when the bacteria spread to the lymph nodes, genitourinary system, gastrointestinal system, pleura, or skeletal system.[3] Miliary TB is the term used for infection that has spread throughout the body, forming multiple tuberculomas across the affected systems.[3]

The highest risk for infection with TB occurs among individuals with HIV, recent organ transplant, diabetes mellitus, or other immunocompromising condition.[3] However, even those that are not included in those categories are at risk for infection when in an exposed, high-transmission environment. Refugees do not pose a transmission risk simply due to the high burden of cases in their country of origin. While this does contribute to the infection rate, the refugee experience itself involves high levels of exposure and is a risk factor for TB transmission.

Risk Factors of Refugee Populations

Constant political upheaval and global conflicts result in a constant stream of refugees from various countries into the United States on a yearly basis. The experience of a refugee from the onset of political upheaval to the chaotic and crowded escape process, continuing through the high-density waiting process is an environment that puts refugees at high risk for transmission of airborne TB. As Figures 1, 2, and 3 show, the distribution of TB cases across the globe readily coincides with displaced populations due to violence or natural disaster.

On August 15, 2021, the Taliban took over the capital city of Afghanistan in a complete political coup.[7] Up to eighty percent of Afghans were forced to flee their homes, and the United States expected up to 50,000 of them to seek refuge in the United States.[8,9] During this crisis, Afghans were welcomed into the United States through Operation Allies Welcome. This military operation placed thousands of refugees onto military bases as guests of the federal state. This was an exception to the typical asylum process; it was put in place to ensure Afghans could escape the country without long delays of paperwork processing preventing their safe relocation. They were allowed to live in these accommodations while they awaited further processing of their cases and arranged their placement with a relocation organization. During this time, I had the opportunity to interact briefly with Afghan guests at Fort Pickett in Blackstone, Virginia. My observations in this environment were that despite specific efforts made towards sanitation and public health, refugee status elevates the risks of pathogen transmission. While at Fort Pickett, I was instructed to be careful of a foot/hand/mouth disease outbreak, which had reportedly been difficult to mitigate due to the crowded environments and limited sanitation practices among children. While this observation was short-term in nature and not exhaustive in its scope, past

Figure 1. TB case incidence across the globe. The highest burden of TB cases is seen in sub-Saharan African countries, south Asian and middle eastern countries, and southeast Asian countries. From Global Tuberculosis Report 2022.[4]

