Ref: Ro J Pharm Pract. 2022;15(2)
DOI: 10.37897/RJPhP.2022.2.1

# Pre-COVID19 pandemia vaccines could have a nonspecific effect in preventing SARS-CoV-2 infection in the pediatric population

Vlad DIMA[1], George IANCU[2,3], Roxana-Elena BOHILTEA[2,3], Raluca Mariana STANESCU[4], Adrian Ioan TOMA[5], Valentin-Nicolae VARLAS[2,3], Ana-Maria DAVITOIU[3,6]

*[1]Department of Neonatology, Filantropia Clinical Hospital, Bucharest, Romania*
*[2]Department of Obstetrics and Gynecology, Filantropia Clinical Hospital, Bucharest, Romania*
*[3]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
*[4]"Alessandrescu-Rusescu" National Institute for Mother and Child Health, Bucharest, Romania*
*[5]Memorial Life Hospital, Bucharest, Romania*
*[6]"Victor Gomoiu" Clinical Hospital, Bucharest, Romania*

## Abstract

*The COVID-19 pandemic raised an unexpected challenge for the medicine and pharmaceutical industry. The primary goal in a short timeframe was to fight the spreading of SARS-CoV-2 by any means, starting from social distancing, wearing face masks, and, in the end, finding a vaccine as effective as possible in preventing the virus spread.*

*Studies were published from the first months of the pandemic, trying to show the way that this virus attacks the host and how it is transmitted in communities. Some data were contradictory, but one fact became obvious – children have a lower risk of infection with SARS-CoV-2. Data collected from many studies showed that some vaccines that were already in use before the COVID-19 pandemics are efficient in preventing SARS-CoV-2 infection. In this paper, we tried to summarize the nonspecific effects of preexisting vaccines against SARS-CoV-2 infection.*

**Keywords:** COVID-19, children, vaccines, nonspecific effects, studies

## INTRODUCTION

SARS-CoV-2 is responsible for the COVID-19 pandemic that was first identified in China at the end of 2019 and rapidly spread worldwide [1]. Children represent a small part of all patients with COVID-19 [2]. The number of children presenting to hospitals decreased during the pandemic due to isolation, reduced circulation of transmittable diseases, and increased anxiety regarding hospitals [3]. Children faced a change in their social and family life, mostly due to the closure of schools, a measure implemented in most countries around the world to reduce the impact of the pandemic [4]. The immunological mechanisms that lead to a lower spread or severity in children and adolescents are not completely clarified. The immune modification encountered in those children who had

*Corresponding author:*
Vlad Dima
*E-mail:* dima.vlad@yahoo.com

*Article History:*
Received: 21 June 2022
Accepted: 24 June 2022

multisystem inflammatory syndrome (MIC-S) is still not completely understood [5].

The COVID-19 pandemic has led to economic imbalance worldwide and mass closures of social programs, kindergartens, and schools. Almost 90% of students around the world had their education ceased by the end of April 2020 due to school closures [6]. Until now, the scientific data used as motivation for school closures to prevent transmission of SARS-CoV-2 remain controversial. Some papers showed a limited reduction in mortality rates of 2–4% after school closures [7]. There are some reports of significant outbreaks tied to the opening of schools [8], but these results were not demonstrated in similar situations [9,10]. Given these facts, it is crucial to understand children's role in transmitting the SARS-CoV-2 virus [11].

## TRANSMISSION OF SARS-CoV-2 IN CHILDREN

Children presented a lower risk of transmission especially to other children, with an average of less than one secondary case for each primary case. There was limited proof of transmission inside schools or other children's facilities [12,13,14].

Children are not an important contributor to the spreading of COVID-19, but teenagers could play a role in transmitting the virus. Almost half of the children diagnosed with COVID-19 at school were teenagers from high school. But it may be an underestimate because not all age groups were studied in detail [11].

Probably, the low immunity of children, who didn't t show an overwhelming immune response against the virus as in the adults, could be the explanation for the lower severity of SARS-CoV-2 infection in this age-related group. Children have fewer memory cells specific to other existing coronaviruses and therefore they are less prone to start an important cell-mediated attack on the alveoli and interstitial tissue inside the lung for a new kind of infection [15,16].

