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REVIEW ARTICLE

Potential role of Bacillus Calmette-Guérin (BCG) vaccination in COVID-19 pandemic mortality: Epidemiological and Immunological aspects

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Abstract

SARS-CoV-2 had already killed more than 400,000 patients around the world according to data on 7 June 2020. Bacillus Calmette-Guérin (BCG) vaccine is developed from live-attenuated Mycobacterium bovis, which is a microorganism found in a cow. Discovered by Dr. Albert Calmette and Camille Guérin since 1921, the BCG has served as a protection against tuberculosis and its complications. It is noticeable that countries which use mandatory BCG vaccination approach had lower COVID-19 infection and death rate. Current review aims to clarify this issue through epidemiological illustration of correlation between national BCG immunization and COVID-19 mortality, in addition to biological background of BCG-induced immunity

Epidemiological data shows that universal BCG policy countries have lower median mortality rate compare to countries with past universal BCG policy and non-mass immunization BCG. (18 May 2020). Still, the links between BCG vaccination and better COVID-19 situation in certain countries are unclear, and more data on actual infection rate using SAR-CoV-2 antibody testing in large population sample is crucial for disease spreading comparison.

Two immunological mechanisms, heterologous effects of adaptive immunity and trained innate immunity which induced by BCG vaccination, may explain host tolerance against COVID-19 infection, however, there is no direct evidence to support this biological background. Clinical trials related to BCG vaccination against COVID-19 are under investigation. Without a strong evidence, BCG must not be recommended for COVID-19 prevention, although, this should not be absolute contraindication. Risk of local and systemic complications from the vaccine should be informed to individual, who request BCG immunization.

Key words: Bacillus Calmette-Guérin, BCG, Coronavirus, COVID-19, immunization, SARS-CoV-2, vaccination

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Introduction

Since December 2019, SARS-CoV-2 had killed more than 400,000 patients around the world (Data on 7 June 2020). Every nation puts all effort to mitigate COVID-19 epidemic such as implementing lock-down policy ranging from city to national level. The lock-down policy caused not only local, but also global-scale economic crises. The hope to be back to normal life before pandemic relies solely on vaccine discovery. International collaborations among groups are currently developing various type of SARS-CoV-2 vaccines. Many prototypes are in non-human primate testing or clinical trial phase. However, vaccine readiness for mass immunization is not deterministic.

Bacillus Calmette-Guérin or BCG vaccine is a vaccine developed from weakened-live Mycobacterium bovis, which is

a microorganism found in a cow. Discovered by Dr. Albert Calmette and Camille Guérin, BCG has been used as a protective vaccine against tuberculosis (TB) and its complications since 1921. There has been a hypothesis that mass BCG immunization can alleviate the severity of disease and may even decrease the COVID-19 spreading since late March 2020.[1] It is noticeable that countries that adopt mandatory BCG vaccination approach had lower number of COVID-19 infection and lower death rate **Figure 1**. Many recent literatures concerning BCG vaccination and COVID-19 pandemic correlation were online published, there are both backing and opposing this assumption.[1-5]

Figure 1. Median per capita death rate of country group according to national BCG immunization policies.
The median deaths per million population of the country groups in accordance with vaccination policies were illustrated by ignoring the number with zero respect to date (15 Feb 2020 to 20 May 2020). A. Daily median per capita mortality rate B. Accumulative median per capita mortality rate. Python programming language with Pandas library was used as data processor. The plots are generated with the Pyplot library from Matplotlib. Abbreviations: BCG, Bacillus Calmette-Guérin; NBV, Non-mass BCG Vaccination; PBV, Past universal BCG Vaccination; UBV, Universal BCG Vaccination.

Apart from TB protection, BCG vaccine has been utilized for several purposes. It is notable for its 'heterologous immunity' against many non-mycobacterial pathogens such as virus, parasites, and bacteria.[6] BCG is also used as the treatment and possible protective agent in some malignant tumors. Intravesical BCG has become adjuvant treatment for early-stage bladder for nearly 40 years. BCG induced both dendritic cell activation and bladder cancer cells to release group of cytokines, that result in killing of tumor cells by immune-mediated cytotoxic cells. In addition, intralesional BCG injection in late stage melanoma is included as a standard treatment in the national treatment guidelines.[7]

Presently, there is no SARS-CoV-2 vaccine. The heterologous effects of BCG vaccination may have potential role on reducing disease severity or even spreading of COVID19. World Health Organization (WHO) still does not recommend BCG vaccination for SARS-CoV-2 prevention due to the lack of clinical evidence. Newly or booster vaccination in adults may risk complications. Randomized controlled clinical trials (RCT) focus on proving BCG efficacy against COVID-19 are currently conducted in several countries. Current review aims to clarify this issue through epidemiological illustration of correlation between national BCG immunization and COVID-19 mortality, in addition to biological background of BCG-induced immunity.

Data sources

Epidemiologic data was gathered from publicly open-data sources including Worldometer (Report cases and deaths of COVID-19 pandemic),[8] Our World in Data (Time-series COVID-19 deaths), BCG world atlas (BCG vaccination policies),[9] WHO (BCG coverage),[10] United Nation (Country population by age group),[11] and World Bank Group (Country income).[12] Immunological literatures were obtained from online database including Pubmed, Scopus and Google Scholar.