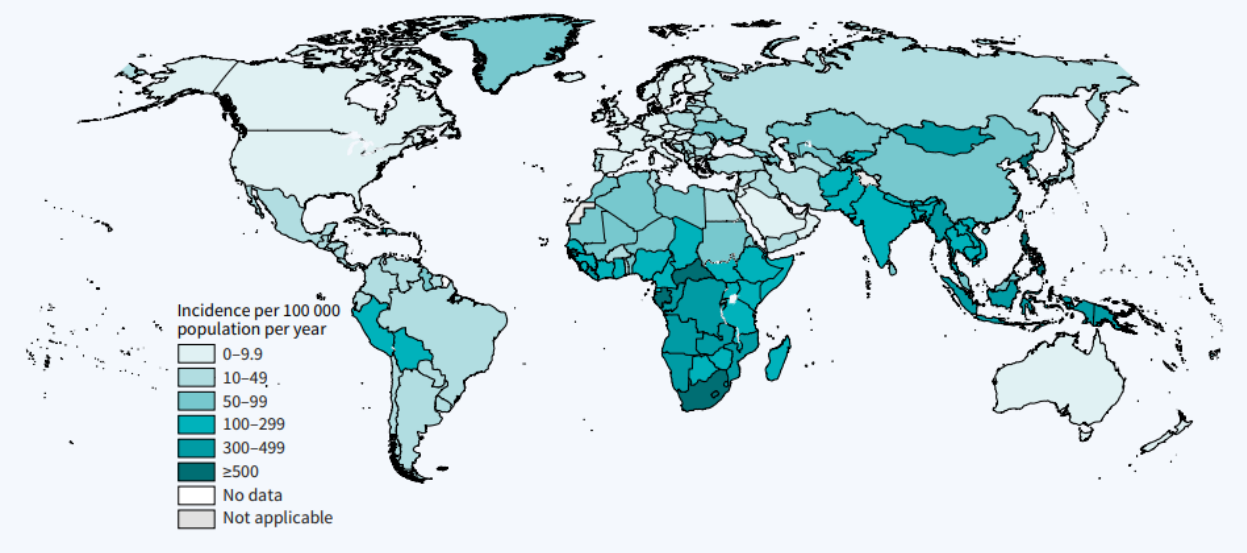


Figure 2. Incidence of displaced persons due to conflict and violence across the globe 2021. The highest incidence of displaced persons due to violence and conflict occurs in central Africa, South Asia, the Middle East, Southeast Asia, and northern countries of South America. The highest incident countries include Afghanistan, Yemen, Syria, Somalia, Ethiopia, Sudan, Democratic Republic of the Congo, Nigeria, Burkina Faso, and Colombia. From Internal Displacement Monitoring Centre.[10]

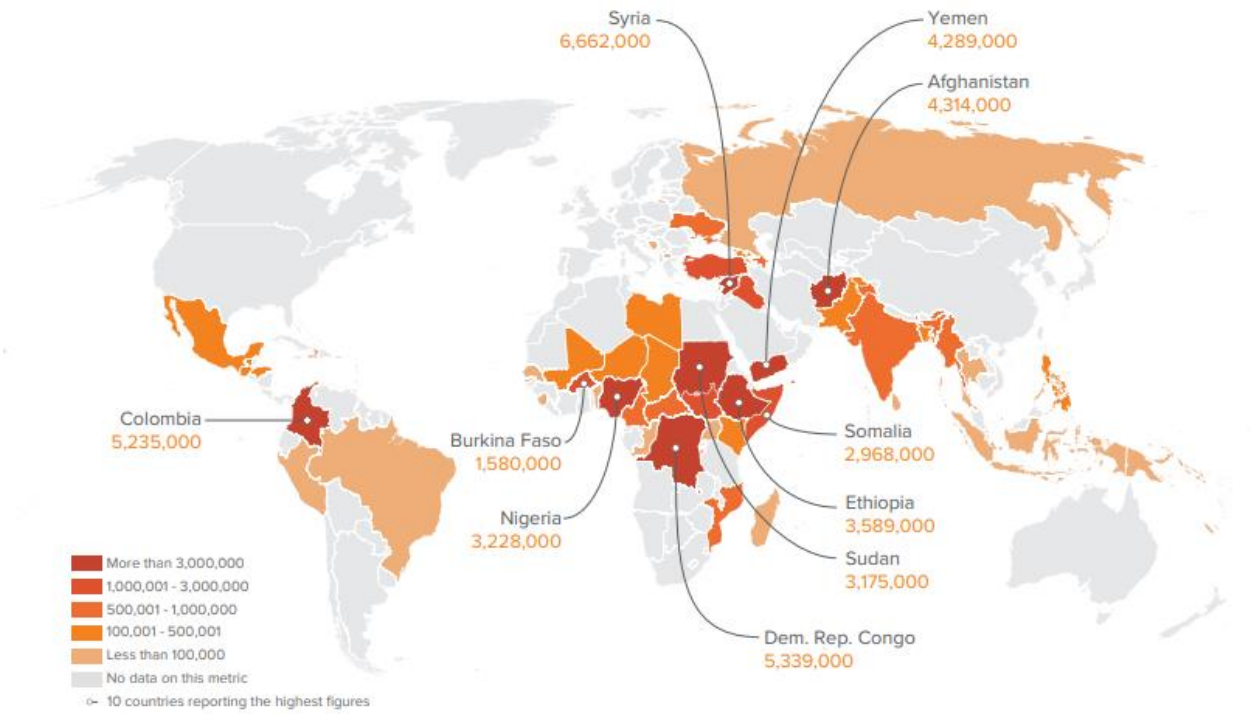
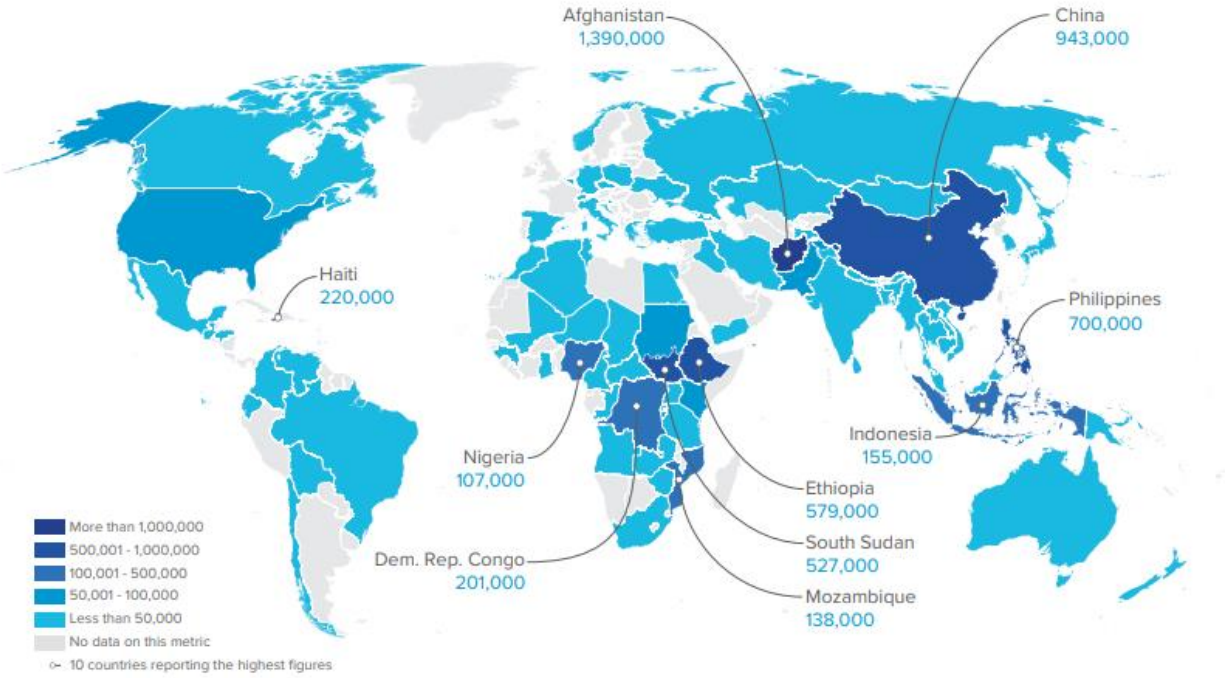


