

The use of non-specific protective effects of live vaccines to prevent SARS-CoV2

Summary

The current COVID-19 pandemic once again revealed unpreparedness of the International public health community to the emergence of novel pathogens leading to limited options for medical countermeasures. While extreme quarantines and the emphasis on personal hygiene and social distancing produced clear effect in China and South Korea, development and deployment of effective vaccines and antiviral treatments is still at least several months and possibly years away. There is a clear and urgent need for non-specific tools that could protect populations from this and other emerging infectious diseases. Here we propose that well-documented non-specific protective effects of licensed live attenuated vaccines could be used to slow down the spread of coronavirus and help to buy time for the development of specific products and therapies.

Background

Non-specific protective effects of Oral Polio Vaccine (OPV) have been demonstrated during early phases of its development. A 1959 poliomyelitis outbreak in Singapore caused by type 1 poliovirus was successfully stopped by the use of monovalent type 2 OPV (1). Monovalent OPVs do not induce cross-neutralizing antibodies so the only explanation is the viral interference. Large-scale clinical studies of OPV and other non-pathogenic enteroviruses (Live Enterovirus Vaccines, LEV) conducted in 1970s in the Soviet Union showed that they were effective against influenza, reducing morbidity by 70-80%, i.e. more than specific influenza vaccines (2). OPV and LEV were also effective against other viral diseases, including chronic herpes virus infections (3). Mass immunization by OPV helped to control an outbreak of acute poliomyelitis-like disease caused by Enterovirus 71 in Bulgaria (4).

More recent studies confirmed these observations on OPV. Data from a randomized trial of OPV at birth in Guinea-Bissau, West Africa, found that OPV vs. no OPV reduced infant mortality by a third (5). In addition, an analysis of the effect of frequent national OPV immunization campaigns showed that these campaigns reduced all-cause mortality by 19%, with each additional campaign reducing it further 13%(6). On average, immunization of 68-230 children resulted in one prevented death(6). These observations were made in the complete absence of poliovirus circulation, emphasizing their non-specific nature. In randomized clinical trials comparing OPV against IPV, it was found that OPV reduced the burden of diarrheal disease in infants in Bangladesh (7, 8). In Finland OPV vs. IPV was associated with less otitis media (9). A retrospective study from Denmark found that the use of OPV was associated with reduced hospital admissions (10).

These beneficial non-specific effects may not be limited to OPV/LEV. Other live vaccines such as vaccine against measles, BCG, and live pertussis vaccine have also been associated with pronounced non-specific protective effects. Non-live vaccines in contrast do not seem to have the same effects. Recently, WHO reviewed the evidence for non-specific effects of BCG and measles vaccine and concluded that both the use of BCG and measles-containing

vaccines (MCV) was associated with significantly reduced childhood mortality, much more than explained by the prevention of the target diseases (11).

The duration of the non-specific protection induced by live vaccines is unknown, but has been observed to last for many months after vaccination. It is likely that to some extent it is mediated by viral interference, which may be of shorter duration. However, the mechanism may be more complex and diverse. In a recent study of experimental live attenuated vaccine against pertussis it was found that it was also protective against heterologous infections, as well as non-infectious inflammatory diseases (12), suggesting that an immunomodulatory mode of action. For BCG, numerous studies have shown that it induces “trained innate immunity” (13) and this can lead to altered responses to unrelated pathogens. For instance, Dutch volunteers who received BCG vs. saline 4 weeks prior to a yellow fever vaccine had significantly lower yellow fever viral load (13). These effects have been shown to persist for months to years. Such mechanisms may also play a role for the protective non-specific effects of the viral vaccines (14). In conclusion, the emerging body of evidence suggests that besides inducing adaptive humoral and cellular immune responses, live vaccines also activate other branches of immune system, thus increasing resistance to a broad spectrum of pathogens. Stimulation of innate immune responses may be especially important for prevention of, or reducing the severity of COVID-19 because reports indicate that infection with SARS-CoV-2 results in suppressed innate immune responses (15, 16). One could also surmise that lower prevalence of COVID-19 among children could in part be explained by live vaccines that they receive.

