Tuberculosis and COVID-19: an overview of two health emergencies

Karen Jazmín Cevallos Salazar[1]; Ana Patricia Jiménez Arias (PhD)[1,2]

[1]Universidad de las Fuerzas Armadas ESPE. Departamento de Ciencias de la Vida y la Agricultura. Sangolquí 170501, Ecuador
[2]Grupo de Investigación en Sanidad Animal y Humana. Sangolquí 170501, Ecuador

Abstract

Currently, a battle against the clock has been unleashed to deal with SARS-CoV-2, which to date has caused approximately nine hundred thousand deaths. Science has made significant efforts to characterize the COVID-19 virus and understand it from its origin to its transmission. Goals of the scientific community include controlling the propagation of the disease by developing hundreds of diagnostic tools and the future generation of a vaccine for this recent infection. Its counterpart, the *Mycobacterium tuberculosis* bacillus, causes more than 1.5 million deaths a year despite being an ancient disease. Its diagnostic methods are debatable due to the scarcity of effective options. Consequently, tuberculosis has spread mainly in developing countries that are not currently able to mitigate the infection. This paper compares two infectious diseases through a global narrative review and comprehensively describes what is known to date about two global health emergencies: tuberculosis and COVID-19.

Introduction

Infectious diseases are caused by pathogens, including bacteria, viruses, parasites and fungi.[1] These microorganisms have been responsible for provoking a great health threat worldwide with greater repercussions since the 20th century due to the resurgence of tuberculosis (TB), the increase in patients with acquired immunodeficiency syndrome (AIDS), severe acute respiratory syndrome (SARS) as well as influenza, and finally, the pandemic caused by coronavirus disease 2019 (COVID-19).

In 2018, TB caused 1.5 million deaths, and 10 million people became ill. It is estimated that a quarter of the world population has latent TB, wherein they carry the bacillus but do not transmit it or experience the disease.[2] Two years later, COVID-19 appeared, which within seven months of onset, has caused more than 19.7 million confirmed cases and approximately 730 000 deaths.[3]

COVID-19, the acronym for "coronavirus disease 2019", is a disease generated by the SARS-CoV-2 virus, which emerged in December 2019. This disease caused a clinical picture of high fever and respiratory distress in patients from Wuhan, Hubei Province, China.[4] The disease spread in such a way that on January 31, 2020, the World Health Organization (WHO) confirmed it to be a "Public Health Emergency of International Concern."[5] Nations worldwide have struggled with the large number of positive cases of COVID-19 that are reported daily, while improving access to rapid diagnostic tests, researching medical treatments that reduce mortality, and conducting a search for an effective vaccine.

Given the limited number of studies linking both illnesses, this report supports the literature with a narrative review comparing two infectious diseases considered by the WHO as global health emergencies: TB and COVID-19. In this way, it covers issues such as transmission, pathogenicity, diagnostic tools, clinical manifestations and treatment for SARS-CoV-2 and *Mycobacterium tuberculosis* (MTB), as well as current topics of discussion such as the role of the BCG vaccine on the pandemic. The purpose of the document is to discern particularities between both microorganisms so that the treatment and diagnosis of TB is not neglected during the pandemic, or in turn, special attention is given to patients who carry a co-infection with COVID-19. Furthermore, the article encourages authorities and governments to protect society from curable and preventable diseases such as TB by strengthening health systems and managing them responsibly.

We considered relevant articles published since 2000 in these databases: PubMed, Google Scholar, ScienceDirect, ClinicalTrials.gov, along with the WHO guidelines. Original research, book chapters, cohort studies, and reviews written in English and Spanish were searched using the keywords: COVID-19, tuberculosis, epidemiology, pathogenicity, transmission, and co-infection. This was done without location restriction. Non-indexed information and any studies based on SARS, MERS and *Mycobacterium tuberculosis* complex (MTBC) were excluded.

Etiology

SARS-CoV-2 belongs to the betaCoV category of the Coronaviridae family.[6] It is a single-stranded positive-sense RNA virus (ssRNA+) enveloped with glycoproteins as a crown, and has a 30-kb genome (Figure 1). The translation of two-thirds of the genome produces two polyproteins (pp1a and pp1b), which after proteolytic processing, give rise to 16 nonstructural proteins (nsp) that participate in the synthesis of negative chain RNA, the

