

Oral Polio Vaccine to Protect Against COVID-19: Out of the Box Strategies?

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The global coronavirus disease 2019 pandemic has raised significant concerns of developing rapid, broad strategies to protect the vulnerable population and prevent morbidity and mortality. However, even with an aggressive approach, controlling the pandemic has been challenging, with concerns of emerging variants that likely escape vaccines, nonadherence of social distancing/preventive measures by the public, and challenges in rapid implementation of a global vaccination program that involves mass production, distribution, and execution. In this review, we revisit the utilization of attenuated vaccinations, such as the oral polio vaccine, which are safe, easy to administer, and likely provide cross-protection against respiratory pathogens. We discuss the rationale and data supporting its use and detail description of available vaccines that could be repurposed for curtailing the pandemic.

Keywords. immunity; nonspecific effect; oral polio vaccine; SARS-CoV-2; vaccines.

The global coronavirus disease 2019 (COVID-19) pandemic has forced the medical community to explore every possible solution to slow transmission, with the hope that lives will eventually return to normal. There are growing concerns from a public health perspective given ongoing challenges regarding vaccine equity, production, and distribution. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants also threaten to be more transmissible and escape from vaccine-acquired immunity complicated by continued noncompliance with social distancing and disparities among infection control and mitigation strategies between states.

While public health measures, including vaccination against COVID-19, are in full force, alternative therapeutics and methods of protection against infection are being studied and developed. One underexplored option to combat COVID-19 is a safe and available method that has been discussed in the medical literature since at least the 1950s: exploiting the nonspecific effects of live vaccines to combat other infections. Such use has been suggested for the oral polio vaccine (OPV) due to decades' worth of experience and proven efficacy.

OPV was first introduced in 1961 and was in the trivalent form, containing a mixture of the 3 live, attenuated poliovirus serotypes (1, 2, 3) [1]. Monovalent forms of the vaccine

(containing serotypes 1 or 3) and the bivalent formulation (containing serotypes 1 and 3) are those most commonly used in vaccination campaigns. Of the 3 wild types of the poliovirus, types 2 and 3 were declared eradicated in 2015 and 2019, respectively, per the World Health Organization (WHO). There is currently a global campaign to withdraw the use of OPV and switch to inactivated polio vaccine (IPV) for vaccination campaigns. However, the potential benefits of OPV as an agent to prime the immune system and confer protection against other infections warrant a reexamination of this strategy.

DISCOVERY OF THE NONSPECIFIC EFFECTS OF OPV

In the 1950s, Voroshilova proposed that nonpathogenic enteroviruses were useful in the eradication of pathogenic enteroviruses. This finding was supported by the observation that the immunogenic effects of OPV were attenuated by the nonpoliomyelitis enteroviruses that colonized the gastrointestinal (GI) tract [2]. Subsequent studies have explored the effects of live enterovirus vaccines (LEVs) on generating nonspecific immune responses, including an increase of endogenous interferon inducers, T-cell lymphocytes, and overall cellular immunity. In Moscow and Kharkov, large epidemiologic surveys were performed with 6131 children that demonstrated LEV-4 and LEV-7 nonreactogenicity and vaccine safety [2]. The proven safety of LEVs prompted the Vaccine and Sera Committee of the USSR Ministry of Health to permit studies assessing the potential prevention of influenza and acute respiratory disease of up to 320 000 participants with the use of LEVs during the 1960s. Some of these studies demonstrated that LEV 4 and LEV 7 decreased cytopathic agents in the GI tract 4-fold from 29.3% to 7.7% after vaccination [2]. Incidentally, there was also an associated decrease in isolated infections from influenza, parainfluenza,

Received 22 April 2021; editorial decision 6 July 2021; accepted 8 July 2021.

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Open Forum Infectious Diseases® 2021

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respiratory syncytial virus (RSV), adenovirus, and herpesviruses [2]. Additional controlled trials conducted in the former USSR during the influenza seasons of 1968–1971 demonstrated a decreased incidence of influenza and acute respiratory infections (ARIs) in individuals who had received OPV 1–3 and LEV 4, 7 [3–5]. Chumakov et al. (1992) analyzed the results of these controlled trials and found that 60 065 (69.8%) individuals who received the oral Sabin type 1 and 2 vaccines had an average 3.8-fold decrease in acute respiratory infections when compared with 25 924 (30.1%) individuals who were unvaccinated [6]. They also observed that the decrease in incidence of influenza and other respiratory infections was significantly higher in oral Sabin vaccine recipients than influenza vaccine recipients (an analysis for *P* value was not made) [6]. LEV 4, 7 decreased the incidence rate of ARI by 2.6-fold, an effect similar to that of influenza vaccines. These findings led to the hypothesis that LEV and OPV may offer protection against other viral infections.