Figure 3. Incidence of displaced persons due to natural disaster across the globe. The highest incidence of displaced persons due to natural disasters occurs in East Asia, Southeast Asia, the Middle East, and sub-Saharan Africa. The highest incident countries include China, Afghanistan, Ethiopia, South Sudan, Mozambique, the Philippines, Democratic Republic of the Congo, and Indonesia. From Internal Displacement Monitoring Centre.[10]



history of refugee crises have been consistent with these observations, showing that the temporary and emergency nature of refugee accommodations lends itself towards higher transmissibility. During the Syrian refugee crisis in 2015, a study conducted on TB cases in Syrian refugees found that the highest proportion of TB occurred in refugees residing in camp environments. Boyd et al found that 29% of Syrian TB cases in Jordan at the time of study occurred in those living in refugee camps, while only 17% of the Syrian refugee population of Jordan was residing in refugee camps.[11] In 2005, a TB outbreak occurred in Hmong refugees in the United States, who had recently emigrated from the same refugee camp in Thailand. In this outbreak, 46 cases of TB were acutely diagnosed among 9,455 refugees in the United States, six of which were multi-drug resistant. Even after enhanced screening was implemented among refugees arriving from this refugee camp, four additional cases of TB were diagnosed, one of which was a multi-drug resistant strain.[12] The combination of a high-exposure environment, and the limitations of the U.S. screening procedures makes residence in a refugee camp environment a high risk factor for contraction of TB disease.

Before being granted entrance into the United States, refugees undergo a medical history and physical examination as well as a screening for TB. Those 15 years old and older are screened using a chest x-ray, and children are screened with an IGRA test if they come from an identified TB endemic country. If an initial chest x-ray produces a positive result, an IGRA test is performed to further investigate infection, and those with positive IGRA tests are screened with an additional chest x-ray. Active TB cases, as identified by a positive IGRA or TB skin test and notable chest x-ray or signs of TB, are not allowed entrance into the United States until three months after a negative acid-fast sputum smear is obtained.[5] If an individual is found to have a

latent infection, as identified by a positive IGRA or TB skin test, and unremarkable chest x-ray or lack of symptoms, they are allowed entry into the United States for up to 6 months after the tests are completed. Upon arrival to the United States, treatment is advised. However, 13.5% of TB cases occurring among foreign-born individuals occur within the first year of arrival into the United States.[5]

