Ministry of Higher Education and

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Tuberculosis patients and covid 19 infection, prevalence and copmlications.

A graduation project

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Content

Abstract

The aim of the present review is to report the available evidence on the interaction between these two infections. Differences and similarities of TB and COVID-19, compare the risk of death and recovery in COVID-19 patients with and without tuberculosis, and cross-protection of BCG vaccine against covid-19 patient.

Introduction

Coronavirus disease 2019 (COVID-19) is a communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the Coronaviridae family, which also includes severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus(MERS-CoV)[1]. It emerged in Huanan Seafood Wholesale Market in Wuhan, China, in December 2019 and continues to spread around the world.People are generally susceptible to SARS-CoV-2, including children, but the highest burden is in middle-aged and old men[2,3]. This outbreak seriously threatens people's health and life with deaths, closures, and quarantines.

TB is the leading cause of death worldwide from an infectious disease among adults and has been considered a global public health emergency for the past 25 years[4]. Globally, an estimated 10.0 million people fell ill with TB in 2018. There were an estimated 1.2 million TB deaths among HIV-negative people in 2018 and an additional 251,000 deaths among HIV-positive people[5]. During the epidemic period, clinicians still need to follow up, treat, and manage patients with TB, which is a major challenge for clinicians and patients with TB.

While experience on COVID-19 infection in TB patients remains limited, it is anticipated that people ill with both TB and COVID-19 may have poorer treatment outcomes, especially if TB treatment is interrupted. TB patients should take precautions as advised by health authorities to be protected from COVID-19 and continue their TB treatment as prescribed.

Global estimates suggest the lockdowns that have been implemented across the world to prevent the spread of COVID-19 infection, and the slow return to services after these lockdowns, could lead to an additional 6.3 million cases of TB during 2020–2025 and an additional 1.4 million TB deaths. This will set the world back five to eight years in the global fight against TB.

Letreture review

Transmission of TB and COVID-19.

While both TB and COVID-19 spread by close contact between people the exact mode of transmission differs, explaining some differences in infection control measures to mitigate the two conditions. TB bacilli remain suspended in the air in droplet nuclei for several hours after a TB patient coughs, sneezes, shouts, and people who inhale them can get infected. The size of these droplet nuclei is a key factor determining their infectiousness. Their concentration decreases with ventilation and exposure to direct sunlight. COVID-19 transmission has primarily been attributed to the direct breathing of droplets expelled by someone with COVID-19 (people may be infectious before clinical features become apparent). Droplets produced by coughing, sneezing, exhaling and speaking may land on objects and surfaces, and contacts can get infected with COVID-19 by touching them and then touching their eyes, nose or mouth1. Hand-washing, in addition to respiratory precautions, are thus important in the control of COVID-19. Hospital procedures that generate aerosols predispose to infection of both conditions and should only be conducted within recommended safeguards.

Effect of covid-19 on tuberculosis patients

Who, specialized scientific press and newspapers describe that consequence of the COVID-19 pandemic would be a worsening of the TB epidemic globally, for a variety of reasons, such as additional pressures on health systems by COVID-19 resulting in weakening of the National TB programmes[7] and the potential biological effects of the interaction of the two infections, recalling the concept of ‘cursed duet’ which in the past was used for TB and HIV[8].TB patients should take precautions as advised by health authorities to be protected from COVID-19 and continue their TB treatment as prescribed.

People ill with COVID-19 and TB show similar symptoms such as cough, fever and difficulty breathing. Both diseases attack primarily the lungs and although both biological agents transmit mainly via close contact, the incubation period from exposure to disease in TB is longer, often with a slow onset.

Treatment of TB patient infected with covid-19

In most cases TB treatment is not different in people with or without COVID-19 infection. Experience on joint management of both COVID-19 infection and TB remains limited. However, suspension of TB treatment in COVID-19 patients should be exceptional. TB preventive

treatment, treatment for drug-susceptible or drug-resistant TB disease should continue uninterrupted as it is important to safeguard the patient's health.

Effective treatments to prevent TB and to treat active TB have been scaled up and are in use worldwide. It is critical that people who need treatment continue taking it during the pandemic, even if they acquire COVID-19, to increase chances of cure and reduce transmission and the development of drug-resistance. The risk of death in TB patients approaches 50% if left untreated and may be higher in the elderly or in the presence of comorbidity.

Support for uninterrupted TB preventive treatment and treatment of TB disease should be ensured alongside the COVID-19 response. It is critical that TB services are not disrupted during the COVID19 response. While treatment trials are ongoing, no medication is currently recommended for COVID-19 and therefore no cautions on drug-drug interactions are indicated at present [9]. TB patients on treatment should nonetheless be asked if they are taking any medicines, including traditional cures, that may interact with their medication (e.g. risk of additive cardiotoxicity).