Correlation between national BCG immunization and COVID-19 mortality

The apparent correlation between national BCG immunization and COVID-19 situation can be a spurious relationship due to the confounding factors. Therefore, selected outcome reported by vaccination policies should be stratified according to relevant variables to see a clear picture of the issue.

Regional selection criteria for epidemiological illustration were country with more than 1 million in the number of current populations with over 100 of confirmed COVID-19 cases. These criteria are used as indicators of substantial local disease spreading.

All regions are classified base on BCG vaccination policies into 3 categories including universal vaccination, past universal vaccination, and non-mass vaccination country. Universal vaccination means that BCG is a mandatory vaccine and should be administered to all populations in the country at young age usually under 1 year with or without booster dose in later age. Past vaccination is implied when the country uses universal vaccination policy for some periods in the past. If the country has never employed mass BCG vaccination before or limited use in only a specific group that has a high-risk of TB infection, they will be grouped as non-mass vaccination.

Median deaths per million or per capita mortality rate was used to demonstrate severity of SARS-CoV-2 pandemic situation among groups with different immunization policies. Deaths per million of a country is calculated using the cumulative number of COVID-19 deaths divided by the total population of the country in a million unit. It suggests how likely an individual will die from the COVID-19. The advantage of using crude death rate over infection rate is that the number of deaths is continuously adjusting by government authority, and denominator is the number of population instead of infected cases, which may be inaccurate due to the large proportion of asymptomatic infection and limited testing number.[5]

Table 1. The median cumulative deaths per million people on 18 May 2020 according to current national BCG immunization policies adjusted by relevant factors.

Study name	RCT phase	Status	BCG strains	Countries	Participants	Outcomes
BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE)	III	Recruiting	BCG Denmark	Australia	4,170 HCWs	Reduces incidence and severity of COVID-19
Reducing Health Care Workers Absenteeism in Covid-19 Pandemic Through BCG Vaccine (BCG-CORONA)	III	Recruiting	NA	Netherlands	1,500 HCWs	Reduce absenteeism
BCG Vaccine for Health Care Workers as Defense Against COVID-19 (BADAS)	IV	Recruiting	BCG TICE strain	USA	1,800 HCWs	BCG vaccine acts as a defense against COVID-19
BCG Vaccination for Healthcare Workers in COVID-19 Pandemic	III	Recruiting	BCG Denmark	South Africa	500 HCWs	Reduce incidence of HCWs hospitalized due to COVID-19
Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19	III	Not yet recruiting	BCG Denmark	Egypt	900 HCWs	Reduces incidence of COVID-19

Table 1. (Continued)

Study name	RCT phase	Status	BCG strains	Countries	Participants	Outcomes
Performance Evaluation of BCG Vaccination in Healthcare Personnel to Reduce the Severity of SARS-COV-2 Infection (PECET)	III	Not yet recruiting	NA	Colombia	1,000 HCWs	Reduces incidence and severity of COVID-19
COVID-19: BCG As Therapeutic Vaccine, Transmission Limitation, and Immunoglobulin Enhancement (COVID-19 BATTLE trial)	IV	Not yet recruiting	NA	Brazil	1,000 confirmed COVID-19 cases	1) clinical evolution of COVID-19 2) elimination of SARS-CoV-2 at different times and disease phenotypes 3) seroconversion rate and titration.
Efficacy of BCG Vaccination in the Prevention of COVID19 Via the Strengthening of Innate Immunity in Health Care Workers (COVID-BCG)	III	Not yet recruiting	BCG Denmark	France	1,120 HCWs	Reduces incidence and severity of COVID-19
Using BCG Vaccine to Protect Health Care Workers in the COVID-19 Pandemic (BCG-DENMARK-COVID study)	III	Not yet recruiting	BCG Denmark	Denmark	1,500 HCWs	Reduce absenteeism
A Phase III, Double-blind, Randomized, Placebo-controlled Multicentre Clinical Trial to Assess the Efficacy and Safety of VPM1002 in Reducing Healthcare Professionals' Absenteeism in the SARS-CoV-2 Pandemic by Modulating the Immune System	III	Not yet recruiting	VPM1002	Germany	1,120 HCWs	Reduce absenteeism

There are 133 regions, that accounted for 97% of world population, including 109 universal vaccination, 18 past vaccination and 6 non-mass vaccination countries **Table 1**. non-mass vaccination group consists of Belgium, Canada, Italy, Lebanon, Netherlands, and United State of America (USA). Past vaccination countries are including Australia, Austria, Czechia, Denmark, Finland, France, Germany, Greece, Ireland, Israel, New Zealand, Norway, Slovakia, Slovenia, Spain, Sweden, Switzerland, and United Kingdom (UK). All African, South American, and Euro-Asian nations are presently universal vaccination. Non-mass vaccination group have the highest median deaths per million, followed by past vaccination and universal vaccination when adjusted by relevant factors including country income, population age distribution, and climate zone.[13,14] COVID-19 patients, age over 50 years old, have higher chance to die from comorbid underlying disease.[15] Countries with large proportion of high risk people have higher mortality rate. Most universal vaccinations are in tropical zone (between latitude 23.5N and 23.5S). Countries in temperate zone (latitude higher than 23.5N) have higher median deaths per million compare to tropical zone countries. Lebanon has the lowest death rate (4 deaths per million) among non-mass vaccination countries, that also lower than many universal and past vaccination nations. There were 9 territories including Belarus, Indonesia, Japan, Malawi, Nicaragua, South Korea, Sweden, Taiwan, and some states in USA, that did not enforce social distancing policy. Comparing two European countries with 'no lockdown' policy, Sweden (past vaccination country) has 366 deaths per million, while Belarus (universal vaccination country) has only 18 deaths per million.

