

Revisiting the potential role of BCG and MMR vaccines in COVID-19

Science Progress

2022, Vol. 105(2) 1–17

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DOI: 10.1177/00368504221105172

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Abstract

Despite the development and deployment of effective COVID-19 vaccines, many regions remain poorly covered. Seeking alternative tools for achieving immunity against COVID-19 remains to be of high importance. “Trained immunity” is the nonspecific immune response usually established through administering live attenuated vaccines and is a potential preventive tool against unrelated infections. Evidence regarding a possible protective role for certain live attenuated vaccines against COVID-19 has emerged mainly for those administered as part of childhood vaccination protocols. This review summarizes the relevant literature about the potential impact of Bacille Calmette–Guérin (BCG) and measles, mumps and rubella (MMR) vaccines on COVID-19. Existing available data suggest a potential role for BCG and MMR in reducing COVID-19 casualties and burden. However, more investigation and comparative studies are required for a better understanding of their impact on COVID-19 outcomes.

Keywords

MMR, BCG, COVID-19, coronavirus, immunity

Introduction

In December 2019, a novel coronavirus strain was identified and given the name severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ It spread rapidly across

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continents and displayed an alarming exponential growth which made it a universal concern. The disease associated with this viral infection was named coronavirus disease 2019 (COVID-19) and on March 11, 2020, the World Health Organization declared it a new pandemic.² The clinical spectrum associated with the infection is variable ranging from sub-clinical infection to overt disease. Main symptoms include fever, fatigue, dry cough and myalgia, however, some individuals may experience life-threatening complications such as pneumonia and acute respiratory distress syndrome.³

Several features characterize this novel entity. Some of those include a disproportionate burden among different regions and populations. Similar to the Middle East respiratory syndrome coronavirus outcome, the disease was most prevalent among adults.⁴ Epidemiological data reveals that children had low hospitalization and intensive care unit rates, rare case fatalities, and a very mild disease progression.⁵ The reason behind this remains unclear and several factors have been considered. Some of the explanations given are that children's respiratory tracts have not been exposed to smoke and air pollution as much as adults,⁶ children's innate immune response is more stout than that of adults,⁷ and that children may have different ACE2 expression patterns,⁸ Another hypothesis suggests that recent exposure to childhood vaccines allows for low prevalence and milder COVID-19 symptoms among children. Emerging epidemiological and biological evidence suggests that the live attenuated vaccines such as the ones targeting tuberculosis, measles, and polio induce protective nonspecific immunity by a concept of 'trained innate immunity'. This cross-protective immunity has been documented in mice models and humans,^{9,10} and has been exhibited through the action of vaccines targeting seasonal influenza, *Streptococcus pneumoniae*, *Bordetella pertussis* and *Haitalicophilus influenzae type b*.¹¹

Trained immunity, also known as innate immune memory, is a relatively novel concept. It supports the idea that vaccines designed to induce adaptive immunity against a particular pathogen may also induce immunity that mitigates other infectious diseases. Trained immunity is known to be achieved by live attenuated vaccines. Unlike inactivated vaccines which consist of killed or altered pathogens, live attenuated vaccines contain a weakened version of a live bacteria or virus and can replicate inside the body; thus, they allow for an immune reaction that solidly mimics the response against a natural infection that can include non-specific immune effects. Live attenuated vaccines are considered more effective than inactivated vaccines and have been shown to provide stronger and more prolonged broad-based immune reactions.¹²

Several related aspects are under debate and yet to be confirmed. Evidence shows that trained immunity is orchestrated through the action of the cells of the innate immune system including monocytes/macrophages and natural killer cells that function against a broad range of pathogens and microbes. Despite its primary role as a first-line defense against foreign pathogens, the innate immune system can revive a previous foreign encounter and retain immunological memory. This seems familiar when it comes to the action of the adaptive immune system. However, unlike the process of adaptive immunity, trained immunity involves no antibodies, is nonspecific to the primary antigen at the first encounter, and its impact is expected to be short-lived. The action of the innate immune cells in trained immunity is associated with their epigenetic and metabolic reprogramming. The epigenetic changes include methylation, acetylation, or phosphorylation of the histones, resulting in enhanced chromatin accessibility, improved