As previously described, any form of immunosuppression in a human host following formation of a latent granuloma can reactivate the *M. tuberculosis* bacterium, producing an active infection.[3] Research shows that stress results in immunosuppression within the body. Elevated stress hormones cause a shift within the body from adaptive immune response towards innate immune response. In a porcine model, Reiske et al found that stress hormones, such as adrenaline, noradrenaline, and cortisol administered via infusion decreased the presence of adaptive immune cells, such as antibody mediated and T cells, within the blood of pigs.[13] An increase in the presence of innate immune cells, such as neutrophils and monocyte macrophages were observed within this shift.[13] No studies have been conducted on *in vivo* human models, but if this pig model is consistent with human models, the immune response to stress would drastically shift the cellular environment in favor of *M. tuberculosis* growth. Adaptive T_H1 cells combat the bacteria within the body, while innate macrophage cells provide a safe growth environment for *M. tuberculosis*, due to the bacteria's ability to neutralize the lysosomal machinery within innate phagocytic cells. A study completed by Wright et al found that total sleep deprivation greatly increased cortisol production in the body.[14] Total sleep deprivation is likely a common aspect of the refugee experience. My group at Fort Pickett met one Afghan woman who was 9 months pregnant during her escape from Afghanistan. She described standing

in the crowded airport for over 24 hours without rest, hoping for an opportunity to exit the country by airplane. The stress of fleeing one's country due to conflict and danger, being constantly unsure of shelter, food, or personal safety likely elevates adrenaline, noradrenaline, cortisol, and catecholamine levels within the body. It may be concluded that the stress of the refugee experience compounds to increase cortisol, adrenaline, and noradrenaline levels, weaken the immune response against TB, and directly contribute to the conversion of a latent phase TB infection to an active pulmonary or extrapulmonary case.

Since treatment for latent infections is not required upon arrival to the United States, intentional communication oriented towards incoming refugees becomes a key step in preventing further TB spread in the United States.

Treatment Options

Treatments for TB infections are in constant development, with the main barrier to further development being a lack of adequate funding.[2,15] Treatment programs for drug-susceptible strains of *M. tuberculosis* have been generally successful, with close to 90% successful outcomes.[16] However, multidrug-resistant strains have posed a new challenge to conventional treatments in the last two decades, reducing their efficacy and creating the need for new treatment options.

Conventional drug treatments include isoniazid, rifampicin, pyrazinamide, and ethambutol being administered for two months, followed by courses of isoniazid and rifampicin for four months.[2] Isoniazid is the World Health Organization's (WHO) recommendation for treatment of latent TB, but it can have hepatotoxic effects.[3] Infections can vary in their response

to these treatments, with some taking over six months to resolve and others being resistant to rifampicin treatments.

Drug-resistant tuberculin strains are of a high concern. Early appearances of drug-resistant *M. tuberculosis* strains interrupted treatment success dramatically, with only 54% of the 99,165 individuals who began treatment for multidrug-resistant TB (MDR TB) in 2014 being cured.[17] The World Health Organization estimated there to be 500,000 new cases of MDR TB in 2016, and since then, resistant strains have only increased in risk and spread.[17] Treatments of such strains have not been consistently successful, so the development of resistant strains pose the highest risk of death for those infected with *M. tuberculosis.* The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment-2017 conducted a meta-analysis study of 50 studies from 25 different countries, including 12,030 patients with rifampin resistant TB, to evaluate the efficacy of a wide variety of common tuberculin drugs[17]. Of the rifampin-resistant participants, 91.1% of them were documented to have isoniazid resistance too, with the remaining percentages being composed of isoniazid-susceptible isolates or not having isoniazid susceptibility tested.[17] Across the studies, 61% had treatment success against TB disease, 8% had failure or relapse, and 14% died.[17] The highest mortality rate was seen among HIV-positive individuals, especially those who were not receiving any sort of antiretroviral therapy.[17] The results of the drug-susceptibility tests showed that the majority of treatment success against multidrug-resistant strains was found with use of levofloxacin, moxifloxacin, linezolid, and bedaquiline.[17] Linezolid is a drug that is used to treat multiple gram-positive bacterial infections and acts by inhibiting bacterial protein synthesis.[16] Bedaquiline is a drug that inhibits mycobacterial ATP synthase.[16] In another study conducted in South Africa by Conradie et al,

bedaquiline-containing treatment regimens against TB were associated with a lower death risk by any cause than the non-bedaquiline-containing regimens.[16] Pyrazinamide, streptomycin, amikacin, cycloserine, and terizidone were associated with moderate treatment benefits, but this was only seen in susceptible isolates; their success was highly limited in corresponding resistant strains.[17] No significant benefit or occasionally significantly worse outcomes were seen with treatment programs using kanamycin, capreomycin, ethionamide, protionamide, para-amino-salicylic acid, macrolides, and amoxicillin-clavulanic acid used without carbapenems.[17]