Corresponding Author:
Patricia Jiménez Arias
apjimenez@espe.edu.ec

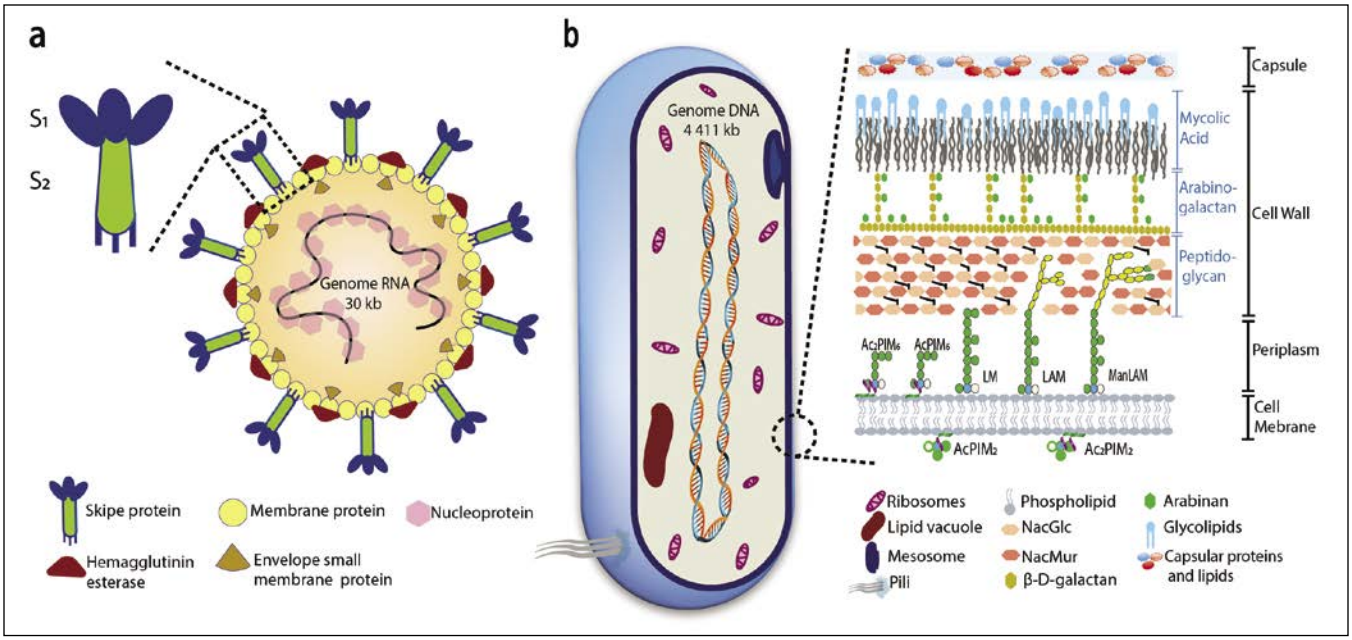

Figure. 1 Structure of SARS-CoV-2 and MTB[9,10]. a) Structure of SARS-CoV-2. The viral particle contains structural proteins, including the nucleocapsid (N), membrane (M), envelope (E), and spike (S) proteins, and has two subunits: the S1 receptor binding subunit and the S2 membrane fusion subunit. b) MTB structure. In the cell wall facing the cytoplasm, the plasma membrane incorporates lipids of four phosphates: monoacyl phosphatidylinositol dimannosides ($AcPIM_2$) and diacyl phosphatidylinositol dimannosides (Ac_2PIM_2); facing the capsule, the plasma membrane incorporates the following lipids: monoacyl phosphatidylinositol hexamannosides ($AcPIM_6$) and diacyl phosphatidylinositol hexamannosides (Ac_2PIM_6). The lipoglycans of the periplasm are lipomannan (LM), lipoarabinomannan (LAM) and LAM with mannose (ManLAM). The peptidoglycan network consists of N-acetyl-glucosamine (GlcNAc) and N-acetyl-muramic acid (MurNAc). The cell wall is characterized by a dense layer of mycolic acids and glycolipids reinforced by the bacterial capsule.

replication of the genome, and the production of subgenomic RNA.[7] One-third of the missing genome encodes the four structural proteins of the virus: the spike (S), membrane (M), envelope (E) and nucleocapsid (N) proteins.[8]

SARS-CoV-2 is phylogenetically related to RaTG13-CoV, SARS-CoV and pangolin-CoV viruses since they share a homology of 96.2%, 79.5% and 91.02%, respectively. This could indicate that it is a zoonotic infection.[11]

Unlike COVID-19, TB does not have a zoonotic origin. In fact, MTB is presumed to have appeared before the Neolithic demographic transition.[12] TB is caused by MTBC that includes several species of Mycobacteria such as *M. tuberculosis*, *M. africanum*, *M. canetti*, *M. bovis*, *M. microti*, *M. pinnipedi*, *M. caprae* and *M. bovis*.[13]

MTB, the etiological agent of TB, belongs to the family Mycobacteriaceae and is characterized by being an acid-alcohol-resistant, Gram-positive, nonmobile and non-spore-forming bacteria. These bacteria are rod shaped and measure 0.2 to 0.6 mm wide and 1 to 10 mm long.[14] The cell wall has a complex structure made up of proteins and lipids on the outside with an internal compartment of peptidoglycan, arabinogalactan, and mycolic acid, which form a thick layer known as the AG-PG-MA complex (Figure 1).[15] MTB is an obligate aerobic pathogen that has a genome of 4 411 529 bp and encodes 4 000 genes, of which 601 are essential.[16]

MTB and SARS-CoV-2 Replication

COVID-19 infection is initiated by interaction of the viral particle with specific proteins on the cell surface. In fact, receptor binding and membrane fusion are critical steps in the S protein and hemagglutinin esterase-mediated infection cycle. Protein S has a hectomer that contains two subunits: S1, which generates a conformational movement to expose its binding domain to the N-terminal receptor peptidase of ACE2 (angiotensin-converting enzyme 2) of the host cell, and S2, which fuses the viral RNA with cell membranes.[17] After receptor binding, the viral envelope and the cell membrane admit the entry of the virus by endocytosis and release SARS-CoV-2.

Using cellular ribosomes, the genetic material of the virus is translated into pp1a/b and into structural proteins. After a process of proteolysis allows them to fragment into small mRNAs that contain nsp1-nsp16 together with S, M, E, and N proteins, replication can begin. The envelope glycoproteins are located in the lumen of the endoplasmic reticulum or the Golgi apparatus to form the nucleocapsid, and enable the formation of viral particles so that they are transported through vesicles and leave the cell by exocytosis.[18]

On the other hand, MTB encodes the secretion complex ESX-1 to generate the lysis of the macrophage cell wall and promote cytosolic translocation.[19] These bacilli have a short generation time of 24 hours. To initiate replication, MTB duplicates its genetic material and its biomass. The two copies of DNA are segregated into nucleoids that are located at the poles of the cell. During this event, the maturation of the FtsZ ring directs the division of the pathogen. The daughter cells invaginate into an envelope layer and are sealed, the autolysin hydrolases digest the excess peptidoglycan between the septa, and the daughter cells are released. Modifications of this process have been contemplated where an asymmetric cell division is generated, especially in drug-resistant MTB.[20]

To avoid pathogen multiplication, macrophages respond by

producing reactive species of oxygen and nitric oxide. MTB detects this oxygen-deficient environment with reduced nutrients and enters a latent state in which it stops multiplying and activates anaerobic metabolism. Bacteria persist in this state in different tissues for a long time, and mycobacteria produce specific proteins that act as reanimation promoting factors capable of resuscitating latent bacilli.[21]

Both microorganisms use the immune system to their advantage. Mycobacteria contain large numbers of cellular receptors which mediate intercellular adhesion and phagocytosis. MTB eludes its degradation by appropriating host proteins such as coronin-1 that prevent phagosome-lysosome fusion. It is hypothesized that mycobacteria could be labeled with antibodies against ubiquitination.[22] Contrastingly, the SARS-CoV-2 virus developed an immuno-evasion mechanism through the formation of double vesicles to prevent recognition of the dsRNA. Moreover, nsp1 degrades cellular RNA to prevent innate immune response while nsp14 and 16 form a cap to evade pattern recognition receptors. The nps3 protein encodes the papain-like protease (PLpro), which cleaves viral polyproteins and antagonizes the IFN response.[23]

Transmission

COVID-19 is an infection that can be contracted by direct contact with the causative agent, and can diffuse among humans through community spread. Transmission arises when an infected person exposes respiratory droplets (5 to 10 μm in diameter) through expectoration or sneezing that enter the nose or mouth of nearby individuals.[24] Since the ACE2 cell receptor is expressed in the intestines, kidneys and heart, in addition to being expressed in the esophagus and lungs, there is a fecal-oral transmission of SARS-CoV-2.[25]