The coverage of BCG vaccination and period of active universal vaccination policy have strong correlation with COVID-19 mortality rate from recent multivariable regression study.[2] Average years of active BCG vaccination policy were comparable between universal vaccination and past vaccination country groups, 44.9 (range 9-92) and 42.8 (range 14-65) respectively. The percentage of BCG vaccination coverage in 1-year-old infant from WHO report were 83.8% (range 38-99) in universal vaccination and 77.1% (range 17-98) in past vaccination group. European countries are suitable for illustrating the proportion of BCG vaccinated population coverage correlation with mortality rate, because Europe continent is one of COVID-19 epicenters, BCG vaccination policies are varied, territories are in the same climate zone and there are only high and middle-income countries **Figure 2**. Estimated the percentage of BCG vaccinated population is calculated from the summation of population age group, that were vaccinated with BCG, multiply by the mean BCG coverage in neonatal age from WHO data.[10] The result is then divided by the total number of populations in that country. Our analysis suggests that countries with BCG-vaccinated population in young age group and estimated coverage higher than 30% tend to have lower death rate.

The links between BCG vaccination and better COVID-19 situation in certain countries are unclear. Even though BCG was a centennial vaccine, many countries has just begun mass vaccination policy only after WHO initiated Expanded Programme on Immunization (EPI) in 1974. Thus, population age over 40 with high chance of mortality if infected with SARS-CoV-2, may never receive BCG immunization. The percentage of COVID-19 infection by age group from Korea Centers

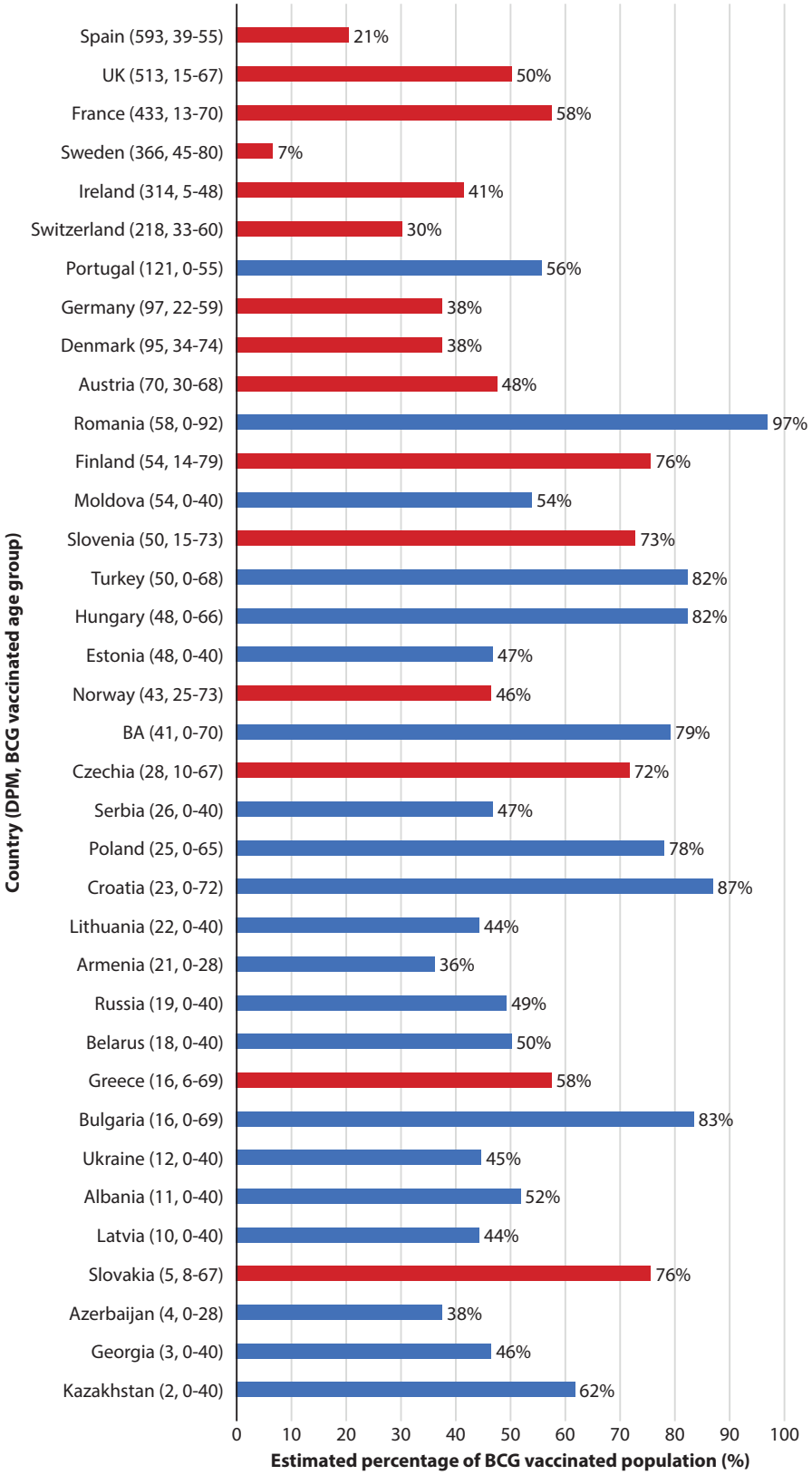

Figure 2. Bar graphs illustrate estimated percentage of BCG vaccinated population among European countries with age coverage and deaths per million inhabitants.