ADDITIONAL EVIDENCE FOR THE NONSPECIFIC EFFECT OF VACCINES

Recent studies have added to the growing evidence that vaccines may offer nonspecific protection against infections. A randomized controlled trial done in Guinea-Bissau looked at the effect of OPV at birth (OPV0) on infant mortality [7]. They enrolled 7012 neonates, of whom 3495 were randomized to the Bacillus Calmette-Guérin (BCG) group (intervention) and 3517 to the BCG and OPV0 group (standard of care). At 1-year follow-up, there were 87 deaths in the BCG arm and 73 in the BCG + OPV0 arm (overall hazard ratio [HR], 0.83). Irrespective of gender, BCG + OPV0 was associated with lower mortality compared with BCG alone [7]. In addition, no incident polio cases were identified during this trial period, indicating that the nonspecific effects of the vaccine could not be explained by decreasing polio cases. Andersen et al. (2020) analyzed 17 national OPV campaigns and examined mortality rates in children between 1 day and 3 years of age. Mortality was lower after OPV-only campaigns, with an adjusted mortality rate ratio (MRR) of 0.75 (95% CI, 0.67–0.85) [8]. Additional OPV campaigns reduced mortality further by 14% [8].

In 2015, Sorup et al. conducted a retrospective cohort study in Denmark and investigated the admission rate of children due to infectious diseases depending on whether the most recent vaccine they had received was OPV, DTaP-IPV-Hib (diphtheria-tetanus-acellular pertussis-inactivated polio virus-*Haemophilus influenzae* type b), or MMR (measles, mumps, rubella). They found that when OPV was the most recent vaccine, there was a lower rate of admission for all type of infections—mostly lower respiratory tract infections—when compared with DTaP-IPV-Hib as the most recent vaccine [9]. They also observed that admission rates were lower when MMR was the most recent vaccine when compared with DTaP-IPV-Hib, but there was no

statistical difference between OPV and MMR when either was given most recently. A similar study was performed in the United States using the MarketScan US Commercial claims database to evaluate the risk of hospital admission due to nontargeted infections (NTIs) in 311 663 children aged 16–24 months, depending on the last vaccine administered [10]. The study found that the risk of hospitalization from nontargeted infections was reduced in those who received a live vaccine vs an inactivated vaccine alone (HR, 0.50; 95% CI, 0.43–0.57). Similar to the findings by Sorup et al., the biggest reduction in NTIs was for lower and upper respiratory tract infections when using live vaccines. In children who received concomitant live and inactivated vaccines, the reduction in NTIs was less significant (HR, 0.78; 95% CI, 0.67–0.91); therefore, the investigators concluded that concomitant use of live and inactivated vaccines may have a “diluted” effect compared with live vaccines, but the effect is still present [10]. Mechanisms by which live and attenuated vaccines protect against NTIs have yet to be fully understood and are discussed below. The evidence thus far indicates that live vaccines present nontargeted benefits against other infectious diseases, improving overall mortality.

