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Commentary

Bacillus Calmette–Guérin vaccine, antimalarial, age and gender relation to COVID-19 spread and mortality



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ABSTRACT

COVID-19 is affecting different countries all over the world with great variation in infection rate and death ratio. Some reports suggested a relation between the Bacillus Calmette–Guérin (BCG) vaccine and the malaria treatment to the prevention of SARS-CoV-2 infection. Some reports related infant's lower susceptibility to the BCG vaccine. Some other reports a higher risk in males compared to females in such COVID-19 pandemic. Also, some other reports claimed the possible use of chloroquine and hydroxy-chloroquine as prophylactic in such a pandemic. The present commentary is to discuss the possible relation between those factors and SARS-CoV-2 infection.

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1. Introduction

COVID-19 affected around 5,000,000 around the world with a different percentage of mortality with overall mortality rate of about 6.6% [1]. COVID-19 disease is related to the respiratory infectious diseases caused by coronavirus, the recent attacks of coronavirus were in 2003 caused the severe acute respiratory syndrome (SARS) followed by the Middle east respiratory syndrome (MERS) in 2012 [2,3]. Animals are the source for coronaviruses, the Camel for MERS and Civet for SARS, the virus is transferred to these animals from bats [3,4].

The COVID-19 is transmitted during close contact with infected subject via droplets and fomites. Till now the airborne spread of new coronavirus has not been proven and so this route of transmission is not believed to be the main driver of virus transmission, but also it is possible for the new virus to be transmitted through

airborne in specific conditions (e.g. aerosol generating procedures) [5,6].

Another route which is suspected to play a role in transmission of the infection is the fecal-oral route [7]. This possibility was supported by the results of stool samples analysis through PCR for 8 subjects that were confirmed to be infected with the new coronavirus [7]. Also, another study showed that the genome of the new coronavirus was also detected in the esophagus, stomach, and intestine and this support the possibility of the gastrointestinal route transmission [8].

The majority of subjects have a mild presentation to the infection and mainly start with fever and dry cough that recovers without any interventions; also the flu-like symptoms, malaise, headache, and muscle pain might develop early [9]. Younger subjects represent the majority of mild cases [10]. These mild symptoms might develop to more severe presentation presented as shortness of the breath, that mainly occurs after one week from initial presentation [11], and pneumonia which require hospitalization of the infected subjects. The severity of the infection might progress to develop respiratory failure, multi-organ failure or septic shock [11].

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2. Vaccine, age and gender relation to COVID-19 infection

The infection started in China in which more than 80,000 confirmed cases were diagnosed with the new coronavirus, the death rate in China is around 4%, while it is greater than 10% in Italy. SARS-CoV-2 transferred from China to most countries around the world. The spread of the disease became higher in Europe and the USA compared to China (Table 1). The number of confirmed SARS-CoV-2 cases detected in countries neighbouring China e.g. Kazakhstan, India, and Korea was lower than that detected in The USA and Europe e.g. Italy, Spain, France, and the UK. To the extent that a close contact area to COVID-19 source, Hong Kong, has around 1000 confirmed-cases with very low mortality-rate of 0.71%. The USA now became the highest country with confirmed COVID-19 cases and progressing. One confusing debate raised right now is the possible relation between the vaccination schedule in different countries and its possible relation to the prevention of the spread of SARS-CoV-2 infection. Also, during the current COVID-19 outbreak, it was reported that infants are less susceptible to such a violent virus [10,12]. One of the proposed explanations is the presence of cross reaction between SARS-CoV-2 and any of childhood vaccines [13]. One of the vaccines that were related to COVID-19 is the Bacillus Calmette–Guérin (BCG) which originates from an attenuated strain of *Mycobacterium Bovis* for prevention of *Mycobacterium tuberculosis* infection that causes disseminated and meningeal tuberculosis [14]. Many countries stopped using BCG vaccine except for high risk vulnerable groups [15] e.g. Italy, the USA, the UK, Spain, and France. Other countries are still using BCG vaccine till now e.g. African and Asian countries as shown in Fig. 1A [16]. Correlating different countries' SARS-CoV-2 infections and the recorded death rates (Table 1 and Fig. 1B) with Fig. 1A suggests that there is a possible effect of BCG vaccination in decreasing COVID-19 spread and mortality rates in those countries receiving the BCG vaccine. The USA, Spain, Italy, and the UK have the highest number of confirmed cases of SARS-CoV-2 infection and mortality even compared to the disease country of origin, China (Table 1 and Fig. 1B).

