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Mucosal immunity and the eradication of polio.

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Epidemics of paralytic disease due to polio were an annual occurrence in the early 20th century. In 1916 there were two thousand deaths in New York City alone from the nationwide epidemic. Closures of swimming pools and movie theaters and not shaking hands or handling money during summertime polio epidemics predated the social distancing we practice today due to the SARS-CoV-2 pandemic.

Prevention of polio epidemics by vaccination was a signature success of science in the 20th century. Cultivation of poliovirus in the laboratory was reported in this journal in 1949 by Enders, Weller and Robbins (1). A short six years later Jonas Salk made an injectable polio vaccine (IPV) by formalin inactivating the cultured poliovirus, with effectiveness tested in a herculean vaccine trial involving nearly two million children (2). Announcement of successful vaccination led to a nationwide celebration with Salk invited by Eisenhower to the White House. Arguably even today the faith in and support for scientific research by the American public is founded on polio vaccination.

By the beginning of the 1960s there were two polio vaccines, IPV and the oral OPV. Combined these have been the tools for polio eradication. OPV was developed by Albert Sabin by attenuating live poliovirus by passage in laboratory culture. OPV and IPV result in systemic immunity that protects from paralytic polio. Vaccination with the live virus vaccine OPV additionally provides mucosal immunity that prevents infection in the gut.

IPV and OPV thus are not only tools in global eradication, but led to our understanding that there are distinct systemic and mucosal immune systems. Systemic immunity encompasses the entire body and utilizes in part IgG antibody that circulates throughout the body via the bloodstream. In contrast, mucosal immunity utilizes locally produced IgA antibody to protect the respiratory, gastrointestinal and urogenital tracts. Thus, mucosal immune responses provide a first layer of defense to limit the replication and invasion of pathogenic microbes to the systemic circulation (3).

Understanding why OPV protected from intestinal infection with poliovirus came about from the discovery that only OPV induced the production of IgA antibodies against poliovirus in the duodenum (4,5). We now understand that the mechanism by which OPV makes IgA in the gut is by inducing antibody-producing B cells facilitated by gut associated CD4⁺ T helper cells, locally produced cytokines, and vitamin A (3,6,7). B cells in the mucosa, but not systemically, express the J or joining chain, which links two IgA molecules

together and facilitates IgA transport across the epithelium resulting in dimeric secretory IgA in the gut lumen (7). Duodenal secretory IgA is positively correlated with intestinal immunity to poliovirus (8) and is predicted to be the main mechanism through which this vaccine prevents viral colonization and shedding (8,9), although T cell-mediated protection is likely a player as well.

In contrast, the inactivated polio vaccine (IPV), which is administered by injection, only stimulates a systemic response of IgG and monomeric IgA (4,9). Likely because of its inability to induce a mucosal immune response, viral colonization and shedding can still occur after infection (8,9). OPV therefore is an essential tool in global eradication of polio due to its unique ability to stimulate infection and colonization-blocking secretory IgA.

Unfortunately OPV is also the Achilles heel of global eradication. In this issue Macklin and colleagues report on the emerging problem of outbreaks of type-2 vaccine derived poliovirus (VDPV2) in Africa and Asia (10). Since OPV is composed of attenuated poliovirus, it is excreted as live virus in the stool after vaccination, with family members and community contacts infected in a bystander fashion (11). Person-to-person spread of OPV is a potential problem as poliovirus can rarely revert from its attenuated state to circulate in populations and even cause paralysis. Multiple outbreaks of VDPV2 began in 2016 in Nigeria and the Democratic Republic of the Congo and are now widely spread across Africa and parts of Asia.

Paradoxically this situation arose from the success of the Global Polio Eradication Initiative that has eliminated transmission of type 2 in 2015 (and type 3 wild poliovirus in 2019). In April 2016 OPV2 was withdrawn from the trivalent OPV in order to prevent outbreaks of VDPV2. It had been expected that there would be some VDPV left over from the OPV2 component in trivalent OPV, and that these outbreaks could be controlled by campaigns of mass vaccination with a monovalent OPV2. However Macklin et al used the rate of mutation in poliovirus protein 1 to determine the timing of when the VDPV arose. The important finding was that the majority of these outbreaks occurred after the switch, and that the majority of cases could be linked to an mOPV2 campaign within the same country as the VDPV2 isolation.

The dilemma to polio eradication therefore is that eradication of VDPV2 requires the use of mOPV2, fighting fire with fire as it were. In response to this problem is the development of “new” OPV2 currently fast tracked in clinical trials. The new OPV2 candidates are engineered to prevent loss of the major attenuating mutations in the viral 5’ untranslated region that controls viral protein production (12,13). It is a not unreasonable hope that the new OPV2 will be the answer to the current relapse in the global eradication campaign. As we face the COVID-19 pandemic as scientists it is heartening to see the same application of science to public health in the last four months for the SARS-CoV-2 virus as for the last 70 years of poliovirus research.

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