Bar charts demonstrate comparison percentage of BCG immunized population between European countries with age coverage period and mortality rate. Universal BCG Vaccination country will have coverage at age 0. Abbreviations: BA, Bosnia and Herzegovina; BCG, Bacillus Calmette-Guérin; UK, United Kingdom.

for Disease Control and Prevention shows nearly 60% of 11,142 confirmed cases are younger than 50 years old. This means infection rate in low-mortality age group is quite larger than high mortality group.[16] O'Neill and Netea hypothesized that BCG vaccinated children are less prone to SARS-CoV-2 infection, therefore resulting in the lower rate of spreading to elderly people.[17] However, recent research letter from JAMA reported that there was no statistically difference of infection rate in suspected symptomatic patients between those who were vaccinated and non-vaccinated with BCG and strongly concluded that there is no effect of BCG on COVID-19 spreading.[2] However, the study did not take into account of those who have mild or no symptom which could be up to 80% of actual cases,[18] and the number of asymptomatic cases in both immunized and non-immunized group may not have the same proportion as symptomatic patients, these protocol biases may cause misinterpretation of the result. Further epidemiological study of infection rate using COVID-19 antibody testing might solve this issue. The other explanation could be faster viral clearance from trained innate and adaptive immunity of BCG vaccinated population, this hypothesis also requires valid clinical studies.

Rational of BCG in decreasing the severity of COVID-19 infection

The immune response to COVID-19 was reviewed using insight lessons from the outbreak of SARS-CoV and MERS-CoV.[19] Innate immunity is the first line of host defense mechanism against viral infection. However, the data on biological aspect of BCG interaction with COVID-19 is extremely limited. Current review proposed the possibility of two immunological mechanisms that may decrease severity of SARS-CoV-2 infection. First, heterologous effect of memory T cells which can be activated in an antigen-independent manner from cytokines stimulated by a secondary infection. Second, BCG vaccination induces epigenetic reprogramming and metabolic changes of monocytes at the promoter sites of genes encoding for inflammatory cytokines such as IL-1β, TNF-α and IL-6, resulting in a more active innate immune response upon reinfection, which called trained immunity **Figure 3**.

There are several literatures ranging from epidemiological research, animal study, RCT and meta-analysis that demonstrated protective effect of BCG vaccination against non-mycobacterial respiratory tract infection.[20-27] This indirect benefit of BCG was called 'non-specific effect' which are orchestrated by innate and adaptive immune systems. Recent narrative review showed data in humans and mice that BCG vaccination could prevent subject from various DNA/RNA viruses such as Yellow fever virus, Influenza, Respiratory syncytial virus (RSV), and Herpes simplex virus (HSV).[28] A large-scale prospective study from two cohorts reported that BCG vaccination could reduce the risk of acute lower respiratory tract infections among children less than 5 years of age ranging from 17 to 37%.[29] A systematic review found that BCG vaccination could halve all-cause mortality in children younger than 5 years old in low-income countries, largely due to fewer deaths from pneumonia and sepsis.[30] There are two RCTs which showed protective effect of BCG vaccination in elderly. The first one demonstrated that the BCG immunization decreased the risk of pneumonia in elderly people, age more than 65 years old, with comorbidities, while another found