This possibility could be due to the expected preventive immunization role of the BCG vaccine on the lungs and other organs. What is noticeably parallel between *Mycobacterium tuberculosis*

(TB) and SARS-CoV-2 is that both of them attack primarily the lungs and interfere with host immunity. Besides the main role of the BCG vaccine in the prevention of TB but there is also a sequence of non-specific effects that could be harboured [17]. Such non-specific effects are termed heterologous effects which are commonly accompanied by live attenuated vaccines e.g., BCG, measles vaccine, oral polio vaccine, smallpox vaccine) that have been shown to non-specifically lessen mortality in addition to prevention of the targeted infections especially in low income countries following immunization programs [18] It was reported that live attenuated measles-mumps-rubella vaccine (MMR) could protect against nosocomial infectious diseases and respiratory syncytial virus [19] Heterologous effects of BCG accordingly can protect against non-mycobacterial infections to generally lower respiratory tract infections in children through activation of innate immunity memory based myeloid cells, a process termed trained immunity [20–22]. BCG vaccination is associated with a 30% reduction in mortality rate by pathogens especially in developing countries [23] and 50% reduction in mortality related to pneumonia [24]. The favourable non-specific effects of the BCG vaccine persist for a time after the neonatal period up to 10 years [25]. Trained immunity is referred to innate immune system that could display memory characteristics, after spiked by pathogens or certain live attenuated vaccines (“training effect”), not only toward the same infectious agents but also non-specifically against different pathogens (cross-protection). Trained immunity cannot be defined as sole innate as it is induced only secondary to primary infection. Meanwhile, it is different than adaptive because it shows non-specific response compared to T/B cell responses [26]. The overall values of trained immunity is attributed to long-term sensitivity of innate immune cells to any microbial stimuli, increasing the response to the same and different subsequent stimuli, and consequently increased cytokine production (not only against TB but also against bacteria, viruses, and even parasites) mediated by monocytes and natural-killer (NK) cells with a memory-like effect via and chromatin remodelling through histone modifications, leading to an enhanced gene transcription upon re-stimulation (especially the up-regulation of IL-1 β) [27], and changes in intracellular metabolism [28–31]. When trained immunity is induced in monocytes in response to microbial molecules as β -glucan, there

Table 1

Comparative illustration of relationship between vaccination schedule and total deaths per 1 million people in different countries in a descending arrangement; (data collected on 18 May 2020).

Countries	BCG	MMR	OPV	Total cases	Total cases/1 million people	Total deaths	Total deaths/1 million people
Belgium	No	Yes	Yes	55,280	4,772	9,052	781
Spain	No	Yes	Yes	277,719	5,940	27,650	591
Italy	No	Yes	Yes	225,435	3,728	31,908	528
UK	No	Yes	Yes	243,695	3,592	34,636	511
France	No	Yes	Yes	179,569	2,752	28,108	431
Sweden	No	Yes	Yes	30,143	2,987	3,679	365
Netherlands	No	Yes	Yes	43,995	2,568	5,680	332
USA	No	Yes	Yes	1,527,664	4,619	90,978	275
Switzerland	No	Yes	Yes	30,587	3,537	1,881	218
Canada	No	Yes	Yes	77,002	2,042	5,782	153
Germany	No	Yes	Yes	176,651	2,109	8,049	96
Austria	No	Yes	Yes	16,242	1,805	629	70
Poland	Yes	Yes	Yes	6,347	1,146	298	54
Croatia	Yes	Yes	Yes	2,226	542	95	23
Russia	Yes	Yes	Yes	281,752	1,931	2,631	18
Bulgaria	Yes	Yes	Yes	2,235	321	110	16
Egypt	Yes	Yes	Yes	12,229	120	630	6
S. Korea	Yes	Yes	Yes	11,065	216	263	5
China	Yes	Yes	Yes	82,954	58	4,634	3
Kazakhstan	Yes	Yes	Yes	6,440	343	34	2
India	Yes	Yes	Yes	96,169	70	3,029	2
Hong Kong	Yes	Yes	Yes	1,056	141	4	0.5