Similar to the virus, TB is transmitted by pathogenic bacilli through the expectoration or sneezing of a sick individual. However, unlike COVID-19, TB can spread through the air by droplet nuclei (1 to 5 μm in diameter) containing 1 to 3 bacterial cells, which is a sufficient amount to invade macrophages present in the pulmonary alveoli, and cause infection when a healthy person inhales them.[26]

SARS-CoV-2 can remain viable for 3 to 72 hours on materials such as plastic and stainless steel, which is a shorter period of time than the half-life of MTB.[27] The survival of tubercle bacilli can vary. The drug-sensitive strains survive from approximately 1 to 7 days, while TB-MDR strains survive on surfaces for up to 21 days.[28] Transmission of MTB in a confined environment is more likely than it is outdoors because droplet cores are kept less diluted; this exposes the family and the environment of the patient to a highly contagious ambience. Therefore, shelters, prisons and hospitals are potentially at risk.

Pathogenicity

The lungs are the preferred site for the establishment of SARS-CoV-2 and MTB. To initiate the infection, SARS-CoV-2 crosses the nasal and laryngeal membranes to reach the lungs. After massive replication, the virus is released into the peripheral blood and causes viremia, where it binds to the ACE2 receptor present in spermatogonial, leydig, sertoli, gastric, duodenal and rectal cells. In this way, a variety of organs are involved during the disease.[29,30] COVID-19 is aggravated by the release of pro-inflammatory and immuno-activating cytokines, and creates a self-sustaining inflammatory process that triggers catastrophic respiratory failure.[31]

In primary TB, the bacilli enter the body through the pulmonary alveoli where they are assimilated by macrophages. The bacilli that survive digestion of phagolysosome generate a stage of symbiosis and replicate in macrophages while circulating in the lymph.[32] The pathogen generates lysis of macrophages due to its intense proliferation, and infects new cells in organs that may be of preference, such as the lungs, lymph nodes, bones, kidneys, and larynx. This process causes inflammation of the pleural surfaces in the patient. After 2 to 8 weeks, with the desire to contain the infection, the body responds with a delayed hypersensitivity reaction, and forms a pulmonary granuloma containing infected macrophages, foam cells and epithelioid macrophages in its nucleus surrounded by lymphocytes, T cells, CD4, CD8, B cells, and NK cells.[33] This formation allows the destruction of the pathogen-carrying macrophages and creates caseous necrosis, establishing a hostile environment for bacteria that will persist as latent TB.[32]

In postprimary TB, the patient may experience exogenous reinfection, or latent bacilli may be reactivated in the manner of endogenous reinfection. In the latter case, a process of liquefaction of the caseous centre allows the multiplication of the bacillus and generates great amounts of toxic antigens in the tissue. The walls of the bronchi become necrotic and form cavities, the liquefied material flows into the airways, and can infect other sections of the lungs, ultimately causing extrapulmonary TB.[34,35]

Diagnostic Tools

Coronavirus has different ways to be detected, and the gold standard is reverse transcriptase polymerase chain reaction (RT-PCR), which involves extracting RNA from the virus, synthesizing cDNA, and amplifying its genetic information. This trial has a sensitivity between 66% and 80%, depending on the viral load of the patient.[36] At the same time, the identification of specific genes has been applied using RT–qPCR or by reverse transcription loop-mediated isothermal amplification (RT-LAMP), which has a detection probability of 95%.[37,38] The highest rates of positivity are manifested using samples of bronchoalveolar lavage fluid, sputum, and nasal swabs.[39] Currently, it is preferred to use saliva and nasal swabs, which have sensitivities of 91% and 98%, respectively.[40] In the future, it is planned to use CRISPR Cas 13 as a promising protocol because it recognizes 10 to 100 copies per μL of sample, and can be read in only 1 hour.[41]

Another tool of choice is computed tomography, which is a fast, accurate and effective technique that allows identification of ground-glass opacity and lung anomalies typical of COVID-19. Before manifesting clinical symptoms, the lung shows signs of disease, so the sensitivity of this technique is 97%.

We currently have serological tests that evaluate the patient's response to the virus.[42] When symptomatology for COVID-19 exists, blood, plasma or serum samples are tested using a qualitative assay to identify the antibodies that the host develops from contact with the pathogen. These tests have a sensitivity of 57-69% for IgM and 81-86% for IgG, and are fast as well as inexpensive.[43]

In the case of TB, molecular assays are performed using sputum, urine, or tissue that are placed in a disposable cartridge from the GeneXpert equipment for DNA amplification. This

method detects MTB and its position against rifampicin. Though this technique has a sensitivity of 98.6%, it is expensive, and due to the economic limitations that nations most affected by TB go through, it is difficult to acquire.[44]

Despite the fact that MTB can lodge in any organ, the thorax is more frequently affected, and imaging plays a fundamental role in its diagnosis. Radiography may display cavities, consolidations and centrilobular nodules, and this method has shown a sensitivity of 78% if interpreted by trained personnel.[45]

The Interferon-Gamma Release Assay (IGRA) measures the amount of INF-γ produced by T cells after being stimulated by MTB antigens in the blood. Its sensitivity is 93%.[46,47]

Microbiological methods for diagnosing MTB include Ziehl-Neelsen staining, an accessible technique for developing countries, but with a sensitivity of 55%. Variations in the method have been postulated with the application of auramine-based fluorescence microscopy (LED-FM) to increase its sensitivity by approximately 10%; however, this requires extra equipment for its application.[48] Additionally, the microscopic observation drug susceptibility technique (MODS) allows for the detection of the bacillus and its sensitivity to rifampicin and isoniazid through sputum. It has a sensitivity of 91.3% to 98%, but the disadvantage lies in the operator exposure.[49] The gold standard method to determine the presence of TB is bacteriological culture, generally used on Lowenstein-Jensen solid medium. This assay has the capacity to detect 1×10^2 bacilli per mL, and yields a sensitivity of 93%. The timely diagnosis of diseases is essential for treatment. Unlike COVID-19, the main drawback of bacterial culture for TB is that it can take between 4 to 12 weeks.[50]

The Mantoux intradermal reaction or tuberculin test consists of evaluating the hypersensitivity that an individual produces to a purified protein derivative (PPD) of MTB. Its disadvantage is the generation of a cross-reaction with the tuberculosis vaccine derived from Bacille Calmette Guérin (BCG) or with nontuberculous bacteria. The test is evaluated 72 hours after its application and has a sensitivity of 94%.[47,51]