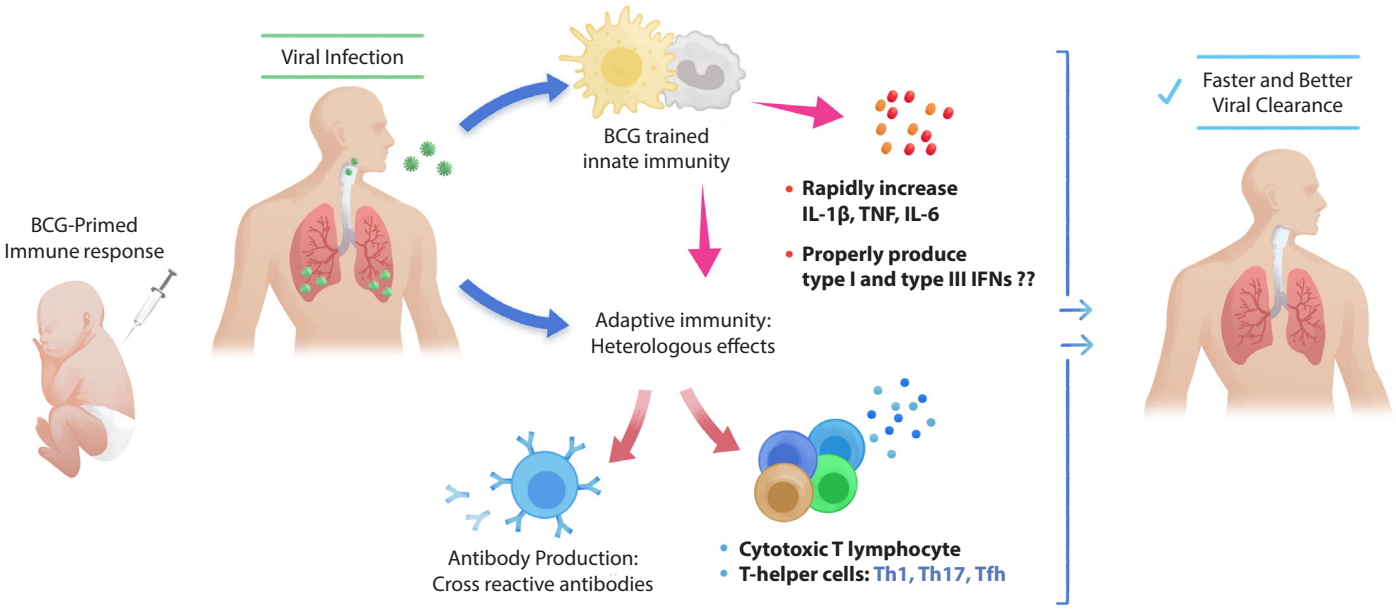

Figure 3. Proposed BCG-primed host immune responses during SARS-CoV-2 infection.
The initial phase of viral infection, BCG trained innate immunity at the site of infection orchestrate effective immune function with adaptive immunity eliminate virus from the target cells before the virus spreads. The trained macrophages recognize neutralized viruses and apoptotic cells and clear them by phagocytosis. The rapidly increasing of pro-inflammatory cytokine production from trained innate immune cells consisting of Il-1b, TNF, IL-6 and properly produce type I and type III IFNs could reduce viremia. Moreover, BCG vaccination could induce heterologous effect against virus via adaptive immune response.

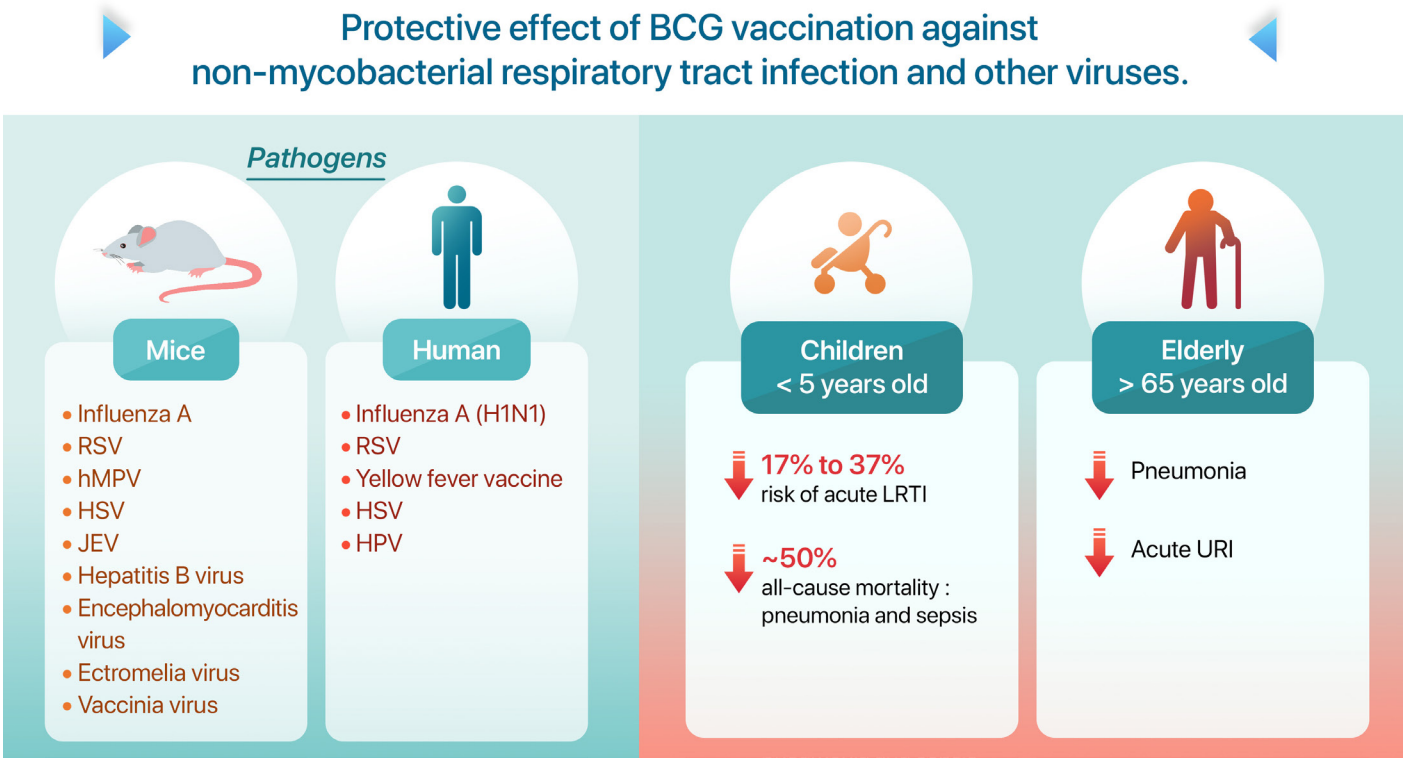

Figure 4. Infographic of BCG vaccine protective effects against various virus and respiratory tract infections.
Abbreviations; RSV: Respiratory syncytial virus, hMPV: Human Metapneumovirus, HSV: Herpes simplex virus, JEV: Japanese encephalitis virus, HPV: Human Papillomavirus, LRTI: Lower respiratory tract infection, URI: Upper respiratory tract infection

that BCG administered once a month for 3 months was significantly prevent elderly from the acute upper respiratory tract infections **Figure 4**.[31,32]