A difference in the distribution, maturation, and function of viral receptors is often cited as a potential reason for the difference in incidence.

SARS virus, SARS-CoV-2, and human coronavirus-NL63 (HCoV-NL63) use angiotensin-converting enzyme-2 (ACE2) as a cellular receptor in humans [17,18].

Previous studies have shown that HCoV-NL63 infection is more common in adults than in children [19,20]. This finding indicates that children could have relative resistance to SARS-CoV-2.

ACE2 expression in the lung of mice was found to decrease with age [21]. This discovery may not be linked to a relatively low susceptibility of children to COVID-19. Studies showed that ACE2 is involved in the protective mechanisms of the lungs and can protect against severe lung damage generated by respiratory virus infection.

ACE2 also protects against severe acute lung injury that can be triggered by sepsis, SARS, and infection with the avian influenza A virus H5N1 [22,23].

## CLINICAL PRESENTATION OF COVID-19 IN CHILDREN

In contrast to many infectious diseases, such as malaria and the common flu, where children are known to be the most vulnerable and drive transmission in homes and communities, SARS-CoV-2 appears to simply not translate through a severe disease, because it occurs frequently in children, especially young children under the age of 10. The severity of COVID-19 symptoms among children is milder, with lower case fatality rates (CFRs), and their recovery is faster [16].

There is a mild clinical presentation of SARS-CoV-2 infection in children, but more severe forms may develop over time. A small percentage of cases are registered in the pediatric age group. The contact tracing percentage mainly refers to symptomatic patients or tests performed for contact tracing and could therefore be underestimated due to the mild clinical presentation.

SARS-COV-2 infection was associated with the altered general condition (12%), fever (48%), cough (73.43%), problems with feeding (42.35%), and rhinorrhea (34, 20%). As SARS-CoV-2 primarily affects the respiratory system, gastrointestinal manifestations (mainly diarrhea and abdominal pain) can also occur (at the beginning or later in the course of the disease) [24].

## DIFFERENT VACCINES FOR DIFFERENT DISEASES - SURPRISING EFFECTS

Many countries have a range of bacterial and viral illnesses. Vaccines can have non-specific physiological effects by modifying the immune response against unrelated organisms, these effects being called heterologous immunity. Non-specific effects of vaccines tend to be more pronounced in girls and appear to be greatest in the first 6 months of life [26] – when the maternal immunity conferred is supplemented by vaccines. Salman and Salem suggest that the cross-immunogenicity of childhood vaccines against multiple viruses may explain the relatively milder infection and severity of COVID-19 in children [27]. Most routine viral vaccines are inactivated or killed viruses that stimulate T-helper-1 cells to produce many different types of cytokines such as interferon-gamma, interleukin-2 (IL-2), and interleukin-12 (IL-12). secrete, enhancing the cytotoxicity of natural killer cells to recognize and destroy cells infected with a new virus [16].

Immune responses to pathogens can sometimes be altered by prior exposure to antigens, and although these heterologous responses may be less effective than specific immune responses to homologous antigens, they can alter the course of infection in a host [28].

The basic biological mechanisms that demonstrated the heterologous protective effect of vaccines are not yet fully elucidated, but based on epidemiological, immunological, and clinical studies, several hypotheses could explain these mechanisms:

a) cross-reactivity between shared epitopes of apparently unrelated pathogens;

b) immunomodulation of innate memory of immune cells (natural killer cells and monocytes), adaptive memory of immune cells (Th cells and CD4) and cytokine (interleukin) responses;

c) the induction of immunity driven by epigenetic reprogramming of innate immunity offers better protection against reinfection;

d) Improved innate immune response (antibody titers) to unrelated antigens [29,30,31,32,33].

## ORAL POLIO VACCINE (OPV)

Several studies have demonstrated the efficacy of the oral polio vaccine (OPV) against 224 respiratory and intestinal infections. Since SARS-CoV-2 mainly infects cells of the respiratory and intestinal tracts, where ACE2 receptors are present, a heterologous protective effect of OPV against COVID-19 has been suggested [34].

The most essential conclusion of this study is that OPV administration was associated with significantly fewer days of diarrhea with stool in the 3 months following vaccination than IPV administration.