Clinical Manifestations

There are risk factors for both infections, including hypertension, lung diseases, diabetes, cardiovascular conditions and obesity. In patients suffering from SARS-CoV-2, their symptoms are aggravated by producing an acute respiratory distress syndrome that can culminate in death.[52] This situation is similar to TB, wherein vulnerable communities suffering from conditions such as HIV/AIDS, diabetes, kidney disease, organ transplants and cancer have weakened immune systems.[35]

A very pronounced difference between COVID-19 and TB is the onset of the disease. The entry of SARS-CoV-2 and its replication from the beginning of the infection occurs between 4.1 to 7 days; however, cases have been reported in which this period has become 12.7 days. On the other hand, MTB is a silent pathogen that can remain latent throughout the life of the host or may even generate gradual symptomatology that has the potential to manifest itself in several weeks or months.[53]

The most common symptoms in patients with COVID-19 are fever, cough, myalgia and dyspnea; less common symptoms include the production of sputum, headache and hemoptysis, as well as gastrointestinal conditions such as vomiting and diarrhea.[4,54,29] These symptoms are similar to those manifested by TB. The main sign is prolonged cough accompanied by sputum that may or may not be bloody with fever, hemoptysis, dyspnea, weight loss, night sweats, and lack of appetite.[55]

COVID-19 strongly impacts the lung, causing pneumonia affecting 3.3 lobes on average. It causes abnormal findings such as alveolar edema and growing ground-glass opacities that, in the worst case, can lead to "white lung."[56,57] A similar image occurs in TB, in which an initial lesion generates pleural effusion, lung cavities, hilar or mediastinal lymphadenopathy, calcified tuberculomas and emphysema due to affected nodes that obstruct the bronchi.[35] In both conditions, there is an asymptomatic population; however, in those with symptoms of advanced TB, it has been shown that they are capable of emanating 1.5 to 4 billion bacilli every day.[53]

Treatment

To date, though there is no specific treatment to combat COVID-19, a method to reduce its effects and help patients overcome the disease has been sought. Supportive therapy is recommended using oxygen 10 L/min and 30 L/min for severe and critical patients, respectively.[58] To neutralize the action of SARS-CoV-2, remdesivir has been used. This antiviral reduces viral load in animal models and appears to decrease recovery time and induce clinical improvement in COVID-19 patients. Improved effects have been observed in combination with lopinavir and ritonavir.[59–61] The antimalarial drug, chloroquine, blocks viral infection in vitro similar to the effect generated by favipiravir tested in humans.[62]

Convalescent plasma therapy has also shown effective results against COVID-19. Patients receive neutralizing antibodies that stimulate the immune battle and decrease the viral titer.[63] Furthermore, intravenous transplantation of mesenchymal stem cells, which secrete anti-inflammatory factors that regulate the immune response and prevent the cytokine storm have been used. [64]

To date, there is no vaccine available for SARS-CoV-2. However, there are 156 candidate vaccines for preclinical evaluation and 42 under clinical evaluation. In this last group, ten vaccines are in phase III and are based on the inactivation of the virus, viral vectors, protein subunit or RNA.[65]

In contrast to COVID-19, TB has a vaccine that has been applied in newborns, but it has a variable effectiveness in adolescents and adults.[66] In the case of developing latent TB, the WHO advises administering isoniazid or its combination with rifapentine.[67] In drug-sensitive tuberculosis, treatment adds rifampin, pyrazinamide, and ethambutol. In cases of drug resistance, the patient's treatment includes drugs such as levofloxacin, moxifloxacin, bedaquiline, clofazimine and cycloserine or terizidone.[68] The effectiveness of the treatment is variable due to the abandonment of therapy, the incorrect and irregular use of medicines, and even the low permeability of the MTB cell wall towards drugs.[69] It has been reported that approximately 60% and 40% of patients with multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB), respectively, are treated successfully.[70] Despite the fact that these drugs are new, resistance to them has already been reported. Such is the case for bedaquiline, which causes side effects such as nausea, hemoptysis, arthralgia and even unilateral deafness, which overwhelm patients and lead them to abandon treatment.[71]

During TB therapy, the WHO advises performing a monthly culture, but most countries opt for microscopic smear to control tuberculosis. Similar to COVID-19, the treatment of TB emphasizes

modifying the immune response through the use of host-directed therapies. This consists of administering small molecules with or without drugs to act by modulating the functions of the host cell. In this way, they counteract reactive oxygen species, cytokine production, autophagy induction, and peptide synthesis. This therapy is promising because it avoids contact with MTB and therefore the generation of resistance.[72,73]

Epidemiology

The reproductive number provides a direct estimate of transmission by showing the infections that may exist after a primary case. SARS-CoV-2 has a basic reproduction rate (R0) of 2.28, meaning that each person carrying the virus transmits the infection to approximately 2 individuals.[74] For TB, the R0 value varies by nation. In developed countries, effective reproduction rates of 0.24 and 0.59 have been reported for the Netherlands and the United States, respectively.[75] For developing nations, an R0 of 3.55 has been calculated in India, a value similar to that found in China (a neighboring country to Southeast Asia that had 44% of new TB cases in 2018), whose effective reproductive number corresponds to 4.3.[76] These data presume that economic and social conditions have an impact on equity in health. Due to airborne transmission of MTB, it has been estimated that in a confined, unventilated site, the effective reproduction rate is 14.22 to 44.13.[77]

The reproductive number is influenced by the genetic variability of the pathogen. SARS-CoV-2 has evolved in different ways according to its nsp. The L form is the main, most frequent and aggressive state that derives from the S form, a secondary type that has been present to a lesser extent during the pandemic.[78] In contrast, it has been reported that MTBC contains 7 lineages associated with different geographical regions. Lineages 1 and 3 are limited to East Africa and Asia. Lineage 2, also known as the East Asian lineage, which includes the Beijing strain family, is distributed in Asia, Russia and South Africa. Lineage 4 or the Euro-American lineage, is typical of Asia, Europe, Africa and America. Lineages 5, 6 and 7 are distributed throughout the Gulf of Guinea, West Africa and Ethiopia.[79] The seven phylogenetically distinct lineages can determine the clinical outcome of pulmonary and extrapulmonary TB.[80] As lineages 2, 3, and 4 are known as modern for their genetic changes and are strongly associated with drug resistance (MDR-TB or XDR-TB) and outbreaks of disease in younger patients, they have significant potential to expand.[81] Further, the migration of patients has caused several of the lineages to leave their geographical region of origin. Such is the case with the Beijing lineage, which is known for its high virulence and is associated with drug resistance. It has been found in South America and Europe.[82,83]