Other live vaccines have also demonstrated mortality benefit. The WHO performed a systematic review and found that BCG had a mortality benefit in children vaccinated at different ages [11, 12]. The effect was lower if the child had been vaccinated at an older age [11]. Investigators in Guinea-Bissau found a reduction in mortality in infants who had a scar after BCG vaccination, attributed to BCG vaccine–nonspecific protection [13, 14]. Prentice et al. (2021) performed an investigator-blind randomized controlled trial with 560 participants who were assigned to BCG at birth (*n* = 280) or at age 6 weeks (*n* = 280). They found that BCG vaccination at birth protected the participants against nontuberculous infectious diseases during the neonatal period [15]. The measles vaccine has also demonstrated a mortality benefit unexplained by preventing measles infection alone [11] and a higher mortality benefit in girls [11, 16–19]. Aaby et al. (2010) performed a randomized controlled trial to evaluate if a 25% difference in mortality existed between children aged 4.5 months and 3 years of age after vaccination with the Edmonston-Zagreb measles vaccine at 4.5 months and 9 months, compared with the standard in Guinea-Bissau of 1 dose at 9 months of age. They randomized 6648 children after their 3 doses of diphtheria, tetanus, pertussis vaccine into 3 groups: Edmonston-Zagreb measles vaccine at 4.5 and 9 months of age (group A), Edmonston-Zagreb measles vaccine at 9 months of age only (group B), and Schwarz measles vaccine at 9 months of age only (group C) [17]. They found that a 2-dose measles vaccination was associated with a 22% reduction in all-cause mortality. They confirmed that prevention of measles infection only explained a small portion of the effect on overall mortality [17]. The nonspecific protective effects may exist in all live vaccines, but this requires further research (Table 1).

Table 1. Characteristics of Live Attenuated Vaccines

Cost [35]	Repeat administration [36]	Induction of innate immunity [21, 37]	Mucosal immunogenicity	Rare complication	Adverse events	Contraindication	Culture [38]	Combination vaccines in USA [36]	Route [36]	US tradename	Criteria
\$21 per dose	Experienced but not performed in USA [39]	All live attenuated vaccines cause induction of the innate immune system as a first step to create immunity	With the intranasal measles vaccine [40]	Subacute sclerosing panencephalitis (0.7/ million) [41]	Serum sickness like arthralgias; febrile seizures [41]	Allergy to neomycin, gelatin, immunocompromised, pregnancy [41]	Chicken embryo fibroblast	Mumps, measles, rubella with varicella	Subcutaneous	M-M-R II	MMR
\$0.15 per dose	Yes	Yes [21]	VAPP (1/million) only with VAPP, fever, OPV2; cVDPV also rare	VAPP (1/million) only with VAPP, fever, OPV2; cVDPV also rare	vomiting, diarrhea [42]	Allergy to vaccine component; pregnancy, it should be used with caution [42]	Monkey kidney cells	bOPV (OPV1 and OPV3; not in use in USA)	Oral	Substituted by Ipol (IPV) in USA	OPV
\$2-3 per dose worldwide; intravesicular use around \$160 in USA [43]	Experienced but not performed in USA [44]		Yes [45]	BCG osteitis [46]	Disseminated disease in immunosuppressed [46]	Immunosuppression, allergy to component of vaccine, active tuberculosis [46]	Surface pellicle on synthetic medium [47]	Not administered as a combination vaccine in USA	Percutaneous intravesicular	BCG vaccine, TICE	BCG
\$18.88 per dose	Yes	Yes [21]	Guillain-Barré syndrome (controversial) [48]	Flu-like syndrome, wheezing, nasal congestion [48]	Flu-like syndrome, wheezing, nasal congestion [48]	Immunosuppression, allergy to component of vaccine, pregnancy, CSF leak, concomitant aspirin, Reye's syndrome [48]	Egg based	Not administered as a combination vaccine in USA	Intranasal	FluMist	Influenza
\$9750 per dose, \$71.88 per dose (pentavalent)	Yes	Yes [21]	Intussusception [49]	Cough, runny nose, fever, vomiting [49]	Intussusception [49]	History of uncorrected congenital gastrointestinal malformation, intussusception, hypersensitivity to component of vaccine, severe combined immunodeficiency disease [49]	Virus from calf and human mixed	Not administered as a combination vaccine in USA	Oral	Rotarix, RotaTeq	Rotavirus
\$212-\$240 per dose	Limited evidence [50]	Experienced [51]	Transmission of virus, anaphylaxis [52]	Headache and injection site reactions [52]	Headache and injection site reactions [52]	History of anaphylactic reaction to component of the vaccine, immune suppression [52]	Use human cell strains	Not administered as a combination vaccine in USA	Subcutaneous	Zostavax (discontinued in USA)	Shingles
\$109.26 per dose	Yes	No sufficient data	Reye syndrome in children following use of salicylates [53]	Fever, injection site reactions, rash [53]	Fever, injection site reactions, rash [53]	History of severe allergic reaction to any component of the vaccine, immunosuppression, moderate or severe febrile illness, active untreated tuberculosis, pregnancy [53]	Use human cell strains	Mumps, measles, rubella with varicella	Subcutaneous	Varivax	Varicella

Abbreviations: BCG, Bacillus Calmette-Guérin; CSF, cerebrospinal fluid; cVDPV, circulating vaccine-derived poliovirus; IPV, inactivated polio vaccine; MMR, measles, mumps, rubella; OPV, oral polio vaccine; VAPP, vaccine-associated paralytic poliomyelitis.