Although this difference is small (~1 day), we would expect the measured protective effect to be improved when comparing a routine IPV-only vaccination schedule with an OPV-only schedule. Furthermore, a longer follow-up period may also reveal a greater effect of OPV on diarrheal disease. When bacterial pathogens were analyzed individually, OPV use was found to be associated with a reduced prevalence of diarrhea caused by C. jejuni/coli in all infants. Diarrhea caused by C. jejuni/coli and Shigella has a similar course since these pathogens cause inflammatory diarrhea, including dysentery. These pathogens are responsible for the vast majority of bacillary dysentery [35].

## BCG (BACILLUS CALMETTE–GUÉRIN) VACCINE

BCG has shown that the innate immune system can develop trained immunity through epigenetic reprogramming of various types of innate immune cells [36] and can help the body respond to viruses. It has been suggested that countries that include BCG in their vaccination schedule have fewer confirmed cases and lower mortality in Sars-Cov-2 patients than countries without [37], suggesting a possible inverse correlation between BCG and COVID incidence and mortality shows -19. BCG vaccination administered in the neonatal period protects against non-tuberculosis infectious diseases in the first weeks of life and already has an anti-tuberculosis effect; The nonspecific effects of BCG on infectious morbidity and all-cause mortality suggest that administration of BCG in the first days after birth should be a priority in areas with a high prevalence of infectious diseases and may also play a role against SARS-CoV-2 [38]. Adult patients, in most cases, have received the same vaccines given to

children throughout their lives, and this aspect may lead to discarding the above theory or considering only their role in acute infections. Further research is needed to identify the link between BCG vaccination and the lower incidence of SARS-COV-2 spread in children.

## DTaP VACCINATION

DTP vaccines can induce cross-reactive T- and B-cell immunity against SARS-CoV-2. DTP combination vaccines have been included in the vaccination schedule since the 1940s-1950s [39]. During infancy, children receive 3-4 doses of DTaP or DTwP, often in combination with inactivated poliovirus, conjugated Hib, and recombinant HBV antigens.

Children also receive a pediatric DTaP booster at ages 4-6 and a lower antigenic load DTaP booster at ages 9-14. Repeated DTP vaccinations will help protect children from SARS-CoV-2 through cross-reactive immunity. Cross-reactive immunity induced by DTP vaccines will eventually decline over time, which is why COVID-19 cases and severity increase with age. It can also be hypothesized that Tdap vaccination during pregnancy could explain the lower incidence of COVID-19 deaths in women. In addition, women vaccinated with Tdap could transmit passive cross-immunity against SARS-CoV-2 to newborns they breastfeed [40].

Additionally, MenB vaccines can induce significant cross-reactive T-cell immunity against SARS-CoV-2. However, MenB vaccines are unlikely to be responsible for the observed resistance to SARS-CoV-2 in children worldwide; MenB vaccines have only been introduced recently, over the past decade, and not universally [41,42].

## MMR VACCINATION

Le Saad et al. proposed two possible mechanisms for the increased incidence of COVID-19 infection and death in an unvaccinated MMR population (Italy) and an MMR-vaccinated population (China): a) By stimulating population-wide immunity, the measles vaccine increases the ability of the immune system to fight pathogens other than measles, including coronaviruses; b) Due to the shared structural similarities between measles and coronavirus, cross-reactivity and immunity generated by measles vaccine and coronavirus results in partial protection against COVID-19 [43].

Franklin et al. identified that rubella virus and SARS-CoV-2 macrodomains share 29% amino acid sequence identity [44]. This finding suggests that the viruses share the same protein fold. Patients with high disease severity had elevated anti-rubella IgG levels (161.9 + 147.6 IU/mL) compared to patients with moderate disease severity (74.5 + 57.7 IU/mL). mL). in case of COVID-19 infection in MMR-vaccinated patients.

Fidel and Noverr support the use of live attenuated MMR vaccine as a preventive measure against pathologic inflammation and sepsis associated with COVID-19 infection [45]. The basis of such a proposal is the induction of nonspecific effects by live attenuated vaccines, which represent “trained innate immunity” released by leukocytes.

