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PERSPECTIVE

Repurposing of the childhood vaccines: could we train the immune system against the SARS-CoV-2

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ABSTRACT

Introduction: The COVID-19 pandemic is a globalized health concern caused by a beta-coronavirus named Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Since December 2019, when this outbreak flared in Wuhan, China, COVID-19 cases have been continuously rising all over the world. Due to the emergence of SARS-CoV-2 mutants, subsequent waves are flowing in a faster manner as compared to the primary wave, which is more contagious and causing higher mortality. Recently, India has emerged as the new epicenter of the second wave by mutants of SARS-CoV-2. After almost eighteen months of this outbreak, some COVID-19 dedicated therapeutics and vaccines are available, and a few are under trial, but the situation is still uncontrolled.

Area covered: This perspective article covers the repurposing of childhood vaccines like Bacille Calmette–Guerin (BCG), Measles, Mumps, Rubella (MMR), and Oral Polio Vaccine (OPV), which are live attenuated vaccines and have been shown the protective effect through 'trained immunity and 'crossreactivity.'

Expert opinion: This perspective article has suggested that combinatorial use of these childhood vaccines might exert a better protective effect along with the available COVID-19 therapeutic and vaccines which could be considered as a preventive option against SARS-CoV-2 infection as well as its subsequent waves.

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COVID-19; repurposing of vaccines; Bacille Calmette–Guerin (BCG); Measles-Mumps-Rubella (MMR); yellow fever; oral polio vaccine (OPV)

1. Introduction

The COVID-19 pandemic is a globalized public health concern and caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which emerged in December 2019 in Wuhan city of China. Due to the emergence of SARS-CoV-2 mutants (more contagious and faster spreading nature), this has led to over 182 million confirmed cases with more than 3.9 million deaths globally (2 July 2021) [1]. SARS-CoV-2 predominantly infects lower airways that create respiratory problems and systemic illness, which more significantly progresses to a severe form of pneumonia-like conditions in 10–15% of patients [2]. World Health Organization (WHO) declared COVID-19 situation as a pandemic on 11 March 2020.

To date, seven coronaviruses {229E, NL63, OC43, HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2} crossover the species barrier and infect the human [3,4]. In past decades, two beta coronaviruses (SARS-CoV and MERS-CoV) have caused the 10000 plus cases cumulatively with the mortality rate of 10% and 37% respectively which were mild and epidemics [4,5]. SARS-CoV-2 is an enveloped positive-sense ss-RNA that belongs to the beta coronaviruses which caused the COVID-19 outbreak. After almost sixteen months of this outbreak, some COVID-19 dedicated therapeutics and vaccines are available and the trial of a few are ongoing, however the situation is still uncontrolled. To manage COVID-19, researchers have suggested repurposing the drugs and vaccines as the potential options which are currently under clinical trials. This perspective article discusses the repurposing of childhood vaccines to prevent SARS-CoV-2 infection and its severity, along with the available COVID-19 therapeutics and vaccines. This combination could be considered as a preventive option against SARS-CoV-2 infection as well as its subsequent waves.

2. Repurposing of the vaccines

Research from epidemiological studies has shown that various vaccines (live-attenuated vaccine and non-live vaccines) like the measles vaccine (MV), Measles-Mumps-Rubella (MMR), yellow fever, Bacille Calmette–Guerin (BCG), oral polio vaccine (OPV), Smallpox, and Diphtheria–Tetanus–Pertussis (DTP) associated with lowering all-cause mortality in children below 5 years of age when administered in single or in combination [6–15]. These nonspecific or heterologous protective effects of vaccines have suggested their repurposing/repositioning. Among these vaccines, some have been repurposed against the various diseases and shown protective effects (Table 1) because they can enhance innate immunity. Most recent epidemiological and clinical studies suggest that SARS-CoV-2 selectively target the adult, elderly peoples, and patients with comorbidities as compared to the healthy young peoples

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Article highlights

- SARS-CoV-2 is the causative agent of COVID-19.
- SARS-CoV-2 mutants are more contagious and causing higher mortality across the globe which is the major cause of its subsequent waves.
- Childhood vaccines exert a protective effect through 'trained immunity' and 'cross-reactivity' against infections.
- Repurposing of childhood vaccines could be considered as a preventive option along with the available COVID-19 therapeutic and vaccines.

and children below 10 years [16,17]. The immunological window plays a crucial role in the protection of healthy young people and children from COVID-19.