In a study conducted by Conradie et al that investigated multiple drugs for use against extensively drug-resistant strains (XDR TB) and MDR TB, use of bedaquiline for two weeks, followed by a lower dose of the same drug for 24 weeks, plus pretomanid and linezolid for 26 weeks produced a 98% success rate of resolved TB cases.[16] Pretomanid is a drug that inhibits mycolic acid biosynthesis, which is an integral component to mycobacterial cell-wall production.[16] This same drug acts as a respiratory poison towards the nonreplicating bacteria under anaerobic conditions.[16] It has shown anti-bacterial activity against drug-susceptible and drug-resistant *M. tuberculosis* strains *in vitro* and was recently approved by the FDA to be used in programs with bedaquiline and linezolid against MDR TB and XDR TB.[16]

Some success has been found with anti-VEGF drugs, and though there are multiple FDA-approved drugs that target isoforms of VEGF and VEGF receptor, this is not a common-use treatment strategy yet.[3] There were little to no studies found in the English language that explored their efficacy in active TB settings. Most studies conducted with anti-VEGF drugs are oriented to reducing angiogenesis in cancerous cells. Further research and development with anti-VEGF drugs for use in active or latent TB cases could be an important component to

eradicating the risk of this contagious disease, as this contributes to angiogenesis of the granuloma. Reducing the bacteria's ability to spread to extrapulmonary organs or maintain a nutrient source could effectively slow the growth of *M. tuberculosis* in the body to allow the natural immune system to eliminate this pathogen.

Treatments are important for addressing latent cases becoming active. Swift and effective treatment can help prevent further spread of TB disease. In addition to successful treatment, prevention measures, such as testing and vaccination, can have a similar benefit for preventing spread of TB within the United States.

Treatment and Prevention Measures

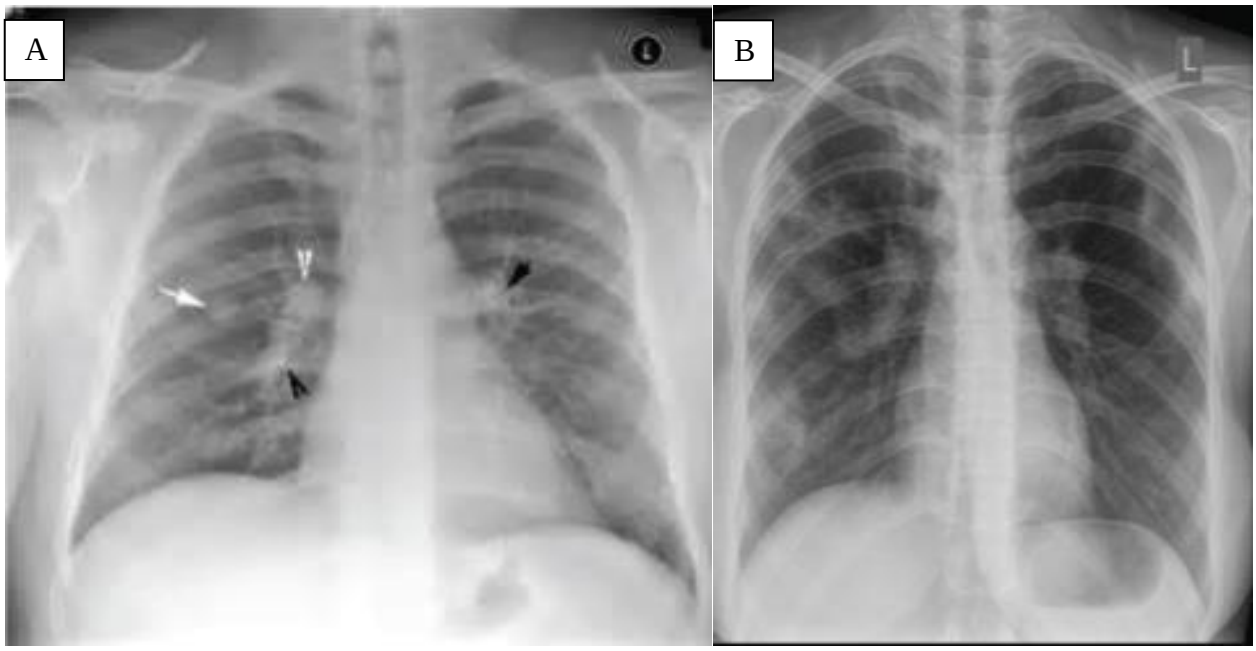
The only vaccination in current common use against TB infections is the Bacille de Calmette et Guérin (BCG) vaccine. This vaccine is an attenuated immunization developed from *M. bovis*.[18] This vaccination has not been associated with major success in preventing active pulmonary TB infections. Variations of this vaccine have been tested, including strains with overexpression of specific cytokines or functional units. However, these variations have found only minimally more success than the BCG vaccine itself.[18]