There are two possible mechanisms of BCG-induced heterologous effects in adaptive immunity. First mechanism in this part is the cross reactivity on the same memory cells between BCG vaccine antigens and antigens from unrelated pathogens which some T- and B-cell epitopes may be shared between pathogens.[33] Another mechanism is bystander activation. This contrast mechanism is performed by an adjacent, nonrelevant T cell with a specificity which is from the different cells involved in the classical immune response. The heterologous T cell is thought to be activated without strong T cell receptor (TCR) ligation, but via cytokines like IL-2 as result of the excessive activation of cells during the classical response.[34] BCG could enhance T-helper 1 and 17 (Th1, Th17) cell polarization, generation of memory CD4+ T cells, Natural Killer (NK) cell memory, and corresponding cytokine induction that are specific for non-targeted antigens.[35-37] An in-vivo study on a small group of young adults immunized with BCG vaccine demonstrated that non-mycobacterial stimuli were able to induce heterologous Th1 and Th17 cytokines, such as IFN-γ, IL-17 and IL-22, up to one year after received BCG.[36] This research showed that antigen-specific memory cells could be induced through bystander lymphocyte activation process and required minimal signals to be activated upon a second unrelated stimulus. In the aspect of T follicular helper (Tfh) cell, the in-vitro study shows that pathogen associated molecular patterns (PAMPs) of BCG are detected by Toll-like receptor 8 (TLR8) on monocytes and dendritic cells. Downstream signaling of this receptor-ligand interaction could lead to selective induction of the IL-12 cytokine and subsequent development of Tfh cells in the lymph node via upregulated IL-12-receptor signaling which killed vaccines do not produce this effect. Previously mentioned process promotes hypermorphic TLR8 polymorphism which in turn stimulate Tfh cell development that induces antibody responses to a broad range of pathogens and also augments the immune effect of other vaccines.[38]

BCG has a potential to promote host immune through innate pathway called 'Trained innate immunity'. This concept describes pathogens activate epigenetic reprogramming and metabolic changes of innate immune cells e.g. monocyte, macrophage, and NK cell, that causes an altered response towards a second challenge by unrelated stimuli.[39] The immunological phenotype of trained immunity has been proven to last up to one year, although heterologous protection against infections induced by live vaccines usually can last up to five years.[40] Recent studies suggested that there could be transgenerational effect through induction of trained immunity.[41,42] This effects of BCG against viral infection via trained immunity have been studied.[28] BCG vaccination could enhanced production of pro-inflammatory cytokines in mice and humans such as IL-1β, tumor necrosis factor (TNF) and IL-6, when monocytes are stimulated with unrelated pathogens.[43] A recent RCT in human demonstrated that BCG vaccination enhanced IL-1β production of monocytes during viral infections, rather than increased IFN-γ production by lymphocytes and NK cells, that reduced viremia during a secondary

infection with yellow fever virus.[44] Although type I interferons (IFN-α and –β) and type III interferons (IFN-γ) from innate immune system are considered to be important cytokines for defense against viral infection, there is no evidence that trained innate immunity could increase both type I and type III IFNs production.

World Health Organization approved three strains of BCG vaccines consisting of BCG–Denmark, BCG–Japan, and BCG–Russia. The different effects on tuberculosis and unrelated infections between different BCG strains have been reviewed.[45] The RCT showed significant differences in level of immune response among these three BCG vaccine strains. The proportion of polyfunctional CD4 T cells in infants immunized with BCG-Denmark or BCG-Japan was significantly higher than with BCG-Russia. The polyfunctional CD4 T cells, which produce IFN-γ, IL-2, and TNF-α, play an important role in protection against TB and provide a reservoir of memory cells that responsible for long-term protection.[46-48] Infants immunized with BCG-Japan had higher concentrations of secreted Th1 cytokines in vivo and IL-6, IL-10, MCP-1 (Monocyte chemotactic protein-1), and MIP-1β (Macrophage inflammatory protein-1beta) were significantly higher after in vitro BCG stimulation. Different from Japan strain, infants immunized with BCG-Denmark had higher proportions of CD107-expressing cytotoxic CD4 T cells (CD4 T cells with cytotoxic activity).[45] It is therefore possible that different vaccine strains have dissimilar heterologous effects. There are also difference in mortality rate among universal vaccination and past vaccination depend on BCG strains **Figure 5**. Japan strain has lower median deaths per million compare to the other WHO approved strains, BCG Russia and Demark.