cell activity, and enhanced transcription of genes necessary for immune response. Metabolic reprogramming leads to the regulation of the levels of certain metabolites involved in this process.^{13,14} This results in elevated production of pro-inflammatory cytokines (e.g. TNF- α , IL-1 β and IL-6) and a more rapid and qualitative defense against different stimulants.¹⁵ Figure 1, represents the process of development of trained immunity and the resultant elevated immune response upon a secondary infection. Some propose that trained immunity may also act by inhibiting pathological inflammation and microbial sepsis through the function of myeloid-derived suppressor cells (MDSCs). Several possible mechanisms underlie this novel form of trained immunity. MDSCs could act by suppressing the septic proinflammatory response, allowing the innate immune cells to combat infection. Another suggestion would be that MDSCs reduce the septic response and differentiate into other innate cells. More work is required to better understand MDSCs and their mode of action.^{16,17}

Protection against COVID-19 is a worldwide priority. Despite the development of vaccines specific for SARS-CoV-2, certain efforts are targeted toward finding and enhancing alternative practices in the fight against the novel virus during this critical period.¹⁸ Bacille Calmette–Guérin (BCG) and measles, mumps, and rubella vaccine (MMR), are

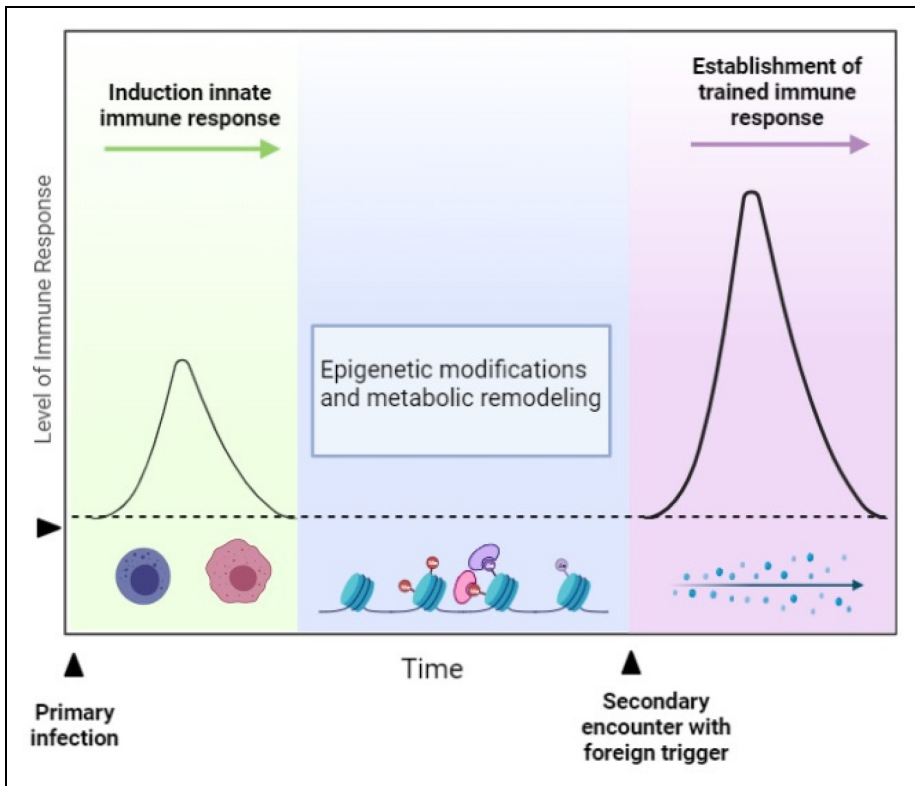


Figure 1. Schematic representation of the development of trained immunity. Created with BioRender.com.

part of childhood vaccination programs and are administered differently between regions.^{19,20} They have been highly linked with differences in COVID-19 impact on various regions and have been considered as possible alternative methods for COVID-19 prevention for several reasons.