Van Der Meeren et al found success in preventing TB with use of the M72/AS01$_E$ immunization.[19] Using a double-blind, placebo-controlled trial with 1786 participants in Kenya, South Africa, and Zambia, they found that this vaccine had 54.0% efficacy against the progression to PCR- or culture-confirmed active pulmonary TB disease.[19] While side effects were observed with use of the vaccine, no evident safety concerns were noted.[19] This vaccine is still undergoing trials under the sponsorship of the Bill & Melinda Gates Medical Research Institute, and it may be a viable prevention option to increase herd immunity of global

populations and prevent further spread among refugees in their home countries or lessen the risk of spread upon arrival to the United States.[19]

Testing for active TB infections is still developing; there are multiple testing strategies in use with varying levels of accuracy. Mycobacterial culture can take up to 8 weeks to receive results.[20] Digital chest x-rays have been used in some triage settings with computer-aided detection, but this method is not a fully definitive test.[2] As seen in Figure 4, small calcifications are the sign of TB, but even when they are easy to identify on xray, as pointed out by the arrows (A), they can be identical to a non-tuberculoid hilar lymphadenopathy (B), making this test less definitive. Urinary tests that identify the presence of lipoarabinomannan, a byproduct of *M. tuberculosis* bacterial replication within human hosts, can be administered at point of care. The MTB/RIF test can detect genetic material from the *M. tuberculosis* bacterium, including mutations that cause resistance to rifampicin.[2] Other nucleic acid amplification genotypic tests are under development, and others including RealTime MTB, FluoroType MTBDR, and BD MAX MDR-TB are commercially available.[2] Latent infection testing options include the tuberculin skin test and the interferon-γ release assay (IGRA).[2] While they are approved by the World Health Organization as dependable tests, they each have their own limitations—they are unable to accurately differentiate between latent TB infections as opposed to active TB infections, and they have lower sensitivity in immunocompromised individuals.[2] With the difficulty of identifying latency or active state with IGRA and the inconclusive nature of chest x-rays, it may be possible that an IGRA positive test would indicate an active case, but the lack of a formed granuloma would falsely imply a latent state, resulting in a misdiagnosis. These tests

Figure 4. X-ray images of active TB and unknown infection. Hazy patches on a chest x-ray can designate cases of primary tuberculosis (A), but hazy patches on a chest x-ray can also reveal only a hilar lymphadenopathy, which could be a sign of TB or another non-tuberculoid type of lung infection (B). From *The Radiological Diagnosis*.[21]



are generally unable to predict progression from latent to active infections, which creates further risk of false confidence in a non-contagious latent case.[2]

Mayito et al are currently attempting to develop an alternative TB screening method: monocyte to lymphocyte ratios (MLRs).[22] Their research, begun in 2020, builds off the idea that higher MLRs occur in active TB cases compared to latent infections. This test can be used to not only identify cases but also monitor the success of treatment programs, marking the decline of an active TB case. This test can produce rapid results, using MLR cut-off values for various disease state designations. It is inexpensive and has been previously used in Kenyan individuals with HIV to differentiate between latent and active infections.[22] If development of this MLR biomarker is successful, it could also be used to fine-tune MDR treatment programs. If researchers can identify nuanced decrease in *M. tuberculosis* growth, they may be able to develop a combined drug regimen of existing drugs to combat TB until new drugs can be developed.