The Infectious Disease Vulnerability Index, RAND, is based on the political, economic, public health, demographic, developmental, and environmental factors to rank nations according to their susceptibility to infectious diseases.[84] The ranking indicates that the so-called "infectious diseases hot spot belt" is led by 5 countries in the African continent; this is consistent with the figures of TB, as 2.5 million people in Africa fell ill in 2016.[85] Nonetheless, the RAND ranking does not explain the transmission of COVID-19 given that until 10 August 2020, the entire African continent had only registered around 895,696 positive cases of COVID-19 and 16,713 deaths. This is a reduced number compared to United States – a country that is not vulnerable to infectious diseases – which, as of the same date, had 4.9 million cases with 160,989 deaths.[3] These data confirm that developed countries have had the resources to overcome outbreaks of infectious diseases such as TB; however, developing countries see the greatest impact. In the case of COVID-19, this event has not been observed due to the lack of available treatments and the speed of infection initiation.

The End of TB program has been in force since 2016 and seeks to diagnose and treat infectious cases until the incidence is reduced by 90%.[86] Unfortunately, it is stated that the goal of eliminating TB by 2035 is unlikely to be met, as progress is still very slight.[87] The WHO suspects that the number of TB deaths has increased because of the pandemic. This entity assumes that a 50% reduction in global detection during 3 months of confinement could increase the number of deaths by 26%.[88]

In the nations most affected by TB, it has been found that the cases focus on vulnerable groups, which include low-income and low-education families, people deprived of liberty, those with poor living conditions, people with pre-existing diseases, malnutrition, or HIV, indigenous communities, populations in border crossings, those who are migrating, and those who have limited medical access.[89] In the case of COVID-19, the vulnerable sectors have not yet been clearly established. Several studies argue that low educational level, being a man, not married, coming from a low to middle income country, and socioeconomic deprivation associate a higher risk of death due to SARS-CoV-2.[90–92] It is expected that in the future COVID-19, as well as TB, will end up being associated with people with limited resources.[91,93]

BCG Vaccine and Its Relationship to COVID-19

BCG is the only vaccine developed to fight TB. It has been used for almost 100 years since Albert Calmette and Camille Guérin attenuated the strain from *M. bovis*.[94] In the current pandemic, a link between BCG vaccination and morbidity and mortality of COVID-19 has been discussed. It is conjectured that countries without a BCG vaccination program show a higher number of people affected by SARS-CoV-2. This is presumed to be the case in Europe where the nations most affected by the pandemic have abandoned the application of BCG for decades.[95]

BCG vaccination reduces infant mortality from infections other than TB due to a potential heterologous effect.[96] It has been determined that the population previously immunized responds more effectively against nonmycobacterial diseases, such as influenza A, as it produces a high antibody response.[97] The beneficial effect of BCG vaccination on different diseases can be explained by the intervention of the vaccine on the patient's immunity. Its application stimulates gene promoter regions to participate directly in the remodeling of signal transduction molecules and in the inflammatory response based on the production of proinflammatory cytokines such as TNF-α and IL-6. High IL-1β levels showed a protective effect in viral infections.[98,99] This causes the host to reprogram monocyte epigenetics and respond to a stimulus with trained immunity or innate immune memory.[100] Certain literature states that vaccination has a protective effect in the course of the SARS-CoV-2 pandemic; in countries that use BCG vaccination, the mortality is 5.8 times lower than that in those regions that have suspended its application.[101] Additionally, it has been exposed that SARS-CoV-2 has caused a case fatality rate of 5.2% and 0.6% for countries that have abandoned vaccination

and for those that still administer it, respectively.[102] These values are subject to variation due to circumstances, including the start of the pandemic, migration, demography, and health systems among others.[103] At the moment, there is no clear evidence of a relationship between the two factors. To clarify this, several trials are in the process of evaluating the performance of the BCG vaccine in medical personnel exposed to the virus. Such is the case of a study developed in Medellín-Colombia, a nation with compulsory vaccination, and wherein the incidence of COVID-19 will be measured after the application of the vaccine and a placebo.[104] Other trials have assessed the capacity of the centennial vaccine in countries with optional vaccination, such as the Netherlands, seeking to minimize absenteeism in medical personnel by applying the BCG vaccine.[105]

Conclusions

Both infectious diseases, TB and COVID-19, are etiologically different, but they selectively attack the lungs, and several symptoms are analogous. For these reasons, they generate a similar clinical picture. Although TB can be treated with a range of drugs, every day their effectiveness is counteracted by their improper use and evolution of the bacillus. In contrast, COVID-19 does not have a defined therapy, but fortunately there are cases of recovery. Airborne transmission of TB is a critical factor for its progression, and people with this condition are at high risk of acquiring a simultaneous infection with COVID-19.

Currently COVID-19 has hit the world due to its transmission capacity and the lack of optimal treatment; however, TB is a curable and preventable disease that, despite having been declared by the WHO as a world emergency in 1993, continues to claim victims and has not been controlled. It is necessary to strengthen the health system to encourage prevention and proper treatment of TB, especially in developing countries, which at present have the largest number of cases.

Due to the continuously developing information about SARS-CoV-2, the data are not currently definitive. Nevertheless, the need for knowledge has generated the union of the scientific community in order to safeguard health. It is essential to provide resources for health and research that allow us to intervene quickly in the face of new diseases such as COVID-19 and to combat older ones such as TB.

The narrative and global scope of this review misses the geographically nuanced factors that affect pathogenicity, treatment, diagnostic tools, and other aspects of both tuberculosis and COVID-19. This article denotes the most valuable aspects of both microorganisms through an exhaustive analysis of the most recent literature. Given that TB is a worrisome social disease, in the future it is expected to have safer drugs without side effects, faster, more sensitive diagnostic methods and global access.