PROPOSED MECHANISMS FOR THE NONSPECIFIC EFFECTS OF VACCINES

Live viral vaccines have been known to activate the innate immune system utilizing various pattern-recognition receptors, including Toll-like receptors (TLRs) and nucleotide binding oligomerization domain-containing protein 2 (NOD2). Live vaccines closely mimic natural infections and activate TLRs and NOD2, producing a stronger immune response when compared with nonlive vaccines [19–22]. Live vaccines can then confer immunity by activating immune effector cells, which neutralize viral replication, promote opsonophagocytosis of pathogens, activate the complement cascade, bind to active sites of toxins [21], or kill cells via direct contact or cytokine production. CD4⁺ T lymphocytes, activated by dendritic cells in response to vaccines, differentiate into T-helper subsets that have unique functions: T-helper (Th) 1 cells produce interferon (IFN)- γ , tumor necrosis factor (TNF), and interleukin (IL)-2 and protect against intracellular pathogens; Th17 effector cells protect mucosal surfaces and produce IL-17, IL-22, and IL-26; and Th2 cells mediate production of immunoglobulin (Ig) E via IL-4, IL-5, and IL-13 to protect against extracellular pathogens [21]. While antibodies produced from vaccination help prevent disease, the immune training by live vaccines is thought to decrease the severity of disease and the amount of damage to organic tissue, including mucosal surfaces, by reducing viral shedding and invasive pathogens, allowing for nonspecific protection against other pathogens. This effect was demonstrated by Uppill-Brown et al. (2017), a randomized controlled trial that found that OPV use was associated with decreased prevalence of *Shigella* and *E. coli* diarrhea among male children and of *Campylobacter jejuni* diarrhea among children of both sexes in Bangladesh [23].

In addition to promoting adaptive immunity, live vaccines provoke a reconfiguration of the innate immune cells by epigenetic manipulation of these cells, as seen with the BCG vaccine. Kleinnijenhuis et al. (2012) demonstrated that monocytic phenotype modification occurred at least 2 weeks after BCG vaccination in humans. The CD14⁺ monocyte population markedly increased after vaccination, with a positive associated change in CD11b and TLR 4 expression that was still present at 3 months postvaccination, mediated by PRR NOD2 by methylation of histone H3 at lysine 4 [20]. This led to a 2-fold increase in release of cytokines in response to nontargeted bacterial and fungal pathogens and an early enhanced antimicrobial capacity by the innate immune system [20]. Brook et al. (2020) demonstrated that BCG vaccination in neonatal mice was associated with marked improvement in survival during sepsis by utilizing emergency granulopoiesis as a potential protective mechanism [24]. Its mechanism is thought to be due to an increase in hematopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin-1 β , and interleukin-3, -6, within a few hours after BCG vaccination [24].

Kavanagh et al. (2010) examined the effects of the attenuated pertussis vaccine BPZE1 on severity of pertussis infection in animal models. They found that attenuated BPZE1 was associated with reduced bronchial hyperreactivity and inflammatory infiltration of the airways compared with mice who were not immunized and challenged with a virulent pertussis strain [16]. BPZE1 reduced ovalbumin-induced IgE and increased IFN- γ , suggesting predominant induction of Th1 rather than Th2 cells. Cauchi and Lochter et al. (2018) proposed that BPZE1 offered heterologous protection against other respiratory pathogens, including influenza and RSV, by cross-reactive B and T cells. BPZE1 was associated with decreased death and lung colonization by *B. bronchiseptica* and reduced inflammation, neutrophil, and tissue damage in the lungs of mice. More importantly, BPZE1 protected against lymphocyte depletion and cytokine hyper-response, evidenced by decreased levels of IL-1 β , IL-6, and granulocyte-macrophage colony-stimulating factor [18]. This effect may be mediated by the adenylate cyclase toxin (ACT) in PTX-deficient strains (a virulent factor important for transmission), inhibiting the expression of genes coding for proinflammatory cytokines IL-1 β , TNF- α , and IL-8, hence opposing inflammatory responses [18]. These mechanisms may be the foundation of possible benefits against SARS-CoV-2, some examples of which are illustrated in Figures 1 and 2 and Table 2. A summary of the evidence of the non-specific effects of vaccines can be found in Table 3.