Proposal

The exact mechanism of non-specific protection induced by live vaccines needs to be elucidated further. However it is very likely that their use could have beneficial protective effect against coronavirus infection, because OPV was successfully used to prevent another respiratory disease, influenza. Clinical studies of this hypothesis could begin immediately because the vaccines in question are licensed and have an excellent safety record. The trials could begin with immunization of the most vulnerable population such as front line health care workers, police force, or elderly and then expand to general population in the epicenters of disease. Countries still using OPV in their routine vaccination programs could expand its use to people of all ages by conducting regional immunization days using monovalent or bivalent OPV. The endpoint of such study could be the difference in morbidity / mortality between immunized and unimmunized populations, and the duration and severity of disease. Similar studies in countries that no longer use OPV, such as the US, Italy, and the rest of Europe could use their supply of monovalent OPV stockpiled for emergency response to possible polio outbreaks. Since OPV induces strong herd immunity, its effect on coronavirus infection would be maximal if the entire population of a region is immunized synchronously, to break the transmission of the virus. The study could begin with monovalent OPV1, followed by mOPV3 (after about 3-5 weeks). Additional vaccination with measles vaccine and possibly BCG could also be considered. Clinical trials involving off-label use of various drugs licensed for other indications are currently underway. The existing scientific rationale suggests that the same should be done for OPV and other live vaccines.

Conclusion

Here we propose a low-risk, low-cost study that can potentially have a significant impact on the spread of SARS-CoV2 until the time when specific vaccines and antiviral therapies are ready.

References

1. Hale JH, Doraisingham M, Kanagaratnam K, Leong KW, Monteiro ES. Large-scale use of Sabin type 2 attenuated poliovirus vaccine in Singapore during a type 1 poliomyelitis epidemic. *Br Med J*. 1959;1(5137):1541-9.
2. Chumakov MP, Voroshilova MK, Antsupova AS, Boiko VM, Blinova MI, Priimiagi LS, et al. [Live enteroviral vaccines for the emergency nonspecific prevention of mass respiratory diseases during fall-winter epidemics of influenza and acute respiratory diseases]. *Zhurnal mikrobiologii, epidemiologii, i immunobiologii*. 1992(11-12):37-40.
3. Voroshilova MK. Potential use of nonpathogenic enteroviruses for control of human disease. *Prog Med Virol*. 1989;36:191-202.
4. Shindarov LM, Chumakov MP, Voroshilova MK, Bojinov S, Vasilenko SM, Iordanov I, et al. Epidemiological, clinical, and pathomorphological characteristics of epidemic poliomyelitis-like disease caused by enterovirus 71. *Journal of hygiene, epidemiology, microbiology, and immunology*. 1979;23(3):284-95.
5. Lund N, Andersen A, Hansen AS, Jepsen FS, Barbosa A, Biering-Sorensen S, et al. The Effect of Oral Polio Vaccine at Birth on Infant Mortality: A Randomized Trial. *Clin Infect Dis*. 2015;61(10):1504-11.
6. Andersen A, Fisker AB, Rodrigues A, Martins C, Ravn H, Lund N, et al. National Immunization Campaigns with Oral Polio Vaccine Reduce All-Cause Mortality: A Natural Experiment within Seven Randomized Trials. *Frontiers in public health*. 2018;6:13.
7. Upfill-Brown A, Taniuchi M, Platts-Mills JA, Kirkpatrick B, Burgess SL, Oberste MS, et al. Nonspecific Effects of Oral Polio Vaccine on Diarrheal Burden and Etiology Among Bangladeshi Infants. *Clin Infect Dis*. 2017;65(3):414-9.
8. Aaby P, Benn CS. Beneficial Nonspecific Effects of Oral Polio Vaccine (OPV): Implications for the Cessation of OPV? *Clin Infect Dis*. 2017;65(3):420-1.
9. Seppala E, Viskari H, Hoppu S, Honkanen H, Huhtala H, Simell O, et al. Viral interference induced by live attenuated virus vaccine (OPV) can prevent otitis media. *Vaccine*. 2011;29(47):8615-8.
10. Sorup S, Stensballe LG, Krause TG, Aaby P, Benn CS, Ravn H. Oral Polio Vaccination and Hospital Admissions With Non-Polio Infections in Denmark: Nationwide Retrospective Cohort Study. *Open forum infectious diseases*. 2016;3(1):ofv204.
11. Higgins JP, Soares-Weiser K, Lopez-Lopez JA, Kakourou A, Chaplin K, Christensen H, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *Bmj*. 2016;355:i5170.
12. Cauchi S, Loch C. Non-specific Effects of Live Attenuated Pertussis Vaccine Against Heterologous Infectious and Inflammatory Diseases. *Frontiers in immunology*. 2018;9:2872.
13. Arts RJW, Moorlag S, Novakovic B, Li Y, Wang SY, Oosting M, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. *Cell host & microbe*. 2018;23(1):89-100 e5.
14. Benn CS, Netea MG, Selin LK, Aaby P. A small jab - a big effect: nonspecific immunomodulation by vaccines. *Trends in immunology*. 2013;34(9):431-9.

15. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pacific journal of allergy and immunology*. 2020;38(1):1-9.
16. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cellular & molecular immunology*. 2020.