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Clinical Perspective: Potential use of Polio Vaccine for COVID-19 Prevention

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Abstract: The novel coronavirus disease 2019 (COVID-19) pandemic that caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a detrimental effect on every fabric of society. Childhood poliovirus vaccination is believed to have a causative link between SARS-CoV-2 immunity. This report was aimed to explore the effect and evidence of the polio vaccine in preventing COVID-19 infection. Literature has shown that the oral polio vaccine produces broader protection against unrelated pathogens. Both the poliovirus and coronavirus belong to the same positive-strand RNA virus category, which can be eliminated by common innate immunity mechanisms. Vaccination against the poliovirus triggers an adaptive humoral immune response that raises antibodies that cross-react with SARS-CoV-2.

Keywords: Poliovirus; Coronavirus; SARS-CoV-2; Infection

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a novel pathogen that causes coronavirus disease 2019 (COVID-19). SARS-CoV-2 is a lipid membrane enveloped, plus sense RNA virus that fuses with the membrane to enter host cells and replicate[1,2]. The symptoms of COVID-19 evolve and sometimes patients presented with no symptoms of infection[3,4]. After two years since the emergence of COVID-19 pandemic, its vaccines are still continuously being tested and developed. There are in total more than eight COVID-19 vaccines that have been granted World Health Organisation emergency use listing status[5] The Emergency Use Listing (EUL) of the World Health Organization (WHO) Prequalification Units is a one-of-a-kind WHO-facilitated regulatory pathway that can only be used in a declared public health emergency of international concern or another public health emergency designated by the WHO Director-General. The prominent example of the manufacturers of these vaccines are Oxford–AstraZeneca, Pfizer-BioNTech, Sinopharm, Moderna, Sinovac and Janssen. WHO's emergency use listing is a prerequisite for pooled facility vaccine supply and international procurement. Furthermore, regulatory agencies at

different countries can apply the ratification rules to grant for mass vaccination use. However, there is still a great shortage of COVID-19 vaccines especially in developing countries[6,7].

Other than seeking new technologies to create a potent cure, the exploration of existing medications for new therapeutic objectives, known as drug repurposing, is heavily relied to slow down the spread of pandemic. Comunale, Engineer [8] at Johns Hopkins University in the United States looks into the link between SARS-CoV-2 immunity and childhood poliovirus vaccination. This vaccination has been given to about 90% of the world's population, but the antibodies it produces diminish with time and are essentially non-existent by the end of adolescence which points out to the need of having booster dose for further protection[8]. Polio vaccines are vaccines used to prevent poliomyelitis (polio). Historically, Albert Sabin developed oral polio vaccine (OPV) in the 1950s, which is made up of live attenuated polioviruses of the three serotypes. Early clinical trials revealed that, in addition to protect against poliomyelitis, OPV vaccination lowered the number of other viruses that could be recovered from inoculated infants when compared to placebo recipients[9]. Two types are used: an inactivated poliovirus given by injection (IPV) and a weakened poliovirus given by mouth (OPV). This report was aimed to explore the effect of the polio vaccine in preventing COVID-19 infection

2. Repurposing Vaccine for COVID-19 Prevention

Considering the emergency situation, the drug repurposing approach is being widely applied to quickly identify therapeutic solutions due to availability of their pharmacokinetic, toxicological and manufacturing data[10]. Drug repurposing includes drugs that are either FDA approved, investigational, withdrawn or shelved molecules. Although there are studies of the repurposing and marketed drugs which proposed several candidates for SARS-CoV-2 treatment[11] .

Drug repurposing involves the investigation of existing drugs for new therapeutic purposes[12]. Worldwide large-scale clinical studies of oral polio vaccine against nonspecific prevention of disease found that it was effective against infection caused by non-polio virus[13,14]. The secret lies in the weakened viruses that stimulate the innate immune system more broadly to fight new pathogens[15].