The result is that the precursors in the bone marrow are more effective against larger attacks of infection. Based on data from previous studies of the BCG vaccine in infants, vaccine-induced formed cells are expected to remain in circulation for approximately 1 year [16].

## HEPATITIS A VACCINE

The hepatitis A vaccine is highly immunogenic. Determines seropositivity in 95% of adults after a single dose and in 97% of adults and 100% of children after 2 doses. This vaccine also causes HAV-specific proliferation of peripheral blood mononuclear cells and the release of IFN-γ [46].

Sarialioglu et al reported differences in the extent to which COVID-19 has affected some countries such as the United States, China, Italy, France, England, Spain, Belgium , and the Netherlands more severely than others such as India, Pakistan, countries in Africa and South America, which had lower infection and mortality rates at the time of the study, countries where HAV vaccination is routinely performed [47]. The authors hypothesize that routine vaccination against the hepatitis A virus (HAV) leads to high immunity in populations of countries with low COVID-19 prevalence, while immunity is quite low in countries highly industrialized.

The authors conclude that the hepatitis A vaccine-induced immune response may protect against COVID-19 infection through a possible adaptive immune cross-reaction. Patients with asymptomatic COVID-19 disease could indirectly indicate patients

protected against HAV seropositivity. Hepatitis A vaccine may help maintain COVID-19 infection at mucosal colonization and may prevent lower respiratory tract involvement and death [47].

## DISCUSSION

However, given the serious risks posed by the COVID-19 pandemic and the strain on healthcare infrastructure, it is important to strengthen vaccination policies and harness the non-specific effects of vaccines to overcome the pandemic situation and prevent further outbreaks from occurring. It seems reasonable to prevent as the development of vaccines against COVID-19 accelerates, and vaccine tracking and post-market surveillance are becoming increasingly important.

SARS-CoV-2 has had several known mutations since 2019. Given the potential for future strains and the resulting pandemic, using existing vaccines in combination with his specific COVID-19 vaccine could be the right tool. To prevent more serious infections and deaths from these infections. The pandemic has changed people's behavior about health services, resulting in some countries suspending routine childhood immunizations for the duration of the pandemic.

This can lead to outbreaks of infectious diseases in children. Therefore, we need to focus on providing children with minimal vaccines.

## CONCLUSION

"Trained immunity" and "cross-reactivity" are the two most fundamental properties of repurposed vaccines, enhancing the overall innate immune response and protecting the host against unrelated infections.

It has been almost three years since a human infection with the new Coro-229 virus was documented in Wuhan, China, but it continues to attract the attention of the scientific community interested in diagnosing, treating, and controlling 231. There is one fact about him. handle:

Reduced susceptibility of children to SARS-CoV-2 infection and development of severe forms of COVID-19. Reuse of live attenuated vaccines (BCG, MMR, and OPV) demonstrates the potential for innate immune cell development. Their antigenic similarity can also prevent unrelated infections and reduce disease severity. Using existing childhood vaccines such as MMR to address the increased morbidity and mortality associated with COVID-19 remains a low risk for all populations until the pandemic trajectory shows a sustained decline.