Cultural Adjustments for Successful Mitigation

Refugees come from various countries, entering the United States with differing languages, religions, political norms, communication preferences, cultural practices, and views on the role of medical care. Extra care taken to understand norms concerning medical care and communication will improve efficiency and effectiveness of both TB prevention and treatment. The Afghan refugees that recently entered the United States during the 2021 political coup serve as a relevant example to identify cultural adjustments needed in mitigation procedures for refugees from TB endemic countries.

Communication

Thorough communication adjustment has been proven to improve success in cross-cultural doctor-patient relationships and increase patient participation. Thorough communication in TB testing, prevention, and treatment will similarly improve treatment adherence, increase awareness, and ultimately decrease transmission. At a primary communication level, language translation is needed in the languages of Dari, Farsi, Pashto, Uzbek, and Turkmen for Afghan refugees.[23] However, language is not the only communication barrier facing American health care professionals and Afghan refugees. W. Jay Moon, an American university professor of intercultural studies, who previously lived and worked in West Africa, writes "How something is said is just as important as what is said".[25] His commentary on effective communication between oral and print preference highlights the need for further cultural communication adaptation within refugee medical care beyond simple translation.

With illiteracy being a highly influential factor in the communication needs of a potential TB patient or risk population, understanding the literacy rates within the community and adapting medical communication accordingly will contribute to treatment success. If a TB patient is illiterate, they will likely need attentive health care communication for accurate education since gaps in communication will not be filled in with supplementary reading materials. The current data collected by UNICEF estimates that one in every two Afghan children in the appropriate age group had completed primary school in 2015. However, adult Afghans endured a period of Taliban rule from 1996-2001 that involved a ban on female education.[24] This means that many mothers of families that entered the United States during the 2021 Afghan refugee crisis may likely be vastly illiterate. Gender discrepancies in education can remain large due to cultural barriers to female education in conservative communities.

Regardless of education, literacy is only truly acquired if the practices of literacy are integrated within the social reality of the learner; even if a population has a robust education status, they may still have a non-literate communication preference.[24] Growing research in the field of non-Western communication has discovered oral communication preference as the majority communication preference among non-Westerners.

Oral communication preference is characterized by a reliance on visual communication, mutual-trust, and story-like instruction.[25] This communication style is not the primary preference among Americans, which could produce a non-linguistic communication barrier between American health care providers and non-Western refugee populations, such as Afghans.[25] While refugees come from a variety of countries and cultures of origin, those that come from developing countries or countries with continual political upheaval may have higher rates of illiteracy, due to the inconsistency of centralized education. While orality is not limited to only illiterate contexts, it is the main communication preference in illiterate cultures. Primary orality is a complete dependence upon oral means of memory and interaction with information due to complete illiteracy. It is most common in illiterate communities. Secondary oral communicators may be able to read and write functionally at varying levels but continue to prefer oral means of communication.[25] Table 1 provides a comparison of oral preference and literate or print preference communication in multiple contexts.

The first step to communicating effectively across oral/print communication preferences is assessment of both the communicator and the listener. This can be done using tools, such as the one created by Abney, which is included in the appendix. The communicator can alternatively identify the communication preference of their patient's culture of origin, as well as

Table 1. Individuals with oral preference or print preference have noticeable differences in manner of communication that impact diverse contexts. Adapted from Understanding Oral Learners.[25]

Category	Oral Preference	Print Preference
Dialogue	Learn in dialogue with others, communication in groups.	Learn alone, communicate one-on-one.
Oral Art	Clarity and style of speech are appreciated through oral art forms.	Clarity and validity of reasoning is appreciated through interesting literature.
Experience	Learning is retained when connected to events, people, or real life experiences.	Learning is retained through analysis, comparison, and classification removed from people or experiences. Events are used as brief examples of classification.
Holism	Matters are viewed in reference to their context, including all people involved.	Matters are viewed abstractly and analytically before application to people.
Mnemonics	Devices such as story, symbol, song, ritual, and repetition are effective memory aids.	Written words are recalled. Brevity and concise summary are valued. Stories are used for brief illustration of points.
Participation	Active participation through response to a speaker in a storytelling event is common.	Silent listening and independent reading are expectations in participation.

their own, through general study and analysis of the two styles. If the patient's communication preference is identified to be most consistent with orality, as most Afghans will likely be according to literacy rates, the provider can best communicate with them by incorporating dialogue, art, human experience, holism, and mnemonics into the explanation of preventative measures, treatment options, and quarantine details.[25] Examples of this in application include repetitive blurbs for important prescription instructions, connection to the family unit as to how they are affected by the diagnosis and how their involvement makes the treatment program important. Experiential examples/stories in video form for programs, outcomes, and treatment options benefit understanding, and dialogue among the individual and their primary community, involving active participation or response of a previous blurb, increases patient understanding.