1. The COVID-19 vaccines currently issued have been proven to be effective against the original SARS-CoV-2 strain.²¹ In fact, most clinical trials for COVID-19 vaccines have targeted the original SARS-CoV-2 spike protein.²² However, different SARS-CoV-2 variants with different genomes and more forceful modes of transmission and infection have unfolded in the United Kingdom, Brazil, South Africa, and India. This continuing rise of COVID-19 variants questions the long-term efficacy of the recently developed vaccines.²³
2. Despite the establishment of mass COVID-19 vaccination campaigns, hesitancy toward COVID-19 vaccines is tangible in different regions. This may result in the delay and even refusal of the uptake of the new COVID-19 vaccines.²⁴
3. A large part of the world remains in short supply of the newly instituted vaccines and disparate vaccination between low- and high-income countries often persist²⁵

Differences in the accessibility to the novel COVID-19 vaccines are a major reason behind considering BCG and MMR as alternative non-specific preventive measures against SARS-CoV-2 and its resulting sequelae. This is because for low- and middle-income countries, BCG and MMR vaccines are often easily accessible and affordable.²⁶ Also, most developing countries lack the proper transportation and storage utilities needed for COVID-19 vaccines such as Pfizer and Moderna, which require storage at extremely low temperatures between -90°C and -15°C . However, BCG and MMR vaccines remain stable at lower attainable temperatures.²⁷

Methodology

An electronic search was carried out using PubMed, Medline, and Google Scholar. Clinicaltrials.gov was used for clinical registries. Keywords included: “COVID-19”, “coronavirus”, “SARS-CoV-2”, “BCG vaccine”, “MMR vaccine”. The references listed were manually searched and selected and excluded reviews. Only articles published in English were reviewed. The correlation between COVID-19 outcome and each of the two vaccines BCG and MMR was discussed in separate sections.

BCG and COVID-19

BCG is one of the first live attenuated vaccines to be administered in humans. BCG is isolated from *Mycobacterium bovis* and provides protection against tuberculosis (TB), an infectious bacterial disease that affects the lungs and other organs.²⁸ Many countries such as Japan and China enforce BCG vaccine as part of the vaccination requirements for infants. Other nations such as Spain, France, and Lebanon have suspended the mandated BCG vaccination policies mainly because of their low TB incidence.²⁹ BCG is administered during infancy and has been shown to reduce mortality in children,^{30–32} The reason

behind the reduction in mortality is hypothesized to be a decrease in the subsequent risk of other diseases and infections unrelated to tuberculosis. Those infections include herpes, influenza, malaria, and others.³³

BCG is also known for its durable effect and has been shown to provide protection against TB for prolonged periods of time.³⁴ Some studies demonstrated that the BCG vaccine could provide prevention and protection against TB even after more than 30 years following vaccination.^{35,36} The durability and impact of BCG derived different hypotheses regarding its role in containing the spread of COVID-19 and reducing the burden of the virus in countries with continuing BCG immunization programs.³⁷

Different data have reported that trained immunity is provided by BCG vaccine against various viral infections, and certain studies have proposed that the BCG vaccine could have a protective effect against COVID-19 and a capacity in reducing associated lung inflammations and sepsis.³⁸ Miller et al., obtained data from COVID-19 cases and deaths for different countries with different BCG vaccination policies and found that countries without universal policies of BCG vaccination such as Italy, the Netherland, and USA have been associated with more severe morbidity and mortality compared to countries with long-standing BCG vaccination policies.³⁹ To further support Miller's study, case fatality rate (CFR) was compared among 12 countries with severe COVID-19 burden and established BCG vaccination policies. Countries that include the BCG vaccine as part of their immunization calendar displayed a significantly lower CFR compared to countries that do not administer BCG to their newborn children.⁴⁰ Similar results were obtained in a retrospective study on 174 countries. Those with high BCG coverage displayed a lower COVID-19 incidence.⁴¹ Sala and Miyakawa from Fujita Health University using linear regression modeling, found that the numbers of total cases and deaths per one million population were significantly associated with the presence or absence of policies utilizing BCG as a vaccine routinely administered for infants. The amount of variation in the number of cases and deaths was explained by BCG vaccination policy and ranged between 12.5% and 38%. The effect remained significant after controlling for the country's life expectancy and the average temperature in February and March 2020, which themselves are significantly correlated with the cases and deaths, respectively. However, the ratio between deaths and cases was weakly affected suggesting that BCG vaccination may have hindered the overall spread of the virus or progression of the disease rather than reducing mortality rates.⁴² Another study used linear mixed models, as well, and proved that countries with mandated BCG vaccination policies exhibited a significant flattening in the exponential growth of both COVID-19 confirmed cases and deaths.⁴³ To adjust for such variations and parameters, an ecological study was conducted by analyzing data of 61 factors obtained from 173 countries. Results showed that even after adjusting for morbidity, PCR-tests, age, universal health coverage, healthy life expectancy, and other factors, BCG vaccine was significantly correlated to a low COVID-19 mortality but was not associated with a reduction in the morbidity levels caused by the virus.⁴⁴ Those ecological studies unveil valuable documentations but remain limited by the potential disparities between different regions and biases associated with cross-country comparisons.