*Conflict of interest:* none declared
*Financial support:* none declared

## REFERENCES

1. Hobbs CV, Khaitan A, Kirmse BM, Borkowsky W. COVID-19 in Children: A Review and Parallels to Other Hyperinflammatory Syndromes. *Front Pediatr.* 2020;8:593455. doi: 10.3389/fped.2020.593455. PMID: 33330288; PMCID: PMC7732413.
2. Parri N, Lenge M, Buonsenso D. Children with Covid-19 in Pediatric Emergency Departments in Italy. *N Engl J Med.* 2020;383:187–190. doi: 10.1056/NEJMc2007617. Epub 2020 May 1. PMID: 32356945; PMCID: PMC7206930.
3. Buonsenso D, Valentini P, Moscato U, Ricciardi W, Roland D. A Pediatric Strategy for the Next Phase of the SARS–CoV-2 Pandemic. *Front Pediatr.* 2020;8:582798. doi: 10.3389/fped.2020.582798. PMID: 33163467; PMCID: PMC7581723.
4. Buonsenso D, Roland D, De Rose C, Vásquez-Hoyos P, Ramly B, Chakakala-Chaziya JN et al. Schools Closures During the COVID-19 Pandemic. *Pediatric Infect Dis J.* 2021;40(4):e146–e150. doi: 10.1097/INF.0000000000003052. PMID: 33464019.
5. Valentini P, Sodero G, Buonsenso D. The Relationship between COVID-19 and Innate Immunity in Children: A Review. *Children*. 2021;8:266. doi: 10.3390/children8040266
6. Donohue JM, Miller E. COVID-19 and School Closures. *JAMA*. 2020;324(9):845–7. doi: 10.1001/jama.2020.13092. PMID: 32745182.
7. Viner RM, Russell SJ, Croker H, Packer J, Ward J, Stansfield C et al. School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. *The Lancet Child Adolescent Health.* 2020;4(5):397–404. doi: 10.1016/S2352-4642(20)30095-X. Epub 2020 Apr 6. PMID: 32272089; PMCID: PMC7270629.
8. Stein-Zamir C, Abramson N, Shoob H, Libal E, Bitan M, Cardash T et al. A large COVID-19 outbreak in a high school 10 *days after schools' reopening, Israel, May 2020.* Euro Surveill. 2020 Jul;25(29):2001352. doi: 10.2807/1560-7917.ES.2020.25.29.2001352. PMID: 32720636; PMCID: PMC7384285.
9. Heavey L, Casey G, Kelly C, Kelly D, McDarby G. No evidence of secondary transmission of COVID-19 from children attending school in Ireland, 2020. *Euro Surveill.* 2020;25(21):2–5.