References

1. WHO. WHO - Infectious Diseases [Internet]. Geneva; WHO Press. 2020. Available from: http://www.who.int/topics/infectious_diseases/en/ [cited 2020 Apr 21].
2. WHO. Tuberculosis Data [Internet]. Geneva; WHO Press. 2019. Available from: https://www.who.int/es/news-room/fact-sheets/detail/tuberculosis [cited 2020 Apr 21].
3. WHO. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. Geneva; WHO. 2020. Available from: https://covid19.who.int [cited 2020 Aug 10].
4. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020; 395: 497–506. doi: 10.1016/S0140-6736(20)30183-5.
5. WHO. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV) [Internet]. Geneva; WHO Press. 2020. Available from: https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) [cited 2020 Jun 8].
6. Cascella M, Rajnik M, Cuomo A et al. Features, Evaluation and Treatment Coronavirus (COVID-19). In: StatPearls Publishing: Treasure Island (FL), 2020 Available from: http://www.ncbi.nlm.nih.gov/books/NBK554776/
7. Silva SJR da, Silva CTA da, Mendes RPG, et al. Role of nonstructural proteins in the pathogenesis of SARS-CoV-2. J. Med. Virol. 2020; 92: 1427-1429
8. Chen Y, Liu Q, Guo D et al. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J. Med. Virol. 2020; 92: 418-423.
9. Minnikin DE, Lee OY-C, Wu HHT et al. Pathophysiological Implications of Cell Envelope Structure in Mycobacterium tuberculosis and Related Taxa. Tuberculosis - Expanding Knowledge 2015. doi:10.5772/59585.
10. Mishra AK, Driessen NN, Appelmelk BJ, et al. Lipoarabinomannan and related glycoconjugates: structure, biogenesis and role in Mycobacterium tuberculosis physiology and host–pathogen interaction. FEMS Microbiol Rev 2011; 35: 1126–1157.
11. Zhang T, Wu Q, Zhang Z. Probable Pangolin Origin of SARS-CoV-2 Associated with the COVID-19 Outbreak. Curr. Biol. 2020; 30: 1346-1351.e2.
12. Comas I, Coscolla M, Luo T et al. Out-of-Africa migration and Neolithic co-expansion of Mycobacterium tuberculosis with modern humans. Nat Genet 2013; 45: 1176–1182.
13. Bañuls A-L, Sanou A, Van Anh NT. Mycobacterium tuberculosis: ecology and evolution of a human bacterium. J. Med. Microbiol., 2015; 64: 1261–1269.
14. Percival SL, Williams DW. Chapter Nine - Mycobacterium. In: Percival SL, Yates MV, Williams DW, Chalmers RM, Gray NF (eds). Microbiology of Waterborne Diseases (Second Edition). Academic Press: London, 2014, pp 177–207.
15. Alva A, Aquino F, Gilman RH et al. Morphological characterization of mycobacterium tuberculosis in a MODS culture for an automatic diagnostics through pattern recognition. PLoS One 2013; 8. doi:10.1371/journal.pone.0082809.
16. Minato Y, Gohl DM, Thiede JM et al. Genomewide assessment of mycobacterium tuberculosis conditionally essential metabolic pathways. mSystems 2019; 4. doi:10.1128/mSystems.00070-19.
17. Yan R, Zhang Y, Li Y, et al. Structure of dimeric full-length human ACE2 in complex with B0 AT1. Biochemistry 2020 doi:10.1101/2020.02.17.951848.
18. Shereen MA, Khan S, Kazmi A, et al. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J. Adv. Res. 2020; 24: 91-98.
19. Cambier CJ, Falkow S, Ramakrishnan L. Host Evasion and Exploitation Schemes of Mycobacterium tuberculosis. Cell 2014; 159: 1497-1509.
20. Velayati AA, Farnia P. Division-cycle in Mycobacterium tuberculosis. Int J Mycobacteriol 2012; 1: 111-117.
21. Uhía I, Krishnan N, Robertson BD. Characterising resuscitation promoting factor fluorescent-fusions in mycobacteria. BMC Microbiol 2018; 18. doi:10.1186/s12866-018-1165-0.
22. BoseDasgupta S, Pieters J. Striking the right balance determines TB or Not TB. Front Immunol 2014; 5. doi:10.3389/fimmu.2014.00455.
23. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes Metab Syndr 2020; 14: 407-412.
24. Liu J, Liao X, Qian S, et al. Early Release - Community Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, Shenzhen, China, 2020. 2020. doi:10.3201/eid2606.200239.
25. Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal–oral transmission. Gastroenterology 2020. doi:10.1053/j.gastro.2020.02.054
26. Nardell EA. Transmission and institutional infection control of tuberculosis. Cold Spring Harb Perspect Med 2016; 6. doi:10.1101/cshperspect.a018192.
27. van Doremalen N, Bushmaker T, Morris DH et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 2020. doi:10.1056/NEJMc2004973.
28. Eremeeva N, Vakhrusheva D, Scornyakov S, et al. Survival of mycobacterium tuberculosis (MBT) on model surfaces. Eur. Respir. J. 2012; 40. Available from: https://erj.ersjournals.com/content/40/Suppl_56/P2641 [cited 2020 Apr 20].
29. Lin L, Lu L, Cao W et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection–a review of immune changes in patients with viral pneumonia. Emerg. Microbes Infect. 2020; 9: 727–732.
30. Abdullahi IN, Emeribe AU, Ajayi OA, et al. Implications of SARS-CoV-2 genetic diversity and mutations on pathogenicity of the COVID-19 and biomedical interventions. J. Taibah Univ. Medical Sci. 2020; 15: 258–264.
31. Fagone P, Ciurleo R, Lombardo SD et al. Transcriptional landscape of SARS-CoV-2 infection dismantles pathogenic pathways activated by the virus, proposes unique sex-specific differences and predicts tailored therapeutic strategies. Autoimmun Rev 2020; 19: 102571.
32. Zhang Q, Sugawara I. Immunology of tuberculosis. World J Exp Med 2012; 2: 70–74.
33. Wong-Baeza I, Paredes VGG, Silva-Miranda M et al. Mycobacterium tuberculosis extracellular vesicles induce the formation of granulomalike structures in an in vitro model. J. Immunol. 2019; 202: 190.86-190.86.