Revaccinating BCG vaccine: safety and responses

BCG revaccination is not recommended by WHO. However, several countries still administered booster-dose in teenagers. There are 13 territories that are past or present BCG revaccination including Armenia, Belarus, Croatia, Kazakhstan, Malaysia, Moldova, South Korea, Singapore, Taiwan, Tunisia, Ukraine, Uzbekistan, and Fiji. The most common reaction is local reaction following intradermal BCG vaccination. The moderate to severe adverse reactions are BCG lymphadenitis, BCG induced osteitis and disseminated BCG infection. Previous several RCTs, which studied safety and immunological response of BCG revaccination in adults, found that BCG revaccination in adults is safe, well tolerated, and able to boost immune response of Th1, Th17, memory NKT-like and NK

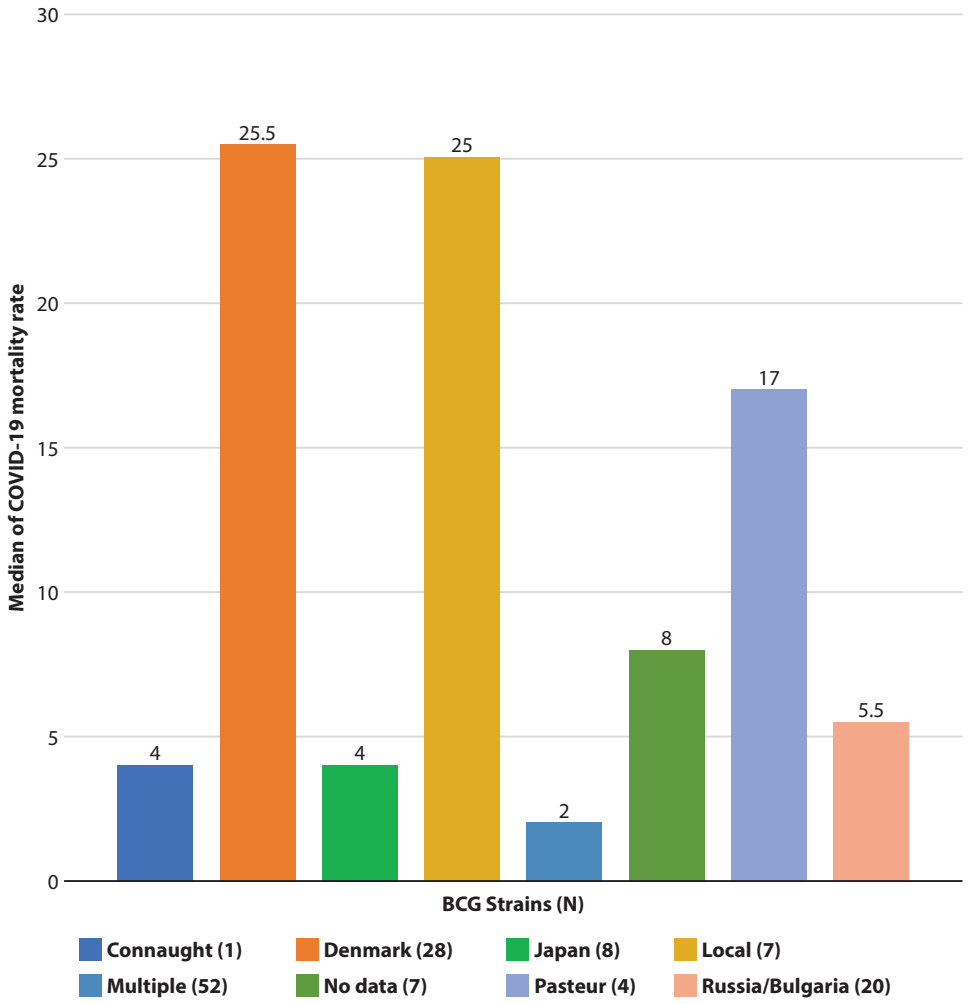

Figure 5. Median cumulative per capita death rate on 18 May 2020 of the country groups according to BCG strains usage. Mortality rate is illustrated by the median cumulative fatalities per million population. Abbreviations: BCG, Bacillus Calmette-Guérin; N, Number of countries.

cells.[49-51] The median deaths rate of COVID-19 on 18 May 2020 between BCG revaccination and other universal immunization country group were comparable, 4 [range 0-159] and 4.5 [range 0-54] respectively. This might suggest that there is no additional benefit of routine national revaccination policy in term of decreasing COVID-19 mortality rate.

Clinical trials related to BCG vaccine and COVID -19

Clinical studies concerning BCG impact on COVID-19 are needed before releasing any recommendations. Currently, at least 10 clinical trials (RCT) are conducted to determine the correlation between protective effect of BCG vaccination and

Table 2. List of registered clinical trials concerning BCG vaccine and COVID-19.

Adjusted factors	UBV group		PBV group		NBV group	
	N	Median DPM [Range]	N	Median DPM [Range]	N	Median DPM [Range]
All	109	4 [0-159]	18	62 [4-593]	6	305 [4-784]
Continent						
Africa	38	2 [0-13]	-	-	-	-
Asia	31	3 [0-84]	1	32	1	4
Europe	15	25 [10-121]	15	95 [5-593]	3	529 [332-784]
Europe, Asia	6	11.5 [2-50]	-	-	-	-
North America	9	5 [2-64]	-	-	2	216.5 [155-278]
South America	10	13.5 [0-159]	-	-		-
Oceania	-	-	2	4 [4-4]		-
Country income						
High	20	16 [0-121]	18	62 [4-593]	5	332 [155-784]
Middle	65	4 [0-159]	-	-	1	4
Low	24	0.85 [0-4]	-	-	-	-
% of high mortality risk age group						
> 40%	9	16 [1-121]	9	95 [16-593]	2	430.5 [332-529]
30-39%	20	15 [0-58]	8	35 [4-153]	3	278 [155-784]
< 30%	80	2 [0-159]	1	32	1	4
Climate zone (latitude)						
Higher than 23.5N	43	10 [0-121]	16	82.5 [5-593]	6	347 [4-784]
Between 23.5N and 23.5S	61	2 [0-159]		-		-
Less than 23.5S	5	6 [2-25]	2	4 [4-4]		

Abbreviations: BCG, Bacillus Calmette-Guérin; DPM, Deaths Per Million; NBV, Non-mass BCG Vaccination country; PBV, Past universal BCG Vaccination country; SD, Standard Deviation; UBV, Universal BCG Vaccination country.