THE NONSPECIFIC EFFECT OF VACCINES AGAINST SARS-COV-2

SARS-CoV-2 is a complex virus that has mechanisms of invasion and evasion of the immune system we have yet to fully understand. It seems to provoke a dysregulated, hyper-immune response leading to severe disease. Arunachalam et al. (2020) proposed that COVID-19 infection impairs the innate immune cells in the peripheral blood by suppressing cytokine production through suppressed TLR stimulation [25]. In addition, SARS-CoV-2 has a N-terminal nonstructural protein 1, which suppresses host gene expression and shuts down parts of the innate immune system involved in antiviral defense, such as IFN- β [26]. Earlier studies of SARS-CoV showed that its papain-like protease inhibits the IRF3 pathway, eliciting a high IFN response as well as inhibiting pro-inflammatory cytokines in TLR3 and retinoic acid-inducible gene pathways (RIG-1) [26, 27]. It also antagonizes the signaling activity of TLR7 for production of interferon, IL-6, and IL-8 [27]. Qian Zhang et al. (2020) found that 3.5% of patients with severe COVID-19 pneumonia had defects at 8 of 13 loci involved in the TLR3 and IRF7 induction of type 1 IFNs, further arguing the importance of such pathways [28]. Therefore, SARS-CoV-2 causes a maladaptive innate immune system response that also affects adaptive immunity [29]. If an impairment of the innate immune system is critical to SARS-CoV-2's transmission and infection, one may hypothesize that