3. Heterologous or nonspecific effects (NSEs) of vaccines

Heterologous protective effects or nonspecific effects of vaccines are also known as off-target effects and can provide better protection than their pathogen-specific intended purpose [19,20]. Epidemiological, immunological, and clinical studies elucidate that vaccines can affect the organism's immune response other than their earlier pathogen-specific use. Bacille Calmette–Guerin (BCG), oral polio, measles, smallpox, and yellow fever vaccines may reduce mortality and severity of disease from infections other than own pathogens related diseases [7–15,21,22]. Among them, some vaccines have shown their heterologous protective effect against specific cancers and autoimmune disorders [13,23]. Basic biological mechanisms which have shown the heterologous protective effect of vaccines are still not fully elucidated, but based on the epidemiological, immunological, and clinical studies, several facts could explore few potential mechanisms [24–28].

- Induction of the trained immunity through epigenetic reprogramming of innate immunity provides a better protective effect against reinfection.
- Immune modulation of innate immune cells memory (natural killer cells and monocytes), adaptive immune cells memory (Th1, Th17, and CD4 cells), and cytokine responses (IL17, IL22, IL 1b, IL6, TNFa1, and IFNc).
- Enhancement of innate immune responses (Antibodies titer) to unrelated antigens.
- Cross-reactivity between communal epitopes of apparently unrelated pathogens.

4. Trained immunity and cross-reactivity: mystery behind the heterologous protective effects of vaccines

Heterologous protective effects of vaccines are usually governed by innate immune cells (natural killer cells and monocytes) that show the memory-like response and are popularly called trained immunity [24,25]. Trained immunity occurs due to epigenetic reprogramming through histone modifications that further transform the expression patterns of several genes and have shown the protective effects against secondary infections [29]. Increased intensity of the pattern recognition receptors on the surface of innate immune cells may involve the recognition of pathogens and further their clearance through inflammatory responses [30]. Earlier research also showed that autophagy, a phenomenon of the proteolytic degradation of cytosolic components at the lysosome, contributed to BCG-induced trained immunity [31]. Cross-reactivity is another means which can contribute to heterologous protective effects of vaccines because these vaccines possess similar cross-reactive antigenic epitopes from the

Table 1. List of childhood vaccines that have heterologous or nonspecific protective effect against various pathogens or diseases.

Vaccines	Types of vaccines	Pathogen-specific intended use	Heterologous or nonspecific protective effect against the pathogens or Diseases	Possible mechanisms	References
Bacille Calmette-Guerin (BCG) vaccine	Live-attenuated	*M.tuberculosis M.leprae and Buruli Ulcers*	Bladder cancer All-cause of infectious diseases, **COVID-19**	Trained Immunity, Immune-modulation Cross-reactivity	[13,14,20,22,23,28,29,31–39,42–48]
Measles vaccine	Live-attenuated	Measles virus	*H. influenzae S. pneumonia*, **COVID-19**	Trained Immunity, Immune-modulation Cross-reactivity	[6,7,50,54]
Measles, Mumps, Rubella (MMR) Vaccine	Live-attenuated	Measles, Mumps, and Rubella viruses	Respiratory infections, **COVID-19**	Trained Immunity, Immune-modulation Cross-reactivity	[8,51–53]
Yellow fever vaccine	Live-attenuated	Yellow fever virus	*H. influenzae S. pneumoniae*	Trained Immunity, Immune-modulation Cross-reactivity	[9]
Smallpox vaccine or Vaccinia vaccine	Live-attenuated	Smallpox virus	All-cause of infectious diseases, Malignant Melanoma	Trained Immunity, Immune-modulation Cross-reactivity	[12,13]
Oral polio vaccine	Live-attenuated	Poliovirus	All-cause of infectious diseases, Diarrhea, **COVID-19**	Trained Immunity, Immune-modulation Cross-reactivity	[11,55–60]
Diphtheria–Tetanus–Pertussis (DTaP) vaccine	A mixture of toxoids (Diphtheria & Tetanus) and killed bacteriaor pertussis antigens	Diphtheria–Tetanus–Pertussis	All-cause of infectious diseases	Trained Immunity, Immune-modulation Cross-reactivity	[18,19]

original antigens as well as antigens of other infectious diseases [28].