COVID-19 infection **Table 2**.[52] Most trials aim to assess the efficacy of BCG vaccination in health care workers (HCWs) in charge of caring COVID-19 patients in aspect of reducing the number of incidence and the severity of COVID-19. Three RCTs are actively recruiting participants including BRACE clinical trial from Australia, BCG-CORONA trial from Denmark and BCG Vaccination for Healthcare Workers in COVID-19 Pandemic trial from South Africa. All three trials are administering the BCG-Denmark vaccine to participants and use normal saline as a placebo control. The Australian RCT recruits 4,170 HCWs, while the Dutch RCT aims to recruit 1,500 participants and follows by 500 participants of South African RCT. Dissimilarity among these RCTs is the BCG immunization policy of each country, Australia and Denmark are past vaccination, while South Africa is universal vaccination. The main outcome is measuring by the number of days of absenteeism over six months to one year from COVID-19 infection to determine whether there is a significant difference between the experimental and placebo cohorts. Though Dutch study plans to compare the length of unplanned absenteeism for any reason not only due to COVID-19 infection. The interesting point of RCT from South Africa is the boosting effect of BCG revaccination in participants.

There are many registered trials that have not begun recruiting. BCG Vaccine for Health Care Workers as Defense Against COVID-19 (BADAS) is a phase IV RCT conducted in United State of America (USA). USA is one of non-mass vaccinations. Expected 1,800 HCWs are allocated into two groups consisting of an experimental arm receiving the TICE strain BCG, procured from Merck (New Jersey, USA), and a placebo comparator arm. The primary outcome of this study is focused on the incidence of COVID-19 rather than the absenteeism. There is a recent phase IV RCT in COVID-19 BATTLE trial from Brazil, which is universal vaccination. The BATTLE study evaluates the impact of previous BCG vaccination (priming effect) or current BCG exposure (booster effect) on clinical evolution of COVID-19, elimination of SARS-CoV-2 at different times, disease phenotypes and seroconversion rate of 1000 cases laboratory or clinical confirmed COVID-19 infection. BCG-DENMARK-COVID study from Denmark, COVID-BCG trial from France, PECET trial from Columbia and application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19 from Egypt, they all administer the BCG-Denmark vaccine for their experimental studies. Multicenter RCT, conducted by Vakzine Projekt Management GmbH, intends to evaluate the efficacy and the safety of VPM1002, a recombinant BCG vaccine, in reducing COVID-19-caring HCWs absenteeism by modulating the immune system. This study aims to recruit 1,120 HCWs.

Discussions

There are some limitations in this review. Using mortality rate has several issues such as it is continuously changed during the pandemic because of ongoing situation, inaccuracy of mortality report due to those who died at homes or nursing care facilities and mistake in the cause of death allegation. Deaths per million is different from case fatality rate (CFR), which is the number of deaths divided by confirmed cases. It is difficult to obtained actual number of cases during pandemic because of limited confirmatory test and unknown number of asymptomatic cases. CFR is used for predicting mortality risk when infected with the virus, but deaths per million or crude mortality rate is risk of dying in certain population. In some regions, foreign migration may made evaluation of BCG vaccination influence difficult or inaccurate depend on proportion of immigrant in that local communities.

Limited COVID-19 spreading and low mortality rate in universal BCG immunization countries may not relate to the policy itself. There are some universal BCG immunization countries with high mortality rate such as Brazil and Ecuador. Brazil has employed universal BCG vaccination for 53 years. However, the number of confirmed cases and deaths is rising sharply in May 2020 probably due to seasonal effect, because June is the beginning of winter season in southern hemisphere.[13] Social distancing and wearing mask have been proven to be effective weapons against SARS-CoV-2 pandemic, while a specific vaccine is unavailable. Intensity and early onset of enforced locked down policy is obviously mitigate COVID-19 epidemic in many regions. Misinformation and disagreement between government authorities may worsen the country disease outbreak.

Conclusions

Epidemiological data shows that the universal vaccination group has lower crude mortality rate compared to past vaccination and non-mass vaccination group (18 May 2020). However, the correlation between BCG immunization policy and COVID-19 mortality is still controversial mostly due unknown confounding or unmeasurable relevant factors. The assumption that COVID-19 spreading is lower in universal BCG immunization countries, which in turn result in lower mortality rate, needs more data on actual infection rate from SAR-CoV-2 antibody testing in large population sample.[5]

Two immunological actions, that can explain improving host response against COVID-19 infection, are heterologous effects of adaptive immunity and trained innate immunity. However, there is no direct in-vitro or in-vivo evidence to support this concept. Experimental studies including many RCTs related to BCG vaccination against COVID-19 are under investigation. While awaiting result from the RCTs, BCG must not be recommended for COVID-19 prevention. However, it should not be an absolute contraindication to administer BCG when request by healthy individuals. Risk of local and systemic complications from BCG vaccination or booster dose injection should be informed before signing the consent for immunization. For more information, visit www.bcg-covid.info.

Conflict of interest

All authors declare no conflict of interest

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