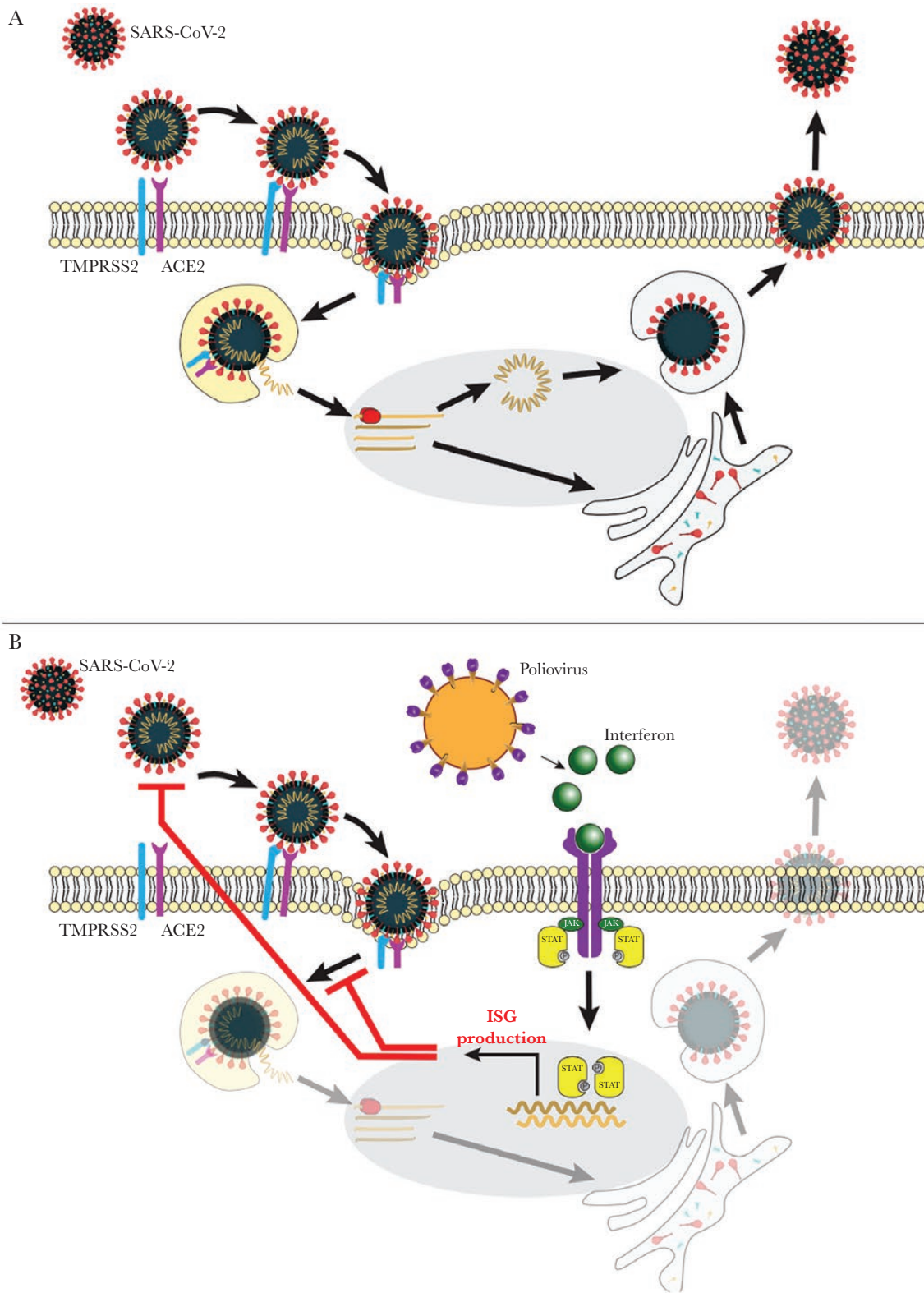


Figure 1. Proposed mechanism of viral interference induced by the nonspecific effects of vaccines. A, SARS-CoV-2 life cycle: SARS-CoV-2 uses ACE2 and PMPRSS2 receptors to gain entry into human mucosal cells. Upon entry, it replicates using viral proteases and viral RNA polymerase enzymes. Viral particles are assembled in the Golgi apparatus and exocytosed through the endoplasmic reticulum. B, Nonspecific viral interference: Viruses that induce a type I interferon response before infection can preemptively block viral replication in susceptible mucosal cells. As shown in this figure, polio virus can induce a type I interferon response that triggers an innate immune response in mucosal cells in an autocrine and paracrine fashion. Upon binding to the interferon receptor, IFN- α promotes production of antiviral ISGs. These ISGs block multiple steps of SARS-CoV-2 replication including entry, transcription, translation, and assembly, resulting in blocking of infection. Abbreviations: IFN, interferon; ISG, interferon-stimulating gene; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