In an epidemiological study, Escobar et al. explored the prevalence of COVID-19 and BCG vaccination policies between different countries to draw a plausible association

between the two. They showed that every 10% increase in BCG index was followed by 10.4% reduction in COVID-19 mortality but stated that such data is hard to validate because of the variations in demographics and COVID-19 control strategies between nations.⁴⁵

Despite much evidence reinforcing the link between the BCG vaccine and COVID-19, certain studies did not support this idea.⁴⁶ Ricco et al., stated that this correlation does not exist and that most studies are ecological ones that do not assess confounding factors. They contend that more evidence is required to eliminate conflicts, validate this hypothesis, and overcome limitations.⁴⁷ One study based in Sweden evaluated a posed hypothesis stating that BCG can reduce COVID-19 incidence and hospitalization rates by 19% and 25%, respectively. Being an individual-based study, it eliminated certain biases and limitations associated with cross-national comparisons. This study was made possible within the same country because Sweden exhibited a low BCG coverage upon its discontinuation in 1975. Results showed no significant impact of BCG on COVID-19 and the hypothesis was rejected.⁴⁸ Similarly, a study was performed on subgroups within the same country. COVID-19 incidence was compared between bladder cancer patients who received intra-vesical BCG as part of their treatment and the bladder cancer patients who did not. Results did not indicate any protective effect for BCG against COVID-19, however, this study may be considered unsubstantial since the subjects under study are cancer patients and are considered more vulnerable to COVID-19 infections.⁴⁹

Another study was performed on the staff of Emirates International Hospital. Early on during the pandemic, the staff was offered a booster BCG vaccine. COVID-19 incidence was evaluated 3 months later. None of the vaccinated hospital staff got infected with COVID-19 while the infection rate was 8.6% among the unvaccinated group.⁵⁰ Table 1, summarizes the findings of the aforementioned research studies and indicates the type of each study and the methodologies used.

With the increasing number of reports and emerging evidence around the impact of BCG on the action of COVID-19, many concerns are yet to be addressed.

1. It is important to note that mortality and morbidity rates have shifted with time for several countries. For instance, South American countries experienced a rise in COVID-19 cases and suffered from detrimental casualties later after August 2020. This implies that the level of correlation between BCG and COVID-19 mortality may fluctuate with time. Some of the studies mentioned were performed earlier before this change and thus cannot be held reliable for providing a conclusive description regarding the impact of BCG on COVID-19.⁵¹
2. Different BCG strains, which differ both genotypically and phenotypically, are used for vaccination against TB. It has been suggested that the different BCG strains may have different levels of immune response and may result in different physiological mechanisms. For instance, one study performed on neonates in Mexico showed that the Japanese BCG strain-induced larger cytokine levels (IL-1 α , IL-1 β , IL-6, and IL-24) and a proinflammatory immune response greater than that of Danish BCG and Brazilian BCG strains.⁵² Similarly, another study suggested that the different strains of BCG and different routes of delivery can lead to distinct immune

Table 1. Characteristics and key results of studies describing the impact of BCG on COVID-19.

Type of Study	Methodology	Findings	Reference
Ecological	Regression analysis	Reduced mortality and morbidity for countries with BCG policies	Miller et al. ⁴⁰
Ecological	Descriptive analysis	Reduced COVID-19 Case fatality rates in countries without BCG vaccination policies.	Dayal et al. ⁴¹
Ecological	Cross-sectional analysis	Lesser COVID-19 incidence	Madan et al. ⁴²
Ecological	Regression analysis	Effector of incidence was associated with countries discontinued or never implemented BCG vaccination. Effector of case fatality rate was associated with countries which never implemented BCG vaccination.	Sala and Miyakawa et al. ⁴³
Ecological	Regression analysis Multivariate model	Flattened growth and death rates for countries reporting BCG vaccination policies	Berg et al. ⁴⁴
Epidemiological	Regression analysis	10% increase in the BCG index is associated with a 10.4% reduction in COVID-19 mortality.	Escobar et al. ⁴⁶
Ecological	Regression analysis	Reduced COVID-19 mortality for countries with BCG vaccination policies	Urashima et al. ⁴⁵
Epidemiological	Regression discontinuity	No association between the BCG vaccination and reduction COVID-19 cases and hospitalizations.	Clément de Chaisemartin, and Luc de Chaisemartin ⁴⁹
Epidemiological	Descriptive retrospective cross-sectional analysis	No association between the BCG vaccination and a reduction COVID-19 cases.	Karabay et al. ⁵⁰
Epidemiological	Statistical analysis	8.6% infection rate in the unvaccinated group versus 0 in the booster vaccinated	Amirlak et al. ⁵¹