3. Repurposed Polio Vaccine's Effect on SARS-CoV-2

US National Institutes of Health to fund Robert Gallo (Institute of Human Virology at the University of Maryland School of Medicine) a large-scale clinical trial to test the polio vaccine's efficacy against SARS-CoV-2[16]. He and his colleagues co-authored a perspective piece in Science last year and in Proceedings of the National Academy of Sciences this year, suggesting that live attenuated vaccines, like the oral polio vaccine, can also produce broader protection against unrelated pathogens, possibly by inducing interferon and other innate immunity mechanisms not yet identified[17,18]. Innate immune responses are the first to respond to an infection, but until recently were not thought to have any immunological memory of the pathogens they come in contact with. The polio vaccine, has been shown to

stimulate innate immune responses for a prolonged period of time, what we refer to as trained immunity[17,18]. Both the poliovirus and coronavirus are positive-strand RNA viruses, which means it is likely that they will induce and be affected by common innate immunity mechanisms[8] (Figure 1). Secondly, RdRp from SARS-CoV-2 and poliovirus had similar molecular weights of approximately 130 kD, with similar tertiary and quaternary structures[8]. Both were bound at one site, at least, by the mouse anti-RdRp monoclonal antibody 4E6[8]. More than one serotype can be used sequentially to prolong protection, and the vaccine is cheap and easy to administer[10,19].

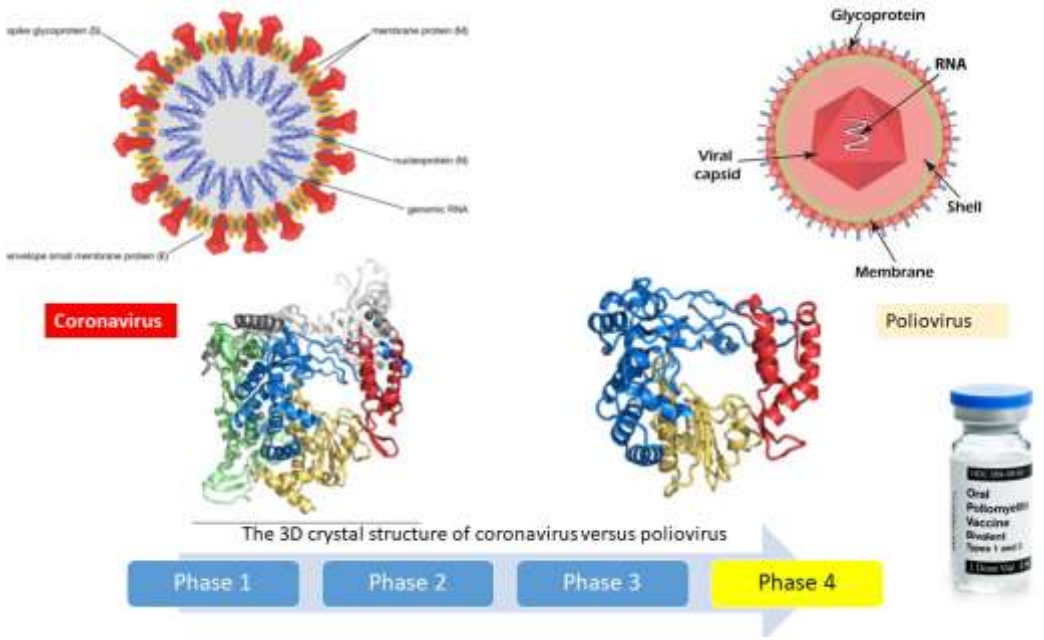

Figure 1. Structural and characteristics comparison between coronavirus and poliovirus.

Early clinical investigations have demonstrated that some vaccines, such as the poliovirus vaccine, can protect people not only against the virus for which it was designed (polio), but also against other, structurally related viruses[20]. In randomised controlled trials done to compare OPV and IPV, OPV reduced the number of bacterial diarrheal illness in Bangladeshi newborns as compared to IPV[21]. In Finland, OPV vaccination was linked to fewer doctor-diagnosed acute otitis media (middle ear infection caused by both viruses and bacteria) than IPV vaccination[22]. According to Gold et al, from World Organization (Watkinsville, Georgia, US) "Analysis of Measles-Mumps-Rubella (MMR) Titers of Recovered COVID-19 Patients" found an inverse relationship between SARS-CoV-2 susceptibility and the severity of COVID-19, as well as mumps antibody titers[23].

The poliovirus and SARS-CoV-2 both have a single-stranded ribonucleic acid (RNA) molecule as their genetic material, and all proteins are transcribed straight from this template strand. The genome is copied off this strand during viral replication in both, using the RNA-dependent-RNA-polymerase (RdRp) protein generated[17]. Inactivated vaccinations against RNA viruses (such as Poliovirus and Coronavirus) stimulate an immune response that identifies the inactivated viral particle's non-structural antigens. Both the coding region and

the 3-dimensional modeling show significant similarities between Poliovirus and SARS-CoV-2 RdRp, as shown in Figure 1.