34. Jain R, Savla H, Naik I et al. Chapter 33 - Novel Nanotechnology Based Delivery Systems for Chemotherapy and Prophylaxis of Tuberculosis. In: Mustansar Hussain C (ed). Handbook of Nanomaterials for Industrial Applications. Elsevier, 2018, pp 587–620.
35. Morán E, Lazo Y. Tuberculosis. Tuberculosis 2001; Revista Cubana de Estomatología 38: 33–51.
36. Kakodkar P, Kaka N, Baig M. A comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19). Cureus 2020; 12. doi:10.7759/cureus.7560.
37. Corman VM, Landt O, Kaiser M et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill 2020; 25. doi:10.2807/1560-7917.ES.2020.25.3.2000045.
38. Udugama B, Kadhiresan P, Kozlowski HN et al. Diagnosing COVID-19: The disease and tools for detection. ACS Nano 2020. doi:10.1021/acsnano.0c02624.
39. Wang W, Xu Y, Gao R et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020. doi:10.1001/jama.2020.3786.
40. Czumbel LM, Kiss S, Farkas N et al. Saliva as a candidate for COVID-19 diagnostic testing: A meta-analysis. Front Med (Lausanne) 2020; 7. doi:10.3389/fmed.2020.00465.
41. Zhang F, Abudayyeh OO, Gootenberg JS. A protocol for detection of COVID-19 using CRISPR diagnostics. 2020: 8.
42. Jin Y, Yang H, Ji W et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020; 12: 372.
43. Xiang J, Yan M, Li H et al. Evaluation of enzyme-linked immunoassay and colloidal gold- immunochromatographic assay kit for detection of Novel Coronavirus (SARS-Cov-2) causing an outbreak of pneumonia (COVID-19). medRxiv 2020; : 2020.02.27.20028787.
44. Pandey P, Pant ND, Rijal KR et al. Diagnostic accuracy of GeneXpert MTB/RIF assay in comparison to conventional drug susceptibility testing method for the diagnosis of multidrug-resistant tuberculosis. PLoS One 2017; 12. doi:10.1371/journal.pone.0169798.
45. Kumar N, Bhargava SK, Agrawal CS et al. Chest radiographs and their reliability in the diagnosis of tuberculosis. JNMA J Nepal Med Assoc 2005; 44: 138–142.
46. Fernández Montero A, Alonso Álvarez A, Rodríguez Mourille A et al. Uso del QuantiFERON-TB Gold en la consulta de Medicina del Trabajo en un medio hospitalario: 8 años de experiencia. Revista de la Asociación Española de Especialistas en Medicina del Trabajo 2016; 25: 58–72.
47 . Lee JE, Kim H-J, Lee SW. The clinical utility of tuberculin skin test and interferon-γ release assay in the diagnosis of active tuberculosis among young adults: a prospective observational study. BMC Infect. Dis. 2011; 11: 96.
48. Thapa B, Reza LW, Kumar AM et al. Light Emitting Diode Fluorescence Microscopy increased the detection of smear-positives during follow-up of Tuberculosis patients in India: program implications. BMC Res. Notes 2015; 8: 596.
49. Arnez-Durán RA, Ayllón-Anzaldo LA, Castro-Soto R et al. El Método MODS, una Alternativa para el Diagnóstico de la Tuberculosis y la Detección de Cepas Multidrogoresistentes. Revista Científica Ciencia Médica 2010; 13: 81-85.
50. Zijenah LS. The World Health Organization recommended TB diagnostic tools. Tuberculosis (Edinb) 2018. doi:10.5772/intechopen.73070.
51. Cascante JA, Pascal I, Eguía VM, et al. Diagnóstico de la infección tuberculosa. Anales del Sistema Sanitario de Navarra 2007; 30: 49-65.
52. Guan W, Liang W, Zhao Y et al. Comorbidity and its impact on 1,590 patients with COVID-19 in China: A nationwide analysis. Respiratory Medicine 2020 doi:10.1101/2020.02.25.20027664.
53. Hunter RL. The pathogenesis of tuberculosis: The early infiltrate of post-primary (adult pulmonary) tuberculosis: A Distinct Disease Entity. Front Immunol 2018; 9. doi:10.3389/fimmu.2018.02108.
54. Guo Y-R, Cao Q-D, Hong Z-S et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Mil Med Res 2020; 7: 11.
55. Shanmuganathan R, Shanmuganathan ID. Clinical manifestation and risk factors of tuberculosis infection in Malaysia: Case study of a community clinic. Glob J Health Sci 2015; 7: 110-120.
56. Pan Y, Guan H, Zhou S et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. Eur Radiol 2020; : 1-4.
57. Tian S, Hu W, Niu L et al. Pulmonary pathology of early-phase 2019 Novel Coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 2020; 0. doi:10.1016/j.jtho.2020.02.010.
58. WHO. Oxygen sources and distribution for COVID-19 treatment centres. Available from: https://www.who.int/publications/i/item/oxygen-sources-and-distribution-for-covid-19-treatment-centres [cited 2020 Nov 21].
59. Grein J, Ohmagari N, Shin D et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med 2020. doi:10.1056/NEJMoa2007016.
60. Song Y, Zhang M, Yin L et al. COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). Int J Antimicrob Agents 2020; 56: 106080.
61. Williamson BN, Feldmann F, Schwarz B et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. bioRxiv 2020; : 2020.04.15.043166.
62. Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269–271.
63. Shen C, Wang Z, Zhao F et al. Treatment of 5 critically ill patients with cOVID-19 with convalescent plasma. JAMA 2020. doi:10.1001/jama.2020.4783.
64. Leng Z, Zhu R, Hou W et al. Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 2020; 11: 216–228.
65. Draft landscape of COVID-19 candidate vaccines. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines [cited 2020 Oct 19].
66. Davenne T, McShane H. Why don't we have an effective tuberculosis vaccine yet? Expert Rev Vaccines 2016; 15: 1009–1013.
67. WHO. WHO Latent TB Infection : Updated and consolidated guidelines for programmatic management. WHO. Available from: http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/ [cited 2020 Oct 29].
68. WHO. WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment. Available from: https://www.who.int/publications-detail-redirect/9789240007048 [cited 2020 Oct 29].
69. Rabahi MF, da Silva JLR, Ferreira ACG et al. Tuberculosis treatment. J Bras Pneumol 2017; 43: 472–486.
70. Rendon A, Tiberi S, Scardigli A et al. Classification of drugs to treat multidrug-resistant tuberculosis (MDR-TB): evidence and perspectives. J Thorac Dis 2016; 8: 2666–2671.
71. Field SK. Bedaquiline for the treatment of multidrug-resistant tuberculosis: great promise or disappointment? Ther Adv Chronic Dis 2015; 6: 170–184.
72. Kolloli A, Subbian S. Host-directed therapeutic strategies for tuberculosis. Front Med (Lausanne) 2017; 4. doi:10.3389/fmed.2017.00171.
73. Young C, Walzl G, Du Plessis N. Therapeutic host-directed strategies to improve outcome in tuberculosis. Mucosal Immunol 2020; 13: 190–204.
74. Zhao S, Lin Q, Ran J et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. Int J Infect Dis 2020; 92: 214–217.
75. Borgdorff MW, Behr MA, Nagelkerke NJD, Hopewell PC, Small PM. Transmission of tuberculosis in San Francisco and its association with immigration and ethnicity. 2000. Available from: https://www.ingentaconnect.com/content/iuatld/ijtld/2000/00000004/00000004/art00002;jsessionid=16bim560du15t.x-ic-live-03 [Cited 2020 Apr 21].
76. Zhang J, Li Y, Zhang X. Mathematical modeling of tuberculosis data of China. J. Theor. Biol. 2015; 365: 159–163.
77. Furuya H, Nagamine M, Watanabe T. Use of a mathematical model to estimate tuberculosis transmission risk in an Internet café. Environ Health Prev Med 2009; 14: 96–102.
78. Tang X, Wu C, Li X et al. On the origin and continuing evolution of SARS-CoV-2. Natl Sci Rev 2020. doi:10.1093/nsr/nwaa036.
79. Coscolla M, Gagneux S. Consequences of genomic diversity in Mycobacterium tuberculosis. Semin Immunol 2014; 26: 431–444.
80. Varghese B, Enani M, Alrajhi A et al. Impact of Mycobacterium tuberculosis complex lineages as a determinant of disease phenotypes from an immigrant rich moderate tuberculosis burden country. Respiratory Research 2018; 19: 259.
81. Ajawatanawong P, Yanai H, Smittipat N, et al. A novel Ancestral Beijing sublineage of Mycobacterium tuberculosis suggests the transition site to Modern Beijing sublineages. Sci Rep 2019; 9: 1–12.
82 . Lagos J, Couvin D, Arata L et al. Analysis of Mycobacterium tuberculosis genotypic lineage distribution in chile and neighboring countries. PLoS One 2016; 11. doi:10.1371/journal.pone.0160434.
83. Jiménez P, Calvopiña K, Herrera D et al. Identification of the Mycobacterium tuberculosis Beijing lineage in Ecuador. Biomédica 2017; 37: 233–237.
84. Moore M, Gelfeld B, Okunogbe A et al. Identifying future disease hot spots: Infectious Disease Vulnerability Index. RAND Corporation, 2016 doi:10.7249/RR1605.
85. Nadjane S, Cristina de Abreu Temoteo R, Maria Ribeiro Monteiro de Figueiredo T et al. Individual and social vulnerabilities upon acquiring tuberculosis: a literature systematic review. Int Arch Med 2014; 7: 35.
86. WHO. Implementing the End TB Strategy: The Essentials. [Internet] Geneva: WHO Press; 2015. [cited 2020 Oct 19] Available from: https://www.who.int/tb/publications/2015/end_tb_essential.pdf?ua=1.
87. MacNeil A. Global epidemiology of tuberculosis and progress toward meeting global targets — Worldwide, 2018. MMWR Morb Mortal Wkly Rep 2020; 69. doi:10.15585/mmwr.mm6911a2.
88. Kasaeva, T. Coping with TB in the time of COVID-19. [Internet] Geneva: WHO Press; 2020. Available from: https://www.who.int/docs/default-source/documents/tuberculosis/tbcovid-webinar-presentation.pdf?sfvrsn=1377b5b1_8 [cited 2020 Oct 19]
89. WHO. Vulnerable populations: risk factors and social determinants. 2020. Available from: http://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/areas-of-work/vulnerable-populations-risk-factors-and-social-determinants[cited 2020 Apr 21]
90 Drefahl S, Wallace M, Mussino E et al. A population-based cohort study of socio-demographic risk factors for COVID-19 deaths in Sweden. Nat. Commun. 2020; 11: 5097.
91. Saunders MJ, Evans CA. COVID-19, tuberculosis and poverty: preventing a perfect storm. Eur Respir J 2020; 56. doi:10.1183/13993003.01348-2020.