Gathering evidence as this pandemic unfolds will be very important, while upholding the norms of professional conduct and patient confidentiality when handling clinical details.

death and recovery in patients with COVID-19.

According to study[10] that include:

- sample consisted of 530 patients, with 106 cases with TB cases and 424 without. The mean age of the total sample was 48.9years, 70.4% were males, 13.4% died, and 67.7% recovered.
- The final sample admitted to hospital included 330 COVID-19 patients, of which 66 had TB (20.0%).

The result: Patients with TB had 2.17 times higher risk of death than those without. When assessed in patients admitted to hospital, those with TB had a similar higher risk of death. recovery in patients with TB was 25% lower than in those without. recovery was similar in admitted patients. There was a 20% higher risk of admission in patients with TB.

BCG vaccine and covid-19

BCG vaccine is A vaccine used to prevent tuberculosis (TB) in people who are at a high risk of TB or where TB is common. It is rarely given in the U.S. It is mandatory in some countries. made from a weakened form of a bacterium called Mycobacterium bovis (bacillus Calmette-Guérin),

which is similar to the bacteria that cause TB. The vaccine may help the body's immune system make antibodies to destroy the TB bacteria.

Multiple studies are being carried out around the world in an effort to associate the beneficial effects of BCG vaccination on COVID-19. Initial ecological studies established that in countries with BCG vaccination programs have less COVID- 19 cases and deaths per population [11,12], suggesting that trained immunity inducing vaccines may provide protection against covid-19 [13]. On the contrary, other studies concluded that BCG vaccination in childhood does not have a protective effect against COVID-19 in adulthood [14]. It is possible that due to the different testing and notification approaches, case and deaths incidences of COVID-19 might not differ in a country with BCG vaccination as it is critical to include different variables of interest such as age structure, income, rurality, and population density. A National Institutes of Health (NIH) study attempted to correct potential confounding variables among countries, such as access to health, education, and stage and size of the COVID-19 epidemic, which observed a strong correlation between BCG vaccination policy and reduction of morbidity and mortality due to COVID-19 in different European countries (10% of the augmentation in the BCG index was associated with a 10.4% mortality reduction from COVID-19) [15]. Similar conclusions were reached comparing the same geographical area with similar socioeconomic conditions between Spain and Portugal, with different high mortality rates have been observed in Spain where TB vaccination is no longer part of the official vaccination calendar [16]. However, it is important to highlight the importance of including new variants to verify the potential of BCG as a vaccine against COVID-19, such as BCG index (proportion of population of a country vaccinated against BCG), HDI score (number of days since one case per million), population density per Km2, population >65 years of age, CPI (Corruption Perception Index, government transparency) and percentage of population living in urban areas.

Only ongoing randomized controlled trials (RCTs) will provide answers to whether BCG reduces the incidence and severity of COVID-19 through its cross-protective effects. The phase III randomized clinical trial ACTIVATE (NCT03296423) confirmed that recent vaccination with BCG in elderly (>65 years) protects against new infections. In this trial in which 198 elderly people participated, it was demonstrated the difference between the incidence of new infections after placebo vaccination (42.3%) and BCG vaccination (25.0%), being most of the protection against respiratory tract infections. Furthermore, vaccinated individuals took longer to get infected (16 weeks) than the ones vaccinated with placebo (11 weeks). Further statistical analysis indicated a 79% decreased on the risk of acquiring at least one new respiratory infection in a 12 months period for BCG vaccinated group.