responses.⁵³ This could result in disparities in the mode of action and efficacy of the BCG-induced trained immunity against COVID-19.

Clinical trials must aim to address these concerns and validate results. Over 20 clinical trials have been initiated around the globe to confirm the presence of an immune response elicited against SARS-CoV-2 and to determine the impact of BCG vaccination on

COVID-19 occurrence and severity. One double-blind study in Brazil is designed to test the effect of BCG as a therapeutic vaccine by recruiting subjects with confirmed COVID-19 symptoms. This would specify the role of the BCG vaccine on the clinical progression of COVID-19 and its capacity to eliminate the virus.⁵⁴ The current ongoing trials mainly involve adult subjects and older patients because of their higher risk of SARS-CoV-2 infection. While those trials will help in proving or eliminating several hypotheses regarding BCG vaccination and COVID-19 burden, more age groups should be included in the trials to have a clear understanding of BCG's effect and mechanism of action.

MMR and COVID-19

MMR is an attenuated combined vaccine that has revealed significant efficacy and safety. It is administered during early childhood and shows advantages in preventing illnesses and deaths caused by all three highly contagious diseases: measles, mumps and rubella.⁵⁵ An interesting finding on the non-specific effects of the measles vaccine was discovered during the measles vaccination campaign in 1979 in Guinea-Bissau, West Africa. The measles vaccination campaign reduced all-cause mortality by almost 70%, much more than could be explained by the prevention of measles infection.⁵⁶ This finding, along with other similar studies from low-income settings, led to the formulation of the hypothesis that the MMR vaccine has non-specific effects in strengthening the immune system and providing increased protection against a broad range of infections.⁵⁷ Measles has been shown to induce long-term damage to the immune system. Studies show that unvaccinated children who were infected with measles would have their immune systems come back but had 'forgotten' what was once learned. The child's immune system would have to start afresh, rebuilding immune protection against viruses and bacteria it had previously fought off.⁵⁸ Interesting similarities are noticed between measles, mumps and rubella viruses and the SARS-CoV-2 in terms of transmission and replication in the upper respiratory tract. This shed light on the presence of commonalities in their structure and pathology and attempts were made to draw a correlation between MMR vaccine and COVID-19.⁵⁹ Also, higher COVID-19 cases and fatalities were noticed in Italy as compared to China which has higher measles vaccination coverage than Italy as part of its childhood vaccination calendar.⁶⁰ This triggered Saad et al., to draw a correlation between COVID-19 burden and vaccination against measles. They suggested that similarities in the structure of measles and SARS-CoV-2 exist. This allows the MMR vaccines to induce partial protection against COVID-19 and the establishment of bystander immunity against the virus.⁶¹ Similarly, a study performed at the University of Cambridge explored the structural biology of SARS-CoV-2, measles, mumps and rubella viruses. Results demonstrated that SARS-CoV-2 and rubella viruses share 29% of their macro domains' amino acid sequence, implying that they have the same protein fold. This amino acid sequence identity includes the surface residues present in the attenuated MMR vaccine. They hypothesized that the derived antibodies against rubella can target SARS-CoV-2 and diminish its activity.⁶²