BCG (Bacillus Calmette–Guérin), MMR (Mumps–Measles–Rubella), OPV (Oral Poliovirus Vaccine).

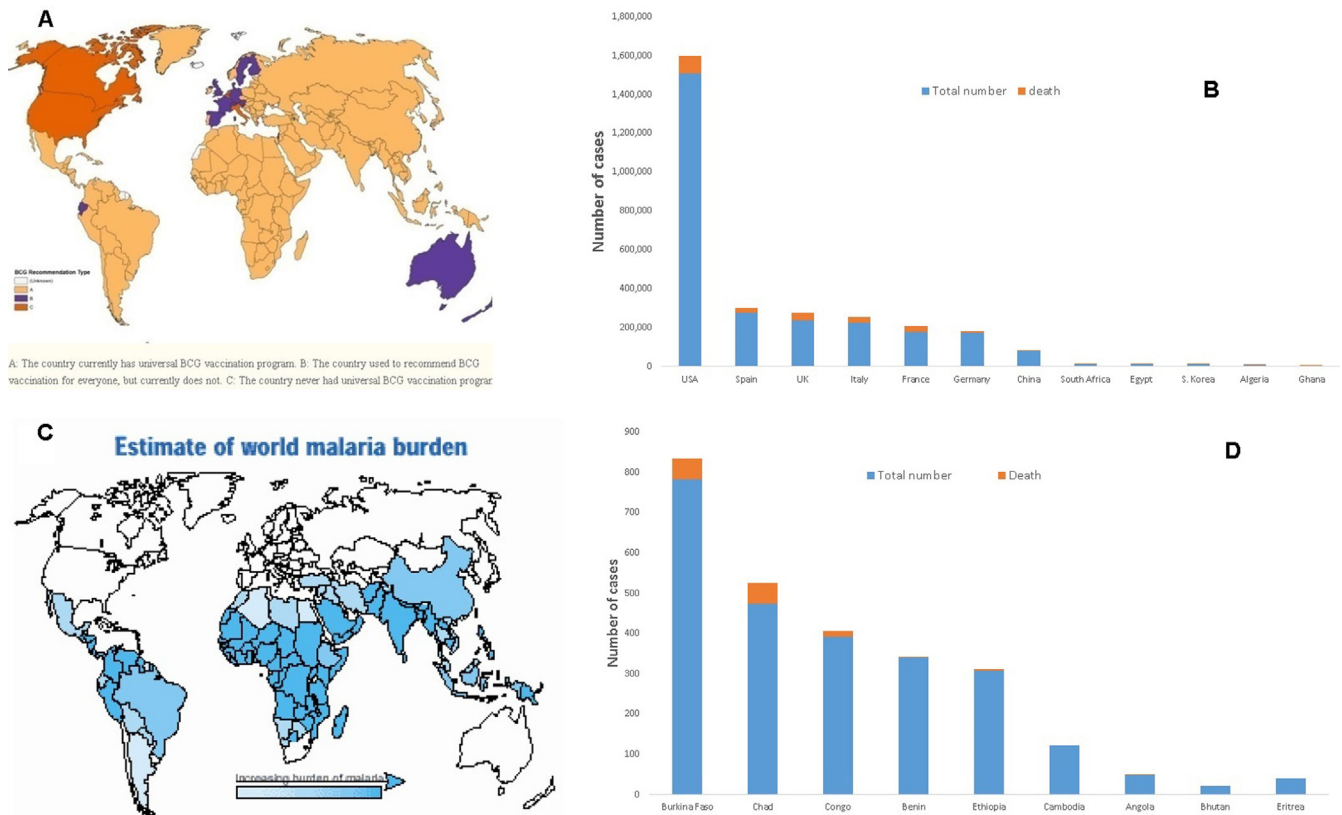


Fig. 1. A. Map displaying BCG-vaccination policy by country (adopted from [16]); B. Number of confirmed COVID-19 cases and death cases in certain countries; C. The estimate of world malaria burden (adopted from [57]); D. Number of confirmed COVID-19 cases and death cases for countries receiving antimalarial treatment.

is a relevant increase in cellular aerobic glycolysis and glutamine metabolism via a central regulatory mechanism of mTOR-HIF1 α pathway [32,33]. Cytokines production after BCG vaccination, illustrated and figured by different studies [34,35], are represented in increasing Interferon-gamma (IFN γ) and pro-inflammatory cytokines Interleukins IL-1 β , IL-2, IL-6, IL-8, IL-10, IL-12, IL-17 and tumor necrosis factor (TNF) as a response to non-mycobacterial stimulation in both infants and adults [22,30,36,37], with higher production in vaccinated females and hence the beneficial effects of BCG is more evident in females [38]. This is remarkable by looking into the percentage of deaths to COVID-19 that was higher in males rather than females. Cytotoxic T-lymphocytes could also be driven by IL-2, IL-12, TNF, and IFN- γ . IFN- γ is secreted by T-cells and Natural-killer (NK) cells and has many roles as antiviral activity, strong regulatory of the-immune response, stimulation of phagocytic bactericidal activity, induction of antigen presentation through major histocompatibility-complex (MHC) molecules, arrangement of leukocyte-endothelium interactions and effects on cell proliferation and apoptosis [39]. IL-8 is crucial in the innate response to bacterial infection by stimulating neutrophil chemotaxis and macrophage triggering [22]. TNF could lead to the activation of beneficial regulatory T cells [30].