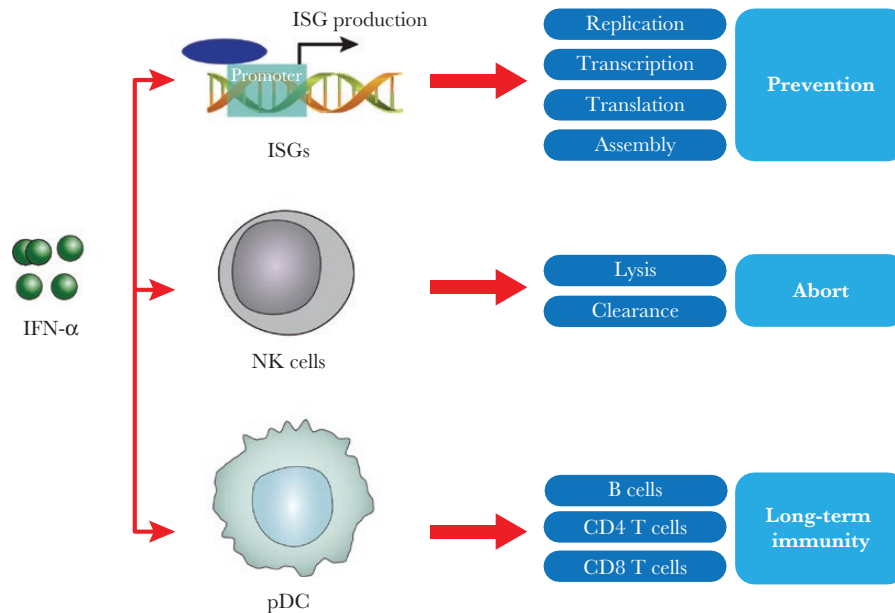


Figure 2. Summary of possible mechanisms of viral interference by live vaccines. Most live vaccines induce strong innate immune responses that lead to induction of IFN-alpha secretion in mucosal surfaces. IFN-alpha stimulates antiviral innate immunity, which may lead to blocking SARS-CoV-2 replication via ISGs and eliminating infected cells via NK cells and priming dendritic cells for long-term immunity against SARS-CoV-2. Abbreviations: IFN, interferon; ISG, interferon-stimulating gene; NK, natural killer; pDC, plasmacytoid dendritic cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

priming the innate immune system before infection can offset infectivity or attenuate COVID-19 disease.

TLR3/TLR7 stimulation is implicated in the nonspecific effect of vaccines by changing cytokine profiles and favoring Th1 rather than Th2 production, which plays a more significant role in response to viral infections [19]. In theory, this stimulation would provoke early activation of the innate immune system, including dendritic cells, which are the main determinants of CD4 T+ cell differentiation [16]. A skewed differentiation toward Th1 cells can lead to higher activation of CD8 T+ cells, extrafollicular B-cell help, enhanced dendritic cell activation, and rapid effector memory T-cell responses in the periphery

to assist in cytotoxic activity against viruses [21]. In addition, the production of IFN-gamma may be beneficial, as it has been known to antagonize fibrosis and tissue remodeling by Th2 in asthma cases, which may help in reducing pulmonary disease in severe COVID-19 disease [16]. “Lifelong” immunity from these vaccines may be conferred by high antibody responses due to antigen persistence, which could lead to production of enough mucosal IgG and IgA to protect mucosal surfaces against viral invasion, ultimately protecting [21] against parenchymal damage by viruses or secondary pathogens [30].

Benn et al. (2020) presented 6 principles of the vaccine paradigm based on assumptions and contradictions regarding the nonspecific effects of vaccines that might be useful in optimizing the use of such vaccines [31]. Principles such as “the most recent vaccination has the strongest nonspecific effects” lead us to hypothesize that even though SARS-CoV-2 suppresses TLR signaling, use of OPV or other live vaccines prophylactically before COVID infection could activate innate immunity via TLRs and prime the immune system for adaptive immunity in the case of subsequent infection with SARS-CoV-2. Though there is an effort by the WHO and UNICEF to withdraw OPV a year after wild polio virus eradication, the potential benefits of OPV regarding COVID-19 warrant prospective studies to assess the impact that OPV may have on decreasing the morbidity and mortality from COVID-19 worldwide. Given the high rates of morbidity and mortality from COVID-19 we have already experienced, it is vital to perform these studies immediately.

Table 2. Immunologic Mechanisms for the Nonspecific Protective Effects of Vaccines^a

Epigenetic modification of monocytes
Cross-reaction between B and T cells, conferring protection from other pathogens
Favored differentiation of Th1 cells, increasing IFN-γ and propagated recruitment of innate immune cells
Production of mucosal IgA/IgG
Competition with invasive pathogens for host factors
Early activation of CD4 and CD8 T cells via PRR, including TLR
Anti-inflammatory properties
Early protection against tissue damage
Increase in granulopoiesis

Abbreviations: IFN, interferon; Ig, immunoglobulin; TLR, Toll-like receptor.

^aSummary of proposed mechanisms discussed in this paper.