5. Repurposing of BCG vaccine against COVID-19

Initially, BCG was used to prevent tuberculosis (TB), Buruli ulcer disease (BUD), and leprosy but due to its nonspecific or heterologous protective effects, however now it has been repurposed to manage bladder cancer and various other infections such as *Staphylococcus aureus, Candida albicans*, and viruses like the yellow fever virus and influenza [13,20,22,23,31,32]. A study based on BCG-randomized controlled trials showed its immunomodulatory effect against respiratory infections [33]. Key points of some studies mentioned below have shown the nonspecific or heterologous protective effect of BCG against respiratory and viral infections.

In the last two decades, BCG-based randomized controlled trials (RCTs) on infants, adults, and elderly peoples showed that a drop in mortality due to pneumonia, and other respiratory infections [20,32,34,35].

- Elder people aged >65 with comorbidities have shown a reduction in the risk of pneumonia and prevent acute upper respiratory tract infections following BCG vaccination [35,36].
- BCG vaccination has reduced viral load in blood or viremia following yellow fever infection, which is probably due to the production of IL-1b [29,34].

These clues suggest that the heterologous protective effects of BCG against some unrelated viral pathogens are due to its ability to augment the body's immunity and prevent respiratory infections. Recently published various epidemiological reports and opinions suggested BCG could be shown protective effects against COVID-19 [37–39]. Based on COVID-19 world epidemiological data, researchers hypothesized countries with universal BCG vaccination have shown lower COVID-19 incidence and mortality than other countries that do not have BCG vaccination policies [39–41]. Various reports suggested that countries using original strains of BCG have shown the better protective effect that leads to lower COVID-19 morbidity and mortality as compared to the other countries which use modified BCG strains (Japan – 5.4%; Brazil – 4.7% and Rússia – 1.4% vs. France – 15.1%, Italy – 14.5% and United Kingdom 14.0%) [40–44]. This protective effect of the BCG is potentially due to the stimulation of the trained immunity which can reduce viral load/viremia from respiratory tract viral infections [24,25,28,34,45–47]. Trained immunity has been triggered by re-programming and immune-modulation of innate immune cells like macrophages, monocytes, and NK cells, which leads to nonspecific Th1 and Th17 responses and cytokine responses (IL17, IL22, IL 1b, IL6, TNFa1, and IFNc). In various countries, more than fifteen BCG clinical trials are ongoing to check its protective effects against the COVID-19 [48]. The USA, Australia, and the Netherlands evaluate the nonspecific effect of BCG vaccination upon healthcare workers dedicated to taking care of the COVID-19 patients. In Germany, researchers also analyzed the protecting effects of the recombinant vaccine strain (VPM1002) derived from BCG on healthcare workers and the older patients from COVID-19 [49]. Still, various trials are ongoing to conclude whether BCG vaccination could protect against SARS-CoV-2 infection, which might shed new light on our understanding of the BCG-mediated immunological mechanisms.

6. Repurposing of MMR vaccines against COVID-19

Mumps, Measles, and Rubella (MMR) vaccines possess attenuated enveloped RNA viruses that are used for infant and child vaccinations. Studies suggest that the reduction in childhood mortality in developing countries by measles vaccine immunization could be probably due to its heterologous protective effects so it may have important implications for the planning of immunization programs [6,50]. This protective effect of the measles vaccine is the main reason behind its continued immunizations, even when measles infection has been eradicated [6–8]. SARS-CoV-2 and MMR viruses shared a similar route of transmission as well as the site of replication (upper respiratory tract). The spike of SARS-CoV-2 has shown sequence similarities with glycoprotein spikes of MMR viruses, around 32%, 31%, and 33% of measles, mumps, and rubella, respectively [51]. These sequence similarities might be responsible to show the antibody-mediated cross-protection against SARS-CoV-2 infection. The heterologous protective effects of MMR vaccines against COVID-19 are probably due to the following reasons.

- Glycoprotein spikes sequence similarities between MMR viruses and SARS-CoV-2 could provide the cross-reactive antibodies.
- Interferons production triggered by MMR vaccines.
- Enhancing the NK cell's activity by MMR vaccines further leads to the lysis of the virus-infected cells.