10. Im Kampe EO, Lehfeld A-S, Buda S, Buchholz U, Haas W. Surveillance of COVID-19 school outbreaks, Germany, March to August 2020. *Euro Surveill.* 2020;25(38):2001645. doi: 10.2807/1560-7917.ES.2020.25.38.2001645. PMID: 32975186; PMCID: PMC7533620.
11. Silverberg SL, Zhang BY, Li SNJ, Burgert C, Shulha HP, Kitchin V et al. Child transmission of SARS-CoV-2: a systematic review and meta-analysis. *BMC Pediatr.* 2022 Apr 2;22(1):172. doi: 10.1186/s12887-022-03175-8. PMID: 35365104; PMCID: PMC8975734.
12. Macartney K, Quinn HE, Pillsbury AJ, Koirala A, Deng L, Winkler N et al. Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study. *Lancet Child Adolesc Health.* 2020;4(11):807–16. doi: 10.1016/S2352-4642(20)30251-0. Epub 2020 Aug 3. PMID: 32758454; PMCID: PMC7398658.
13. Zimmerman KO, Akinboyo IC, Brookhart MA, Boutzoukas AE, McGann K, Smith MJ et al. Incidence and secondary transmission of SARS-CoV-2 infections in schools. *Pediatrics*. 2021;147(4):e2020048090. doi: 10.1542/peds.2020-048090. Epub 2021 Jan 8. PMID: 33419869; PMCID: PMC8015158.
14. Gilliam WS, Malik AA, Shafiq M, Klotz M, Reyes C, Humphries JE et al. COVID-19 Transmission in US Child Care Programs. *Pediatrics*. 2021;147(1):e2020031971. doi: 10.1542/peds.2020-031971. Epub 2020 Oct 14.PMID: 33055228
15. Carsetti R, Quintarelli C, Quinti I, Mortari EP, Zumla A, Ippolito G Locatelli F. The immune system of children: the key to understanding SARS-CoV-2 susceptibility? *Lancet Child Adolescent Health.* (2020) 4:414–6. doi: 10.1016/S2352-4642(20)30135-8
16. Beric-Stojsic B, Kalabalik-Hoganson J, Rizzolo D, Roy S. Childhood Immunization and COVID-19: An Early Narrative Review. *Front Public Health.* 2020 Oct 28;8:587007. doi: 10.3389/fpubh.2020.587007. PMID: 33194993; PMCID: PMC7655788.
17. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020 Feb 22;395(10224):565-574. doi: 10.1016/S0140-6736(20)30251-8. Epub 2020 Jan 30. PMID: 32007145; PMCID: PMC7159086.
18. Hofmann H, Pyrc K, van der Hoek L, Geier M, Berkhout B, Pohlmann S. Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. *Proc Natl Acad Sci USA.* 2005 May 31;102(22):7988-93. doi: 10.1073/pnas.0409465102. Epub 2005 May 16. PMID: 15897467; PMCID: PMC1142358
19. Huang SH, Su MC, Tien N, Huang CJ, Lan YC, Lin CS et al. Epidemiology of human coronavirus NL63 infection among hospitalized patients with pneumonia in Taiwan. *J Microbiol Immunol Infect*. 2017;50:763e70.
20. Lee KH, Yoo SG, Cho Y, Kwon DE, La Y, Han SH et al. Characteristics of community-acquired respiratory viruses infections except seasonal influenza in transplant recipients and non-transplant critically ill patients. *J Microbiol Immunol Infect.* 2021 Apr;54(2):253-260. doi: 10.1016/j.jmii.2019.05.007. Epub 2019 Jun 19. PMID: 31262511; PMCID: PMC7102620.
21. Xie X, Chen J, Wang X, Zhang F, Liu Y. Age- and gender-related difference of ACE2 expression in rat lung. *Life Sci.* 2006;78:2166e71.
22. Gu H, Xie Z, Li T, Zhang S, Lai C, Zhu P et al. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. *Sci Rep.* 2016;6:19840.
23. Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? J *Microbiol Immunol Infect.* 2020 Jun;53(3):371-372. doi: 10.1016/j.jmii.2020.02.011. Epub 2020 Feb 25. PMID: 32147409; PMCID: PMC7102573.
24. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Carducci FIC et al. COVID-19 in children and adolescents in Europe: A multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4:653–661
25. Buonsenso D, Zampino G, Valentini P. Novel Coronavirus Disease 2019 Infection in Children: The Dark Side of aWorldwide Outbreak. *Front Pediatr.* 2020;8:215. doi: 10.3389/fped.2020.00215. PMID: 32426311; PMCID: PMC7203211.
26. Shann F. The non-specific effects of vaccines. *Arch Dis Child.* 2010 Sep;95(9):662-7. doi: 10.1136/adc.2009.157537. PMID: 20716675.
27. Salman S, Salem M. Routine childhood immunization may protect against COVID-19. *Med Hypotheses.* 2020 Mar 25;140:109689. doi: 10.1016/j.mehy.2020.109689. Epub ahead of print. PMID: 32240961; PMCID: PMC7270579.
28. Chen HD, Fraire AE, Joris I, Brehm MA, Welsh RM, Selin LK. Memory CD8+ T cells in heterologous antiviral immunity and immunopathology in the lung. *Nat Immunol.* 2001;2:1067–76. doi:10.1038/ni727
29. Netea MG, Quintin J, Van Der Meer JW. Trained immunity: a memory for innate host defense. *Cell Host Microbe.* 2011;9(5):355–61. doi: 10.1016/j.chom.2011.04.006. PMID: 21575907.
30. Netea MG, Domínguez-Andrés J, Barreiro LB et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol.* 2020;20(6):375–88. doi: 10.1038/s41577-020-0285-6. Epub 2020 Mar 4. PMID: 32132681; PMCID: PMC7186935.
31. Sun JC, Ugolini S, Vivier E. Immunological memory within the innate immune system. *EMBO J.* 2014;33(12):1295–303. doi: 10.1002/embj.201387651. Epub 2014 Mar 27. PMID: 24674969; PMCID: PMC4194120.
32. Ritz N, Mui M, Balloch A et al. Non-specific effect of Bacille Calmette-Guerin vaccine on the immune response to routine immunisations. *Vaccine*. 2013;31(30):3098–103. doi: 10.1016/j.vaccine.2013.03.059. Epub 2013 Apr 10. PMID: 23583897.
33. Covián C, Fernández-Fierro A, Retamal-Díaz A et al. BCG-induced cross-protection and development of trained immunity: implication for vaccine design. *Front Immunol.* 2019;10:2806.
34. Sharma D. Repurposing of the childhood vaccines: could we train the immune system against the SARS-CoV-2. *Expert Rev Vaccines.* 2021 Sep;20(9):1051-7. doi: 10.1080/14760584.2021.1960161. Epub 2021 Aug 6. PMID: 34313516; PMCID: PMC8425442.
35. Hegarty PK, Sfakianos JP, Giannarini G, DiNardo AR, Kamat AM. COVID-19 and Bacillus Calmette-Guérin: What is the Link? *Eur Urol Oncol.* 2020;3:259–61. doi: 10.1016/j.euo.2020.04.001. Epub 2020 Apr 13. PMID: 32327396; PMCID: PMC7152883.
36. Covián C, Retamal-Díaz A, Bueno S.M, Kalergis A.M. Could BCG Vaccination Induce Protective Trained Immunity for SARS-CoV-2? *Front Immunol.* 2020;11:970. doi: 10.3389/fimmu.2020.00970. PMID: 32574258; PMCID: PMC7227382.
37. Prentice S, Nassanga B, Webb EL, Akello F, Kiwudhu F, Akurut H et al. BCG-induced non-specific effects on heterologous infectious disease in Ugandan neonates: An investigator-blind randomized controlled trial. *Lancet Infect Dis.* 2020.
38. Guiso N, Meade BD. and Wirsing von Kvðnig, CH. Pertussis vaccines: The first hundred years. *Vaccine* (2020) 38:1271–6. doi: 10.1016/j.vaccine.2019.1211.1022
39. Reche PA. Potential Cross-Reactive Immunity to SARS-CoV-2 From Common Human Pathogens and Vaccines. *Front Immunol.* 2020 Oct 16;11:586984. doi: 10.3389/fimmu.2020.586984. PMID: 33178220; PMCID: PMC7596387.
40. Kuhdari P, Stefanati A, Lupi S, Valente N, Gabutti G. Meningococcal B vaccination: real-world experience and future perspectives. *Pathog Glob Health*. 2016;110:148–56. doi: 10.1080/20477724.20472016.21195072
41. Soler-Garcia A, Fernandez de Sevilla M, Abad R, Esteva C, Alsina L, Vazquez J et al. Meningococcal Serogroup B Disease in Vaccinated Children. *J Pediatr Infect Dis Soc*. 2019;21:454–9. doi: 10.1093/jpids/piz071
42. Saad M, Elsalamony R. Measles vaccines may provide partial protection against COVID-19. *Int J Cancer Biomed Res.* 2020;5:14-19. doi: 10.21608/jcbr.2020.26765.1024
43. Franklin R, Young A, Neumann B, Fernandez R, Joannides A, Reyahi A et al. Homologous protein domains in SARS-CoV-2 and measles, mumps and rubella viruses: Preliminary evidence that