92. Holman N, Knighton P, Kar P et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol. 2020; 8: 823–833.
93. Wingfield T, Cuevas LE, MacPherson P et al. Tackling two pandemics: a plea on World Tuberculosis Day. Lancet Respir Med 2020; 8: 536–538.
94. Lucas, Mihaescu T. History of BCG vaccine. Maedica (Bucur) 2013; 8: 53–58.
95. Zwerling A, Behr MA, Verma A et al. The BCG world atlas: A database of global BCG vaccination policies and practices. PLoS Med 2011; 8. doi:10.1371/journal.pmed.1001012.
96. Shann F. Nonspecific effects of vaccines and the reduction of mortality in children. Clin Ther 2013; 35: 109–114.
97. Leentjens J, Kox M, Stokman R et al. BCG vaccination enhances the immunogenicity of subsequent influenza vaccination in healthy volunteers: A randomized, placebo-controlled pilot study. J Infect Dis 2015; 212: 1930–1938.
98. Arts RJW, Moorlag SJCFM, Novakovic B et al. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. Cell Host & Microbe 2018; 23: 89-100.e5.
99. Sergerie Y, Rivest S, Boivin G. Tumor necrosis factor-alpha and interleukin-1 beta play a critical role in the resistance against lethal herpes simplex virus encephalitis. J Infect Dis 2007; 196: 853–860.
100. Netea MG, Joosten LAB, Latz E et al. Trained immunity: a program of innate immune memory in health and disease. Science 2016; 352: aaf1098.
101. Shet A, Ray D, Malavige N et al. Differential COVID-19-attributable mortality and BCG vaccine use in countries. Infectious Diseases (except HIV/AIDS), 2020 doi:10.1101/2020.04.01.20049478.
102. Dayal D, Gupta S. Connecting BCG Vaccination and COVID-19: additional data. medRxiv 2020; : 2020.04.07.20053272.
103. Hegarty PK, Sfakianos JP, Giannarini G et al. COVID-19 and Bacillus Calmette-Guérin: What is the Link? Eur Urol Oncol 2020. doi:10.1016/j.euo.2020.04.001.
104. Cataño J, Lopez L. Performance evaluation of BCG vaccination in healthcare personnel to reduce the severity of SARS-COV-2 infection. Clinicaltrials. 2021. Available from: https://clinicaltrials.gov/ct2/show/study/NCT04362124?term=bcg&cond=covid-19&draw=2&rank=2
105. Doesschate T ten, Vaart T van der. Reducing health care workers absenteeism in Covid-19 Pandemic Through BCG vaccine (BCG-CORONA). 2020. Available from: https://clinicaltrials.gov/ct2/show/study/NCT04328441?term=bcg&cond=covid-19&draw=2&rank=1