The Centers for Disease Control (CDC) has recommended MMR vaccination in healthcare workers and elder peoples (high-risk adults), which induces the trained innate immune cells and could provide the heterologous protective effects against the worst sequelae of COVID-19 [52]. Epidemiological and clinical data also suggested that MMR vaccination could reduce the severity of COVID-19 as well as death rates [53]. Recently, a measles vaccine trial was started among the healthcare workers in Egypt to prevent COVID-19 morbidity and mortality [54]. Based on the facts discussed above, we suggest that MMR (booster) vaccination in healthcare workers and elder peoples signify a'low-risk – high-reward' preventive option that could be used to save lives in the emergency period of COVID-19 pandemic.

7. Repurposing of OPV vaccines against COVID-19

Like the BCG and MMR (Figure 1), past studies also provide some information or experimental signals about the heterologous protective effects of the OPV vaccine to enhance the immune responses [55]. Studies based on randomized trials suggested that OPV doses in infants reduce mortality and its protective effects remain up to several months [11].

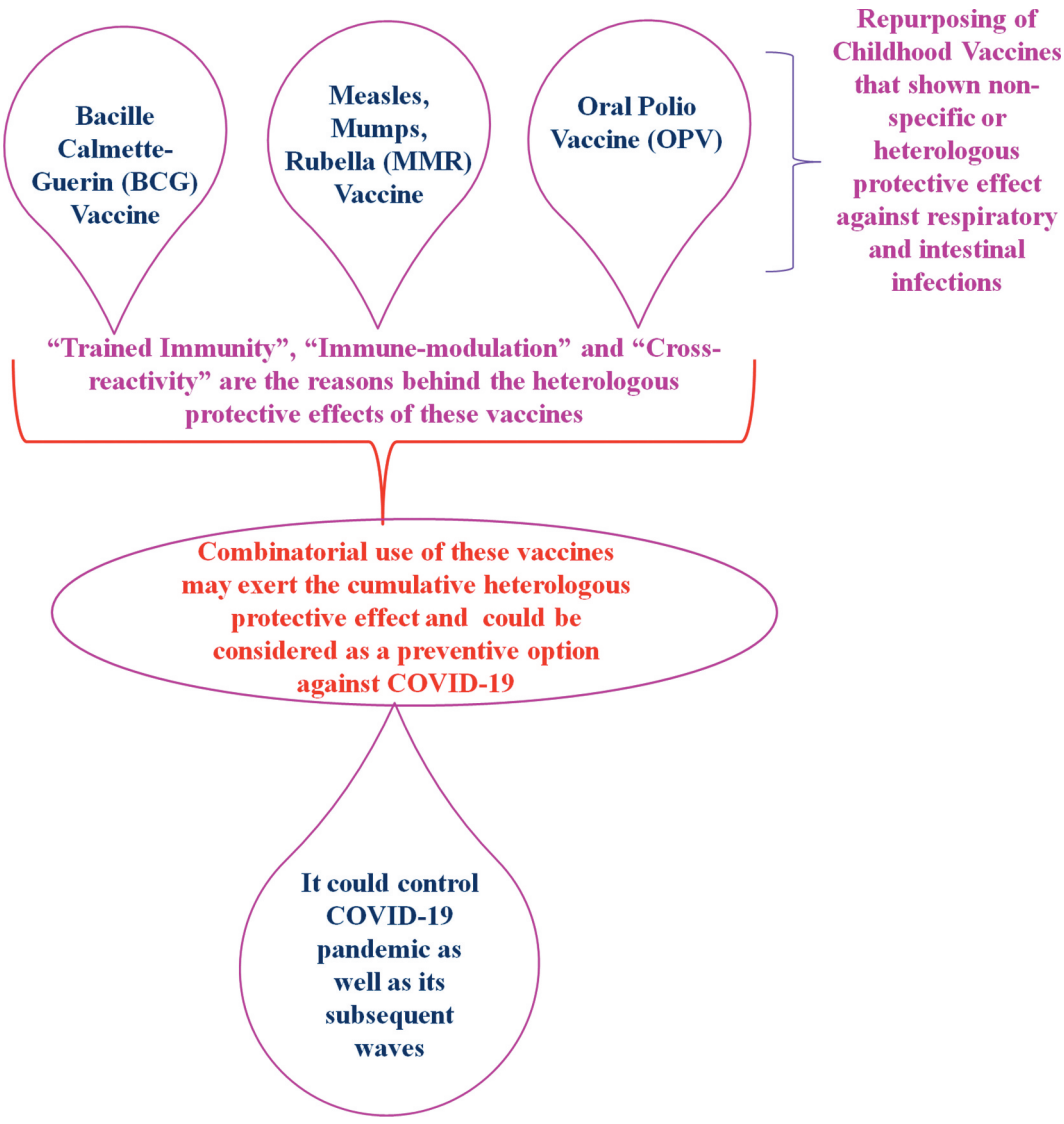

Figure 1. Schematic representation of vaccines repurposing for potential intervention against COVID-19.