For such non-specific mechanisms and evidences, we assume that BCG can be used as an immune modulator to protect against COVID-19 by allocating pulmonary cells under continuous stress which is unfavourable for multiplication of SARS-CoV-2 inside. This strategy will be very helpful in epidemic-control, preventing the spread of infection, limiting the course of the disease and reducing morbidity and mortality rate. This is not the first time to recommend BCG to non-specifically protect or even treat many pathogens other than TB and diseases especially pulmonary diseases. BCG has shown a protective effect against leprosy which is likely due to cross reactivity with mycobacterial antigens [40]. Other

studies reinforced the nonspecific effects against leishmania and malaria decreasing their risks and neonatal mortality [41,42]. Some experimental studies showed that BCG can protect against viral pathogens [41]. BCG was considered as a supplementary treatment for non-muscle-invasive bladder cancer by triggering the body's immune system to release cytokines and activating cytotoxic cells to destroy tumour cells after/with transurethral resection of bladder tumour (TURBT) cytotoxic cells [43,44]. Also, it has a protective effect against other cancers showing an inhibitory effect on tumour growth and was reported to reduce the risk of leukemia and lung cancer [45,46]. BCG has been reported to prevent lung injury by improving the alveolar surface area which is attributed to the preserved IL-13 expression and up-regulation of Nuclear Factor Kappa-B Subunit-1 (NFkB1), Fibroblast growth factor binding protein-1 (FGF.BP1) and Vascular endothelial growth factor A (VEGF-A) genes [47]. Researchers noticed a decreased rate of allergic asthma in children immunized with the BCG vaccine with the general improvement of lung function through increasing the secretion of T-helper type-1 (Th1) cytokines [48,49].