Chumakov *et al*. published a perspective piece in Science in year 2020, suggesting that live attenuated vaccines, like the oral polio vaccine, can also produce broader protection against unrelated pathogens, possibly by inducing interferon and other innate immunity mechanisms not yet identified. The polio vaccine has been shown to stimulate innate immune responses for a prolonged period of time, what we refer to as trained immunity[24]. Trained immunity is developed by innate immune cells, such as monocytes, macrophages, and natural killer (NK) cells, after an infection or vaccination[25]. Chumakov referred to a three-year controlled trial conducted in Russia[26] as the strongest evidence in support of using disease-specific vaccines to broadly ward off other viruses. In the 1960s study, giving adults doses of the oral poliovirus vaccine reduced fatalities from seasonal influenza and acute respiratory infections by thrice, according to researchers[9].

Chumakov and his co-authors also cite other studies and anecdotes in which an oral poliovirus vaccine has effectively prevented another strain of poliovirus, which the vaccine was not specifically designed to treat: Pawlowski et al. examined the immunization records of 137,037 people who had SARS-CoV-2 PCR tests in a 2020 exploratory study. The result demonstrated that polio, Hemophilus influenzae type B (HIB), measles-mumps-rubella (MMR), varicella, pneumococcal conjugate (PCV13), geriatric flu, and hepatitis A/hepatitis B (HepA-HepB) vaccines given in the previous 1, 2, and 5 years are linked to lower SARS-CoV-2 infection rates. Most importantly, polio and HIB vaccinated cohorts generally have the lowest relative risks for SARS-CoV-2 infection[27]. Pawlowski et al. concluded in their study, that individuals who have recently been vaccinated with one of the following vaccines: Polio, HIB, MMR, Varicella, PCV13, Geriatric Flu, or HepA-HepB had decreased rates of SARS-CoV-2 infection. These vaccines appear to be good candidates for preclinical animal investigations and clinical trials in the future[27]. For example, a positive link was found between median population age and SARS-CoV-2 prevalence and death rates, according to analyses of median population age. COVID-19 cases are fewer and less harmful in countries with effective poliovirus immunization procedures and younger populations. Poliovirus and SARS-CoV-2 antibodies were identified in pediatric and adult sera newly inoculated with polio.

Similarly, Comunale *et al*.[8] conducted a retrospective analysis on sera from 204 individuals to investigate the role of poliovirus immunization in reducing COVID-19's impact in a population. The study showed that in all tested samples, poliovirus vaccination raises antibodies that cross-react with SARS-CoV-2, with the primary target of these antibodies being the RdRp of poliovirus and coronavirus. Antibodies detected the RdRp of both viruses in Western blots. SARS-CoV-2 infection of Vero cell cultures was suppressed by sera from polio-immunized people. These findings imply that the anti-D3-pol-antibody generated by poliovirus immunization may protect adults from SARS-CoV-2 in the same way as it protects children[8]. This open up an useful alternative for COVID-19 prevention for children because the safety data for existing COVID-19 vaccine has not been established,

especially the paediatrician is concern of the increased risk of having myocarditis post vaccination[28,29].

Vaccination against the poliovirus triggers an adaptive humoral immune response. Poliovirus vaccine antibodies bind to the RdRp protein of both poliovirus and SARS-CoV-2, preventing SARS-CoV-2 infection. These findings show that proteins other than "spike" proteins could be good foundations for vaccine development and protection[8]. The researchers also found anti-RdRp antibodies in a sample of both adults and children, which were able to recognize the RdRp of both viruses. Higher titers were seen in those who had received IPV. This hints that the use of polio vaccine could be potentially used for both paediatric and adult. Immune serum from these individuals inhibited viral replication in vero cells, with stronger effects being observed when the antisera were added to the cells before viral challenge. If SARS-CoV-2 develops mutation that leads to antigenic drift (and loss of vaccination efficacy), similar to seasonal influenza viruses, the strategy of inducing nonspecific protection may have an advantage over a SARS-CoV-2–specific vaccine. If proven successful against COVID-19, emergency immunization with live attenuated vaccines could be utilized to defend against other emergency outbreak such as bird flu, ebola virus *etc*[18]. Even though clinical trials for polio vaccine are proactively on-going (details shown in Table 1), it's important to note that just because a microbe expresses an antigen that's similar in sequence to a SARS-CoV-2 protein doesn't mean the two will exhibit cross-reactive immunity or any immune response at all, because that sequence may not be processed as an antigen by macrophages or presented to T cells[30]. The whole range of antigenicity determinants is still unknown. The concentration of the antigen, its dissimilarity to its host, where the antigen is expressed within a protein, how the antigen is presented to the immune system, and the inflammatory milieu in which the antigen is processed appear to be among the essential determinants[31].