Mechanism of BCG in protection against SARS-CoV-2

The ancient innate immune system has evolved to employ multiple defense mechanisms to eliminate infection. In contrast to the adaptive immunity, which relies on the antigen-specificity, additional innate immune cell populations may exhibit heterologous memory responses triggered upon microbial exposure. Indeed, several studies demonstrated that macrophages and natural killer (NK) cells, which have experienced previous pathogen encounter, can be "trained" via epigenetic remodeling to respond to unrelated pathogens [17, 18]. BCG vaccine mediate epigenetic reprogramming of monocytes which results in the opening of chromatin sites at the promoters of pro-inflammatory cytokines such as IL-6, IL-1β, and TNFα [19] (Figure 1). It is plausible that a cross-talk between macrophages and NK cells facilitates the fine-tuning of innate immune program during the life-time exposure to microbial insults. In support of this notion, vaccination of healthy volunteers with BCG primes macrophages and NK cells, leading to increased cytokine production after ex vivo restimulation [20,21]. A recent study from Netea et al. demonstrated that the BCG vaccine offers a certain degree of cross-protection against a viral infections through trained immunity related mechanisms. Specifically, the study demonstrated the effects of BCG vaccination on genome-wide histone modifications induced in trained monocytes, which are associated with reduced levels of yellow fever virus (YFV) viremia due to increased IL-1β production and release [22]. This cross-protection effects of BCG against YFV infection confirms the non-specific effects of BCG vaccine described for various viral infections, such as influenza A (H1N1), herpes virus (HSV), respiratory syncytial virus (RSV), and the human papilloma virus (HPV). Since BCG offers protection to TB unrelated viral infections, it was hypothesized that BCG vaccination could also offer protection against SARS- CoV-2 infection in some individuals that have initial defective antiviral responses [23]. To explain this, there is another type of immunological mechanism by which BCG could be inducing cross-protection named heterologous immunity. The term heterologous immunity refers to the immunity that can develop to one pathogen after an individual has been exposed to a non-identical pathogen. In this respect, a recent study addressing the homology between SARS-CoV-2 envelope protein and different Mycobacterium strains, presents one sequence of 12 amino acids of SARS-CoV-2 envelope protein has high homology to LytR C- terminal domain-containing proteins of Mycobacterium sp. [24]. Therefore, a combination of trained immunity and

heterologous immunity by some BCG epitopes could provide immunity through T-cell cross-reactivity that could be responsible for the beneficial clinical effects of BCG.