One study tested the correlation between COVID-19 severity and the levels of mumps titers resulting from the MMRII vaccine. A significant inverse relationship was drawn between the level of mump titers and the burden of COVID-19 on a sample of 50 persons. Individuals with elevated mump titer levels above 134 AU/ml were asymptomatic and functionally immune when contracting COVID-19, while individuals with mump titers below 32 AU/ml had been hospitalized.⁶³ Another association was drawn in a study done in the United States. Infants less than 12 months of age displayed a relatively elevated number of COVID-19 cases as compared to children 2 years of age. This was attributed to the fact that children in the United States do not receive their MMRII vaccination before 12 months.⁶⁴ However, such studies are often based on unreliable data. The coverage of the vaccine and the differences in COVID-19 testing between regions may result in errors in the estimation of the number of cases and fatalities. Despite this, more efforts were invested into understanding the role of MMR. One recent study investigated the potential heterologous immunity provided by the MMR vaccine against COVID-19 by measuring the T-cell response to MMR and SARS-CoV-2. They harvested the T-cells of uninfected individuals that are immunized against COVID-19 and others infected with COVID-19 but are not immunized. They observed, *in vitro*, a similar T-cell response against SARS-CoV-2 antigens and MMR vaccine antigens, and implied that the COVID-19 outcome is reduced in MMR vaccinated individuals through the development of cross-reactive effector memory T-cells (T_{EMR}).⁶⁵

Even though the MMR vaccine has been proven to have relatively satisfactory protection, it has been shown to elicit an immune response only up to 10 years upon its administration. A large subject sample immunized with MMR displayed a reduction in antibody levels after 10 years as reported in an Italian study.^{4,66} This could explain how older adults have more severe COVID-19 outcomes and implies that the MMR memory response has waned off below the desired levels for protection against COVID-19.⁶⁷ Another study was performed on healthcare workers who were priorly immunized against measles using the MMR vaccine due to a measles outbreak in Sweden. The aim was to investigate the role of recent MMR vaccination on COVID-19 infection and disease progression. The odds ratio (OR) for testing positive in recently vaccinated compared to not recently vaccinated females (1.01) was insignificant but was significant for males (0.43) and implied a 57% efficacy for MMR in preventing COVID-19 symptoms and complications among them. However, these results are subject to bias, unrepresentative sampling, residual confounding and cannot be considered conclusive.⁶⁸

To further assess the role of MMR on COVID-19 when administered to adults, one epidemiological study was performed on 257 military personnel of the same age and sharing the same accommodation. 38 subjects have been given the booster MMR vaccination. Two months later, and after one of them tested positive for COVID-19, all individuals were scanned for COVID-19 immediately or after 14 days of quarantine. Results showed that non-vaccinated individuals had higher rates of COVID-19 incidence than the vaccinated ones. However, all experienced similar mild to moderate disease progression.⁶⁹ Another study was conducted in Mexico on 255 subjects who were given the MMR vaccine right before the outbreak of COVID-19 because of a rise in measles cases. The vaccinated individuals were later followed up prospectively. Notably, all MMR vaccinated individuals infected with COVID-19 displayed a mild disease progression. None of the vaccinated

individuals experienced severe complications despite having comorbidities such as hypertension, diabetes, and asthma.⁷⁰ Table 2, summarizes the findings of the aforementioned research studies and indicates the type of each study and the methodologies used.

Very few clinical trials have been initiated in an attempt to study the impact of the MMR vaccine on COVID-19. One blinded, randomized, placebo-controlled trial is currently ongoing. Its primary aim is to evaluate the efficacy of the MMR vaccine in preventing SARS-CoV-2 infection and burden among health workers. An interim analysis showed that MMR did not prevent the contraction of COVID-19, however, the severity of the disease was significantly reduced among the vaccinated participants. Two doses of MMR resulted in a 51% and a 78% risk reduction in COVID-19 symptoms and treatment, respectively.⁷¹ Another international ongoing trial was initiated at the Washington University School of Medicine. It aims to enroll up to 30,000 healthcare workers in Canada, Ghana, Ireland, South Africa, Uganda, United Kingdom, United States, Zambia and Zimbabwe. Depending on the country and its vaccination policies, the participants will be given the MMR vaccines either for the first time or as a booster and its impact on the front liners will be interpreted.⁷² Another trial involving healthcare workers

Table 2. Characteristics and key results of studies describing the impact of MMR on COVID-19.