Table 3. Summary of Evidence for the Nonspecific Effect of Vaccines^a

Live Attenuated Vaccine	Nonspecific Effects/Benefit Observed
Oral polio virus	<ul style="list-style-type: none"> Reduced days of diarrhea ($P = .0025$) and fewer episodes of <i>Shigella/EIEC</i> when compared with IPV in male infants [23] Reduction in detection of <i>C. jejuni/coli</i> in all infants [23] Lower admissions due to lower respiratory tract infections in vaccinated children [9] OPV campaigns associated with significant decreases in mortality rate (MRR, 0.75), with additional doses associated with a reduction of 14% in mortality rate [8] Lower admissions due to lower respiratory tract infections in vaccinated children [9] A risk reduction of up to 35% in hospitalization due to infectious diseases in the second year of life in high-income countries [54]
MMR	<ul style="list-style-type: none"> Reduction in mortality of 3-fold in neonatal vaccinated boys [55] BCG scar associated with lower mortality for children when compared with those without a scar (MR, 0.45; 95% CI, 0.21–0.96) [56] BCG scar associated with a significant reduction in risk of death from malaria [56] An increase of 10% in BCG index was associated with a mortality reduction of 10.4% in COVID-19 mortality [57] Induces emergency granulopoiesis improving survival in neonatal mice during sepsis [24] Produces strong innate immune responses to provide indirect protection against RSV [19]
Monovalent measles	<ul style="list-style-type: none"> Two doses were associated with an all-cause mortality reduction of 22% when given before DTP vaccine in children 4.5–36 months of age [17] Lower mortality among vaccinated children vs unvaccinated children (HR, 0.76; 95% CI, 0.63–0.91), especially for early vaccinated children [58] Early vaccination was associated with a lower risk of hospital admission, particularly for respiratory infections [59]
Attenuated <i>Bordetella pertussis</i> vaccine (BPZE1)	<ul style="list-style-type: none"> In animal studies, protects against inflammation and allergen-driven airway pathology from infections due to <i>Bordetella</i> species, RSV, and influenza [16, 18]

Abbreviations: BCG, Bacillus Calmette-Guérin; COVID-19, coronavirus disease 2019; DTP, diphtheria, tetanus, pertussis; EIEC, enteroinvasive *Escherichia coli*; HR, hazard ratio; IPV, inactivated polio vaccine; MR, mortality rate; MRR, mortality rate ratio; OPV, oral polio vaccine; RSV, respiratory syncytial virus.

^aThis table is not exhaustive of all available data in the literature for all live attenuated vaccines. It summarizes some of the data available that demonstrate the nonspecific effects of vaccines.

POSSIBLE RESISTANCE TO OPV USE

Adverse effects associated with OPV exist; vaccine-associated paralytic poliomyelitis (VAPP) is a serious side effect more often associated with serotype 2 in unvaccinated people. VAPP is rare, occurring every 1 in 2.7 million doses of OPV [32], and there is no evidence suggesting that VAPP causes outbreaks [1]. Circulating vaccine-derived poliovirus (cVDPV) is associated with person-to-person transmission that circulates in a community, but it is also considered rare. From July 2019 to February 2019, 33 outbreaks were reported, with 366 cases identified in 2019 [33, 34]. In 2020, there was an increase of 1037 cases of cVDPV reported; these were attributed to poor-quality response to outbreaks, declining immunity to the type 2 virus after switching from trivalent to bivalent OPV, and poor routine immunization [34]. This was further exacerbated by a 4-month pause in house-to-house polio vaccination campaigns [34]. The major risk factor for cVDPV is low vaccination and low immunity in a community. Outbreaks can be prevented and stopped with high-quality, effective, large-scale immunization events. Furthermore, under the WHO Emergency Use Listing, the vaccine nOPV2 will initiate use in countries where cVDPV2 is causing outbreaks, with the end goal of stopping cVDPV2 [34]. However, transmission of infection via shedding after vaccination is less likely in high-income countries such as the United States, where people are vaccinated at a young age and considered to have lifelong immunity to polio virus.

CONCLUSIONS

The dysregulated immune response in COVID-19 disease is critical in the morbidity and mortality associated with SARS-CoV-2 infection, leading to massive tissue and endothelial damage. “Trained” immunity by live, attenuated vaccines may be a method to prophylactically prevent infection and/or progression of disease by inducing a robust response by the innate immune system, which not only would confer protection against the evasive mechanisms of SARS-CoV-2, but also prime adaptive immunity. This review presents the available evidence for the nonspecific effect of vaccines and proposed mechanisms by which these vaccines may mitigate the severity of COVID-19 disease and likely future pandemics due to respiratory viruses. The low-cost, safety, and proven nonspecific effects of OPV make it an excellent candidate for immediate use while battling SARS-CoV-2 vaccine inequity, distribution, and ongoing infection.

Acknowledgments

Financial support. Partial funding for open access was provided by the University of Maryland Health Sciences and Human Services Library’s Open Access Fund.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed. None to disclose.

Patient consent. This manuscript does not include factors necessitating patient consent.

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