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Oral poliovirus vaccine (OPV), comprising live attenuated viruses, can reduce the incidence of other infections. Albert Sabin, who developed an OPV, administers the vaccine, 1966.

VIEWPOINT: COVID-19

Can existing live vaccines prevent COVID-19?

Live vaccines can prevent unrelated infections and may temporarily protect against COVID-19

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Prophylactic vaccination is the most effective intervention to protect against infectious diseases. The commonly accepted paradigm is that immunization with both attenuated virus (live but with substantially reduced virulence) and inactivated (killed virus particles) vaccines induces adaptive and generally long-term and specific immunity in the form of neutralizing antibodies and/or activating pathogen-specific cellular immune responses. However, an increasing body of evidence suggests that live attenuated vaccines can also induce broader protection against unrelated pathogens likely by inducing interferon and other innate immunity mechanisms that are yet to be identified. The stimulation of innate immunity by live attenuated vaccines in general, and oral poliovirus vaccine (OPV) in particular, could provide temporary protection against coronavirus disease 2019 (COVID-19).

OPV was developed by Albert Sabin in the 1950s and consists of live attenuated polioviruses of the three serotypes. Early clinical studies showed that besides protecting against poliomyelitis, OPV reduced the number of other viruses that could be isolated from immunized children, compared with placebo recipients. Additional evidence of nonspecific effects of OPV came from the 1959 poliomyelitis outbreak in Singapore caused by type 1 poliovirus that was successfully stopped by the use of monovalent OPV that contained only type 2 poliovirus (*1*). Monovalent OPVs do not induce cross-neutralizing antibodies that target other virus serotypes, so the most plausible explanation was viral interference, which presumably is mediated by innate immunity.

Large-scale clinical studies of OPV for nonspecific prevention of diseases were carried out in the 1960s and 1970s. These involved more than 60,000 individuals and showed that OPV was effective against influenza virus infection, reducing morbidity 3.8-fold on average (*2, 3*). OPV vaccination also had a therapeutic effect on genital herpes simplex virus infections, accelerating healing. OPV not only demonstrated positive effects against viral infections but also had oncolytic properties, both by directly destroying tumor cells and by activating cellular immunity toward tumors (*2*). These observations were among the first examples of viral oncotherapy, which is being actively pursued.

To extend the therapeutic effect of OPV against viral infections and cancer, three monovalent OPVs were used sequentially. In addition, several nonpathogenic enteroviruses isolated from healthy individuals [called live enterovirus vaccines (LEVs)] were tested for safety (*2*). They were also used in more than 90,000 individuals for nonspecific protection and found to reduce incidence of seasonal influenza and acute respiratory diseases (*2, 3*). Subsequently, in Bulgaria, mass immunization with OPV helped to control a 1975 outbreak of unrelated acute poliomyelitis-like disease caused by Enterovirus 71 (*4*).

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More recent studies confirmed these broad protective effects of OPV. Data from a randomized controlled trial (RCT) of OPV in Guinea-Bissau, West Africa, showed that OPV given at birth reduced infant mortality by ~32% (*5*). In addition, an analysis of the effect of annual and biannual national OPV immunization campaigns showed that they reduced all-cause mortality by 19%, with each subsequent campaign adding a further 13% reduction (*6*). This means that repeated immunization has an additive effect despite antibodies induced by the first vaccination. Depending on initial age, it was necessary to give OPV to between 68 and 230 children to prevent one death within the first 3 years of life (*6*). These observations were made in the complete absence of poliovirus circulation, emphasizing the nonspecific nature of the OPV-induced protection. In RCTs comparing OPV against inactivated polio vaccine (IPV), it was found that OPV reduced the burden of bacterial diarrheal disease in infants in Bangladesh (*7*). In Finland, immunization with OPV was associated with less doctor-diagnosed acute otitis media (middle ear infection, which can be caused by both viruses and bacteria) than in the IPV-immunized group (*8*). Furthermore, a retrospective study from Denmark found that the use of OPV was associated with reduced hospital admissions for respiratory infections in children.

These nonspecific beneficial effects may not be limited to OPV and LEV. Other live attenuated viral vaccines such as those against measles (*5*) and smallpox (*9*) have also been associated with pronounced nonspecific protective effects against infectious diseases. In Africa, when measles vaccine was introduced in the community, the overall mortality in children declined by more than 50%, a reduction that was far larger than anticipated on the basis of the protection against measles deaths alone (*10*). A large-scale RCT confirmed that the measles vaccine was associated with a 30% reduction in overall mortality in children; only 4% was explained by prevention of measles infection (*5*).