Type of Study	Methodology	Findings	Reference
Epidemiological	Descriptive retrospective cross sectional analysis	Negative correlation between level of mumps titers and COVID-19 severity	Gold et al. ⁶⁴
Epidemiological	Single-center, observational, descriptive and prospective study	Elevated COVID-19 incidence among unvaccinated infants	Cilleruelo et al. ⁶⁵
Epidemiological	Descriptive quantification analysis	COVID-19 outcome is reduced in MMR vaccinated individuals through the development of cross reactive effector memory T cells	Carryn et al. ⁶⁷
Epidemiological	Test negative case-control study	Negative odds ratio for testing COVID-19 positive for MMR-vaccinated males but not females	Lundberg et al. ⁶⁹
Epidemiological	Retrospective cohort analysis	Lower COVID-19 incidence among individuals who received booster MMR vaccination. No difference in COVID-19 morbidity.	Yengil et al. ⁷⁰
Epidemiological	Prospective observational study	Mild diseases progression among all MMR vaccinated individuals infected with SARS-CoV-2.	Larenas Linnemann et Rodriguez-Monroy ⁷¹

was launched at Louisiana State University Health Sciences Center and tends to ambitiously identify the role of MMR in preventing COVID-19 induced sepsis.⁷³

The different hypotheses, scientific derivations, and clinical evidence regarding the impact of BCG and MMR on COVID-19 produce contradictory results. Most studies tend to display a tight correlation between these live attenuated vaccines and COVID-19. However, those population-level associations are questioned. Current statistical evidence shows that the countries with the largest increases in fatalities are Columbia, Peru, Brazil, Mexico, and South Africa, which all have high BCG and MMR coverage.⁷⁴ Those are low-income countries that exhibit unfavorable levels of social determinants of health. The low socioeconomic status, low education levels, high incidence of communicable and non-communicable diseases, malnutrition and absence of health services experienced by these nations can negatively shape healthcare and public health outcomes.⁷⁵ Such social determinants of health have been highly correlated with severe COVID-19 burden.^{76,77} This could possibly explain the high prevalence of COVID in many low-income countries with high BCG and MMR coverage.

Limitations

We reviewed only medical literature published in English language. Publication bias where authors tend to publish mainly manuscripts with positive or statistically significant results has to be considered. Research data regarding the impact of BCG on COVID-19 is more abundant than that on the impact of MMR on COVID-19. Results describing the impact of either BCG or MMR independently on COVID-19 may have been the outcome of both vaccines. The published reports do not describe the simultaneous effect of both vaccines. This review did not consider the impact of COVID-19 pandemic on childhood vaccination programs given the fact that many countries reported a decrease in their routine vaccination coverage as a result of the pandemic.⁷⁸

Conclusion

It is difficult to establish a clear association between COVID-19 infection outcome and BCG or MMR vaccinations given that other live attenuated vaccines and other factors may be involved and can affect the outcome. The present data from published reports display a difference in the severity of COVID-19 symptoms and outcomes among various populations with different vaccination policies. Records also show that while COVID-19 is prevalent among adults, children display a lower incidence rate and experience a mild or complete absence of symptoms. Some observations reported a rise in COVID-19 cases among adolescents and children along with the rise of the Delta variant, however, no significant changes in its severity were documented. The relationship between age and COVID-19 cannot be firmly elucidated yet and requires the induction of well-structured comparative studies. The growing evidence around the impact of MMR on COVID-19 provides a lead for conducting more investigations on this topic. Preclinical trials utilizing animal models can be used to further assess the present findings. Host response to SARS-CoV-2 and its progression can be monitored and evaluated in nonhuman primates upon the administration of the BCG and MMR. Clinical trials

involving different human populations and age groups must also be conducted. Such trials would answer the pool of questions regarding the vaccines' durability, specificity, and overall impact on SARS-CoV-2. Clinical trials involving both MMR and BCG vaccines simultaneously must also be considered when assessing the role of these live attenuated vaccines on COVID-19 burden. Despite the development of vaccines specific for SARS-CoV-2, the COVID-19 pandemic remains a global challenge. With the worldwide hesitancy and unequal access to COVID-19 vaccines, all tools to reduce COVID-19 burden are welcomed. The BCG and MMR would create opportunities for protection for populations with limited availability of COVID vaccines. Also, the continuing emergence of unanticipated variants may render the impact of vaccines developed against COVID-19 less influential. BCG and MMR could be used as an ancillary tool to reinforce trained immunity for non-specific activity against these variants.

Moreover, the rise in COVID cases and fatalities among low-income BCG and MMR-vaccinated populations raises several concerns implying that the negative effects of substandard social determinants of health may outweigh any protective effect exerted by these vaccines.

Validating the hypotheses posed regarding the influence of MMR and BCG vaccines could open the door for reevaluation and restructuring of vaccination protocols worldwide and may allow for the establishment of new emergency guidelines and measures against different pandemic threats.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

An approval from the Institutional Review Board (IRB) was not needed for conducting this review.

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