A retrospective cohort study on children in Denmark suggested that the OPV recipient group has a lower rate of respiratory infections and hospitalization [56]. The 'performance of rotavirus and oral polio vaccines in developing countries' (PROVIDE) study suggested that the heterologous protective effects of these vaccines decreased mortality by reducing the diarrheal burden [57]. A recent study has shown the heterologous protective effects of OPV against diarrhea caused by *Campylobacter jejuni/coli* [58]. Therefore, these facts have shown the effectiveness of OPV against respiratory and enteric infections. Similarly, SARS-CoV-2 predominantly infects the respiratory and intestinal tract cells, which have ACE2 receptors, therefore researchers found the OPV information to analyze the heterologous protective effect of OPV against COVID-19 [59]. Recently, a clinical trial has been started in the USA to analyze the heterologous protective effects of the OPV against the COVID-19 [60]. If the outcome of this trial proves positive, it could be repurposed to protect the SARS-CoV-2 infection.

8. Conclusion

To conclude, this perspective article suggested that repurposing the childhood vaccines (BCG, MMR, and OPV) in combination with the available COVID-19 therapeutics and vaccines could be enhanced the better protective effects against the SARS-CoV-2 infections (especially infection at respiratory and intestinal parts) therefore these combinations could be considered as a preventive option against SARS-CoV-2 infections as well as its subsequent waves.

9. The expert opinion a way forward

After almost sixteen months of this outbreak, various researchers suggested repurposing of the drugs as a potential option for COVID-19 treatment [61], however, some of the dedicated therapeutics and vaccines are now available. Due to the emergence of mutants of SARS-CoV-2 the effect of available therapeutics and dedicated COVID-19 vaccines has compromised. Therefore, pandemic COVID-19 and its subsequent waves

continuously threaten the globe. Based on worldwide epidemiological data, researchers suggest the repurposing of childhood vaccines to prevent SARS-CoV-2 infections and could be managed by the development of COVID-19 and its severity. Heterologous protective effects or nonspecific effects of childhood vaccines are the major reason behind the concept of vaccine repurposing which potentially enhanced innate immunity.

'Trained Immunity' and 'Cross-reactivity' are the two most basic attributes of the repurposed vaccines that enhance the overall innate immune responses and protect the host from unrelated infections.Heterologous protective effects of BCG against some unrelated viral pathogens are due to its ability to augment the body's immunity and prevent respiratory infections. In elder people with comorbidities, BCG vaccination has been reduced the risk of pneumonia and prevent acute upper respiratory tract infections. BCG vaccination has been also reduced viral load in blood or viremia following yellow fever infection, which is probably due to the production of IL-1b.

SARS-CoV-2 and MMR viruses shared a similar route of transmission as well as the site of replication (upper respiratory tract). Spike of SARS-CoV-2 has shown sequence similarities with glycoprotein spikes of MMR viruses, around 32%, 31%, and 33% of measles, mumps, and rubella, respectively. These sequence similarities might be responsible to show the antibody-mediated cross-protection against SARS-CoV-2 infection. The heterologous protective effects of MMR vaccines against COVID-19 are probably due to the sequence similarity of spike between both vaccines, triggering the interferon production and enhancement of the activity of NK cells. Various studies also indicate the heterologous protective effects of the OPV vaccine enhance the immune responses and reduced mortality in infants.

Repurposing of the live-attenuated childhood vaccines (BCG, MMR, and OPV) have shown the potential to train the innate immune cells. Their antigen similarities could also prevent unrelated infections as well as decrease the severity of diseases. Data and facts discussed in this manuscript have shown that BCG, MMR, and OPV could prevent the SARS-CoV -2 and other respiratory infections. We have suggested the combinatorial use of these childhood vaccines (BCG, MMR, and OPV) along with the available COVID-19 therapeutics and vaccines could be considered the most potent preventive option against the more contagious mutated SARS-CoV-2 infections and their subsequent waves.

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Author contributions

DS conceived the idea, designed the concept, drafted, edited, and approved the final manuscript.

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