Repurpusing numerous medications licensed for other uses is currently being tested in clinical trials. As of July 3, there are 3 ongoing clinical trials using polio vaccine as repurposing for COVID-19 prevention: two are conducted in the United States of America and one in Guinea-Bissau. Among the three studies, 2 are using OPV, while the remaining uses IPV (Table 1).

Table 1. List of on-going clinical trial repurposing polio vaccine for COVID-19 prevention.

Vaccine used	**Title**	**Location**	**Status/Phase**	**Sponsor**
Biological: Vaccinated with polio vaccine (IPV)	Polio Vaccine (IPV) for SARS-CoV-2 and Prevention of Coronavirus Disease (COVID-19)	RacIi Md National City, California, US	Phase 4; Completed recruitment of 300 participants	E-MO Biology Inc, US

Vaccine used	Title	Location	Status/Phase	Sponsor
Biological: Biological: oral polio vaccine Biological: Comparable Placebo Drug: NA-831 Drug: Comparable Placebo of drug Combination Product: Combination of oral polio vaccine and NA-831 Combination Product: Comparable Placebo of Oral Polio Vaccine and Placebo of drug	A Phase 3 Randomized Double Blind Efficacy and Safety Study of Oral Polio Vaccine and NA-831 for Covid-19	Coronavirus Research Institute-Testing Site, Los Angeles, California, US	Phase 3; Recruting 3600 participants	NeuroActiva, Inc., US
Standard dose bivalent oral polio vaccine	OPV as Potential Protection Against COVID-19	Bandim Health Project (Denmark)	Recruiting 3400 participants	Guinea-Bissau, Africa

Reference: [32]

Referring to Table 1, it is noteworthy that US Food and Drug Administration (FDA) is currently evaluating E-MO Biology Inc's application on the findings of the phase four clinical study for the emergency use authorisation. The said finding was submitted on June 22 and it highlighted the feasibility of polio vaccine to be repurposed as COVID-19 vaccine[8]. The clinical trial evaluated 300 subjects aged 18 to 80 years old and 100 per cent of the subjects produced an immune response that recognised protein (RdRp) of both poliovirus and SARS-Cov-2 in their blood samples after vaccination. The postulated mechanisms are stronger inhibition of SARS-CoV-2-induced cytopathic effects (CPE) in the cell culture. Furthermore, antisera from immunized individuals prevent SARS-CoV-2 CPE in cell cultures. Subsequently, the antisera successfully reduced RNA replication by inhibiting RdRp activity[8]. The findings aligned well with the postulated mechanism presented above.

Initiative to mass immunize population at risk with OPV is potentially useful for developing countries that have not secured the source of currently approved COVID-19 vaccines[19]. This mass immunization could potentially useful because the ease of oral administration, low drug cost and also proven safety profile[14]. This is especially applicable under the polio eradication programme whereby non-govermental organisation such as Bill and Melinda Gates Foundation has been supporting the cost of OPV for developing countries[33]. The protection caused by polio vaccine could help to prevent not just the polio

infection but potential also other viruses [14]. Indirectly, the health authority could expect the infection curve could be flatten before it could take its toll on the healthcare facilities including critical care unit for patients infected with stage 3 and stage 4 of COVID-19.

4. Conclusion

The drug repositioning strategy is widely used as an alternative approach to drug development since it lowers the risk of safety and toxicity and at the same time saves millions of dollars' worth of pharmaceutical R&D. Worldwide large-scale clinical studies of oral polio vaccine against nonspecific prevention of disease found that it was effective against infection caused by non-polio virus. The main mechanism lies in the weakened viruses that stimulate the innate immune system more broadly to fight new pathogens. Further clinical trial could provide further evidence on its indicated use for COVID-19 prevention.

Conflicts of Interest: The authors declare no conflict of interest.

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