MMR vaccine might provide protection against COVID-19. *medRxiv* [Preprint]. (2020) doi: 10.1101/2020.04.10.20053207
44. Fidel PL, Noverr MC. Could an unrelated live attenuated vaccine serve as a preventive measure to dampen septic inflammation associated with covid-19 infection? *mBio*. 2020;11:e00907–20. doi: 10.1128/mBio.00907-20
45. Sarialioglu F, Belen Apak FB, Haberal M. Can Hepatitis A Vaccine Provide Protection Against COVID-19? *Exp Clin Transplant*. 2020 Apr;18(2):141-143. doi: 10.6002/ect.2020.0109. PMID: 32279655.
46. Shrivastava J, Narang M, Gomber S. Measles, mumps and rubella vaccine and heterologous immunity: a way out of the COVID-19 crisis? *Sudan J Paediatr.* 2022;22(1):10-18. doi: 10.24911/SJP.106-1621869672. PMID: 35958081; PMCID: PMC9361497.
47. Wu D, Guo CY. Epidemiology and prevention of hepatitis A in travelers. *J Travel Med.* 2013;20(6):394-9. doi: 10.1111/jtm.12058. Epub 2013 Jul 29. PMID: 24165384.
48. Mosites E, Gounder P, Snowball M et al. Hepatitis A vaccine immune response 22 years after vaccination. *J Med Virol.* 2018;90(8):1418-22. doi: 10.1002/jmv.25197. Epub 2018 May 1. PMID: 29663458.