While there is little research on medical communication adjustment for oral-preference learners, there has been success within a trial of visually focused materials in non-Western reproductive health education. A visually focused flip book developed by Johns Hopkins University for the World Health Organization was used in an Iranian, Nicaraguan, and Mexican health care settings to study possible improvements in patient participation and decision-making concerning contraceptive methods.[26,27] Use of the visual flipbook tool both increased the amount of information shared from the provider to the patients and significantly increased the overall satisfaction of the Iranian, Nicaraguan, and Mexican patients with the visit experience.[26] The success seen in use of this oral communication style tool suggests that further adaptation of medical care to oral preference will improve care and satisfaction for this demographic. Adapting TB patient education concerning treatment selection and prevention measures according to the

model used in this flip book likely improve effectiveness of these efforts and improve provider confidence to communicate.

Religious Considerations

An important factor in prevention strategies is vaccination. However, simply communicating its importance may not be enough to result in patient compliance. If refugees come from a religious background like the primarily Muslim culture of Afghanistan, they may hesitate to be vaccinated on account of *halal*, permissible, versus *haram*, impermissible, ingredients. Such a distinction can be the deciding factor of the success or failure of a vaccination program. In 2018, the Measles Rubella (MR) vaccination campaign in Indonesia was dramatically interrupted by the concerns of its permissibility in the Muslim faith.[28] A new combined MR vaccine was planned for mass use in measles-rubella immunization, however the local Indonesian Ulama Council, a provincial Islamic body, released a *fatwa*, ruling, declaring the MR vaccine *haram* for ingestion in the Muslim faith due to the porcine origin of the trypsin used in the vaccine.[28] This resulted in widespread refusal of the vaccine, despite the country's previous success in immunization. One province ruled by sharia law saw only an 8% vaccine coverage rate during this campaign.[28] Trypsin, a common product in pharmaceutical use is usually developed from porcine products, and gelatin derived from animal products is occasionally used for stabilization of vaccines. Both products are considered *haram* to consume in the Muslim faith.[28] Due to the M72/AS01$_E$ subunit vaccine still undergoing phase 2 trials, no information was found to be available concerning its established ingredients. If it does contain pork-derived products, it may still be successfully promoted among Muslim refugees in a special case approval. Some vaccines have received a *haram*-permissible designation by such religious

bodies during epidemics, on the grounds that people of the Muslim faith ought to care for their neighbors in such a way as to keep them healthy.[28] Such a designation can only be given by a Muslim governing body. For successful and efficient vaccination programs, it is important to have relevant *fatwa* and ingredient information on the TB vaccine of choice made readily available for any Muslim refugees. Considerations for other minority religions depending on the origin of a refugee population will similarly benefit TB prevention.

Conclusion

TB is a transmissible pulmonary disease that especially affects those in poverty and refugee camp environments. Drug-resistant strains have appeared, making eradication of this pathogen of high importance. Targeting migrant populations, such as refugees from endemic countries, can be effective in reducing the spread of TB. The options for treatment include variants of drug regimen, but multi-drug resistant strains necessitate alternative development, with promising results coming from anti-VEGF drugs. Prevention strategies are still in need of further development, with a notable lack of readily available and definitive testing options and lack of effective immunization options. Communication adaptation is an important key to success with these methods, since refugees, including those from Afghanistan in the 2021 crisis, may communicate with an illiterate or oral preference style. Initial success has been found in adaptations of clinical education materials to a visual-based preference. Religious considerations are similarly important to ensure efficiency of treatment and prevention programs. As TB-related deaths increase and global conflicts continue to run their course, displacing thousands, further development of tested and effective screening, FDA-approved vaccination, and established MDR treatment regimen, as well as practical oral preference-based materials for provider use is an

urgent need. Some sources cite a lack of funding as the main barrier to further development. This is a global health concern of importance within the United States and its allied countries, and delay of eradication elevates the threat of preventable deaths. For eradication to be feasible, this must be a high priority topic of research and development. Allocating government and private research funding is the first step towards producing these developments and effectively eradicating this deadly disease.

Appendix

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