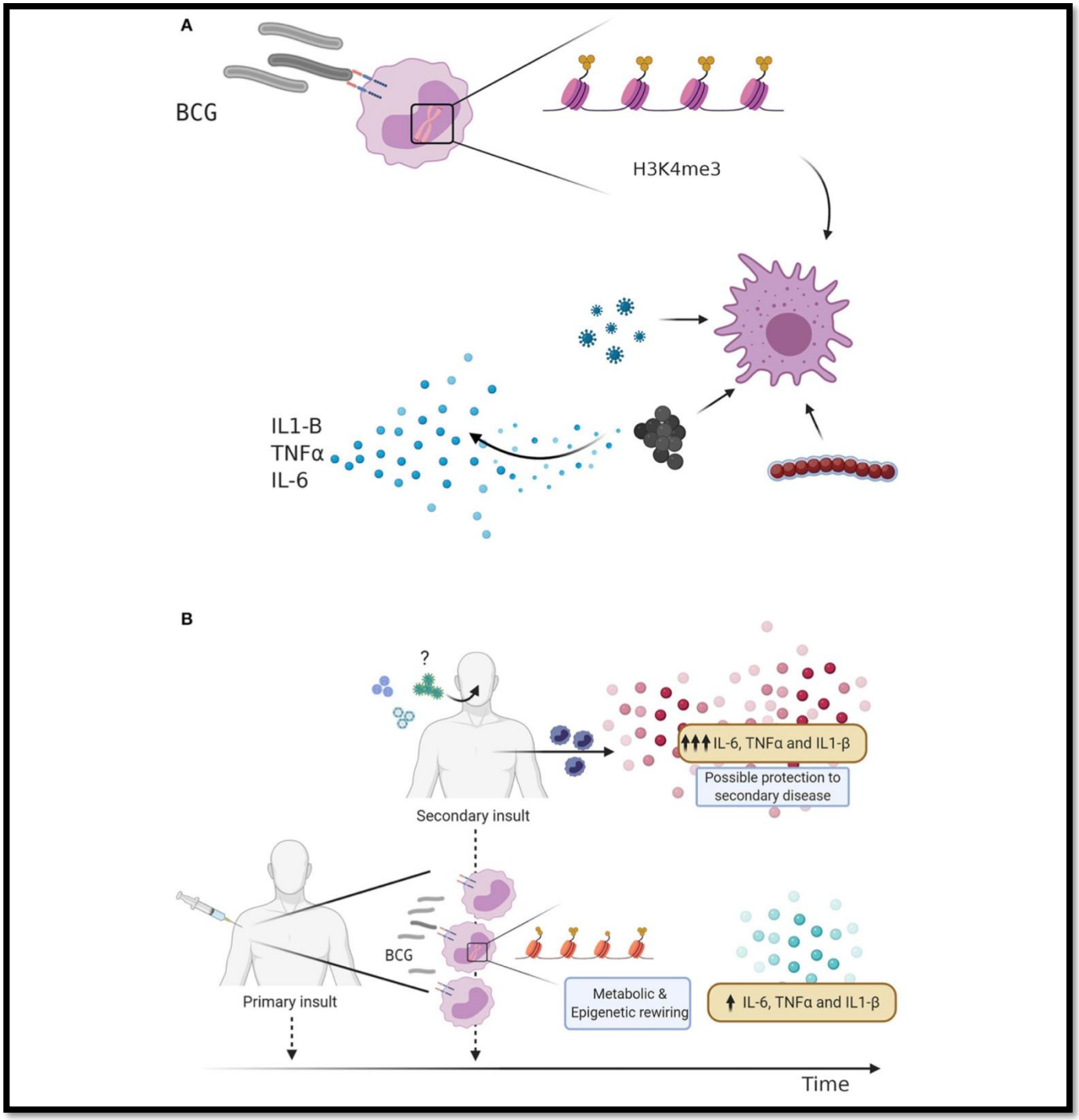

FIGURE 1 | (A) BCG vaccination and Trained immunity. Bacillus Calmette-Guérin (BCG) vaccination induces trained immunity through metabolic changes and epigenetic rewiring. Trimethylation of the H3K4 histone predisposes the innate immune response to a secondary insult, leading to an increased production of pro-inflammatory cytokines. (B) Trained immunity as defense mechanism against respiratory infections. BCG vaccination is given as an initial stimulus, leading to metabolic changes and epigenetic rewiring of innate immune cells, increasing the transcription of pro-inflammatory genes and secretion cytokines. BCG vaccinated individuals display an enhanced innate immune response following a secondary challenge, which may lead to protection against subsequent viral infections such as Influenza A virus or Respiratory syncytial virus (RSV). Could BCG vaccination also protect against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)?

universal BCG vaccination and covid 19

BCG vaccination is currently performed shortly after birth (newborns) in most of the countries, which universally vaccinate, as a protective measure against infantile/pediatric tuberculosis. There are some animal model and observational studies indicating that BCG vaccination can modulate host immunity (designated as 'trained immunity') and may protect against non-mycobacterial respiratory (and even other) infections as well (off target effect), especially in early childhood[25]. However, the effects of BCG vaccination fades with age, even against tuberculosis [26]. Hence, many countries have stopped their universal newborn vaccination programs or never even started that, since infantile/pediatric tuberculosis has become very rare in the economically advanced world. Consequently, there is no biologic evidence that newborn/baby age delivered BCG vaccination may have any protective effects against COVID-19, especially in adults and the elderly (who have received the BCG vaccine as an infant or child). Importantly, Hamiel U et al. [27] analyzed data from Israel and found no difference in the SARS- CoV-2-positive rate between individuals born during the period of mandatory BCG vaccinations and those born outside that period. Lerm M reported that in East Germany with rigorous BCG nationwide vaccination policy for newborns until 1990, the number of COVID-19 cases among those aged <31 years was not higher than that of the older age group. the number of deaths due to COVID-19 has increased rapidly in countries in South America and South Africa, which all have high BCG vaccination coverage. Arlehamn SCL et al. conducted subsequent analysis of updated data and found that the protective association of the BCG vaccination was attenuated [28]

the most convincing support for the "acute BCG protection hypothesis" comes from a very recently published, double blind placebo controlled trial. Giamarellos Bourboulis, et al. [29] enrolled recently hospitalized elderly (>65y old) patients to receive BCG vaccination, or placebo (0.1.ml normal saline) by intradermal injection in a double blinded, randomized fashion. The primary outcome was the time interval to the first infection post hospital. Patients were followed for 12 months. Most importantly, significant protection against respiratory tract infections of probable viral origin was observed in the BCG group.

Conclusion

We can conclude our review by:

1. COVID-19 pandemic would be a worsening of the TB epidemic globally, for a variety of reasons, such as additional pressures on health systems by COVID-19 resulting in weakening of the National TB programmes and the potential biological effects of the interaction of the two infections

2. Patients with TB had 2.17 times higher risk of death than those without. When assessed in patients admitted to hospital, those with TB had a similar higher risk of death. recovery in patients with TB was 25% lower than in those without. recovery was similar in admitted patients. There was a 20% higher risk of admission in patients with TB.
3. a combination of trained immunity and heterologous immunity by some BCG epitopes could provide immunity through T-cell cross-reactivity that could be responsible for the beneficial clinical effects of BCG.this called (acute BCG protection) which mean how take BCG vaccine at recent time and can give some protection agains covid-19 and other viral infection for at least 1 year
4. there is no biologic evidence that newborn/baby age delivered BCG vaccination may have any protective effects against COVID-19, especially in adults and the elderly (who have received the BCG vaccine as an infant or child)

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