Our advice to reallocate BCG for protection against COVID-19 is built on the capability of the BCG vaccine to induce increased cytokine production which will decrease the infectivity of SARS-CoV-2 through antiviral inhibitory cytokines, activated natural-killer cells and activated cytotoxic T-cells. Other studies suggested such correlation between universal BCG vaccination policy at birth and reduced morbidity and mortality for COVID-19 suggesting the induction of trained immunity and consequently protection against SARS-CoV-2 [34,35,50].

Another assumption is based on the continuous cytokine production in pulmonary cells after vaccination with BCG [51] will promote pulmonary cells to be more trained and adapted to cytokines for a long time and will be less responsive to side effects of cytokine storm induced by COVID-19 knowing that the cytokine

storm is the main cause of respiratory failure and death of COVID-19. [52,53] The cytokine storm of COVID-19 is a lethal immune condition characterized by activation and proliferation of macrophages, NK cells, T cytotoxic cells and the overproduction of inflammatory cytokines and mediators. The uncontrolled release of pro-inflammatory mediators, IL-6, IL-8, IL-1 β , and GM-CSF in addition to reactive oxygen species (ROS) could cause acute respiratory distress syndrome (ARDS) leading to pulmonary fibrosis and death [52]. It worth to mention that there are three established ongoing clinical trials, started in March and April 2020, to address such role of BCG vaccination in protection against COVID-19 especially for healthcare workers and WHO will evaluate the evidence when it is available [54–56].

On the other hand, in African countries, the number of confirmed cases is considered very low compared to Europe or even China. The highest country with confirmed cases is Egypt with around 10,000 confirmed cases. Malaria disease is considered as a common disease in those countries, as shown in Fig. 1C [57]. They mostly receive malaria treatment e.g. Angola, Benin, and Ethiopia, with their very low number of confirmed cases and death with low mortality rates (Fig. 1D). This finding in countries encountered malaria could be related to the malaria treatment e.g. chloroquine, which has around 50 days half-life [58], and hydroxychloroquine, which have around 40 days half-life [58], that were proven effective against SARS-CoV-2 virus [59]. This long biological half-life could be the reason for such a low number of confirmed cases and worth further investigation. Hydroxychloroquine lowers the pH which can interfere with the replication of the virus through inhibition of lysosomal activity in antigen presenting cells involving B-cells and the plasmacytoid dendritic cells. This will prevent processing of the antigen [60]. In addition to the role of chloroquine and hydroxychloroquine in immunity modulation, also they have an inhibitory effect on two essential steps needed by the new coronavirus to enter the cells, these steps are binding to receptor (angiotensin-converting enzyme 2 (ACE2)) and fusion to cell membrane through the interfering with the glycosylation of the receptor [61,62]. Again, while the full details are not known, the chloroquine and hydroxychloroquine could be recommended for the prevention of SARS-CoV-2 infection [62]. Hydroxychloroquine, also, is likely to attenuate the severe progression of COVID-19, inhibiting the cytokine storm by suppressing T-cell activation. It has a safer clinical profile and is suitable for those who are pregnant and inexpensive and more readily available. [62] However, the side effect of the chloroquine and hydroxychloroquine and any possible interaction should be taken into account [63,64].

3. Conclusions

BCG vaccine has a very important role in stimulating the immune system but requires time to do so and help in SARS-CoV-2 infection prevention. Antimalarial like chloroquine and hydroxychloroquine has a possible role as prophylactics against SARS-CoV-2 infection and transmission and worth further investigation.

We recommend people in countries like Europe and the USA to take BCG vaccine early enough to stimulate their immune systems to help in any possible next winter COVID-19 pandemic occurrence if a proper production of a vaccine for SARS-CoV-2 virus was not lunched.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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