Attenuated bacterial vaccines such as Bacillus Calmette–Guérin (BCG) against tuberculosis, as well as experimental live attenuated vaccine against pertussis (whooping cough), were also shown to protect against heterologous infections (*5*, *11*). In addition, live pertussis vaccine also prevented noninfectious inflammatory diseases (*11*). RCTs showed that BCG vaccine at birth was associated with more than a one-third reduction of neonatal mortality, because BCG vaccine protected against deaths from septicemia and pneumonia (*5*). In 2014, an expert panel at the World Health Organization reviewed the evidence for nonspecific effects of live vaccines and concluded that they reduced childhood mortality by more than would be expected through their effects on the diseases they prevent (*12*). It is important to note that non-live (inactivated) vaccines do not seem to have the same effects, suggesting that replicating attenuated pathogens induce a broader immune response.

Some of the nonspecific effects of vaccines may be mediated by interferons. However, the mechanism may be more complex and diverse. Numerous studies have shown that BCG activates the innate immune system, resulting in enhanced responsiveness to subsequent triggers, so-called "trained innate immunity" (*13*). BCG given 4 weeks prior to a yellow fever vaccine significantly reduced virus load, confirming that it could modify the course of a viral challenge in vivo. The effects were mediated through epigenetic modifications in innate immune cells, leading to higher innate cytokine production (*13*). BCG can also induce emergency granulopoiesis within hours of administration, leading to a marked increase in the number of circulating neutrophils, providing protection from sepsis (*14*). The duration of the nonspecific protection induced by live vaccines is unknown but has been observed to last for many months to years after vaccination. For example, BCG given at school entry (5- to 6-year-olds) in Denmark was associated with a 42% reduction in the risk of dying from natural causes until the age of 45 years (*9*).

Recent reports indicate that COVID-19 may result in suppressed innate immune responses (*15*). Therefore, stimulation by live attenuated vaccines could increase resistance to infection by the causal virus, severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2). Clinical studies of this hypothesis could begin immediately. BCG trials have already been initiated by immunizing frontline health care workers (NCT04327206, NCT04328441). The endpoint of these trials is the difference in COVID-19 incidence, duration, and severity between immunized and unimmunized populations.

We propose the use of OPV to ameliorate or prevent COVID-19. Both poliovirus and coronavirus are positive-strand RNA viruses; therefore, it is likely that they may induce and be affected by common innate immunity mechanisms. There are multiple important advantages to using OPV: a strong safety record, the existence of more than one serotype that could be used sequentially to prolong protection (*2, 3*), low cost, ease of administration, and availability. Over 1 billion doses of OPV are produced and used annually in more than 140 countries. Although the supply of BCG is limited, a small fraction of OPV intended for the suspended polio eradication campaign would be sufficient for the clinical trials, and provided a positive outcome, production could likely be scaled up quickly.

Another advantage of OPV over BCG is safety. Up to 1% of BCG recipients require medical attention, owing to adverse reactions. The risk of complications due to OPV is extremely low. Vaccine-associated paralytic polio (VAPP) develops in 1 per 3 million vaccine doses given to unimmunized individuals and mostly occurs in immunocompromised children. Sequential use of IPV followed by OPV demonstrated that prior immunization eliminates the risk of VAPP. In populations with inadequate immunity, OPV was also shown to generate circulating vaccine-derived polioviruses (cVDPVs). However, in countries with sufficient vaccine coverage, the risk is minimal: Over 35 years of OPV use in the United States has resulted in no documented case of cVDPV. Therefore, if used properly, OPV is likely a safer choice than BCG.

If the results of RCTs with OPV are positive, OPV could be used to protect the most vulnerable populations. However, OPV would be most effective if the entire population of a country or region is immunized synchronously. OPV produces herd effects, and in addition to protecting vulnerable individuals, could also prevent the spread of SARS-CoV-2 by increasing the proportion of unsusceptible individuals. The strategy of inducing nonspecific protection may even have an advantage over a SARS-CoV-2–specific vaccine if SARS-CoV-2 undergoes mutation that leads to antigenic drift (and loss of vaccine efficacy), similar to seasonal influenza viruses. If proven to be effective against COVID-19, emergency immunization with live attenuated vaccines could be used for protection against other unrelated emerging pathogens. ■

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