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Sequential inactivated and oral poliovirus vaccine schedules: a balancing act

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Inactivated poliovirus vaccine (IPV), developed by Jonas Salk and colleagues and licensed in 1955, was the first poliovirus vaccine.[1] Salk IPV, a mixture of all three poliovirus types, was developed by inactivating wild polioviruses, a method that continues to be used for IPV production. Although multiple safeguards exist to prevent release of wild polioviruses from IPV production facilities, the continued use of Salk IPV poses a substantial risk for disease outbreak because of the potential for accidental release. The last case of indigenous wild poliovirus type 2 was reported in India in 1999.[2] However, in 2000, and then again in 2002–03, wildtype 2 poliovirus was detected in multiple patients with acute flaccid paralysis in India.[3] Genomic sequence analysis determined the type 2 poliovirus to be the MEF-1 strain, which is used for manufacturing IPV. The detection of the MEF-1 strain highlights the importance of using safer strains for IPV production, ideally those that are non-infectious to humans and stable enough to not acquire paralytic potential.

In 2012, Japan licensed IPV manufactured with Sabin strains, the live-attenuated strains of poliovirus used to manufacture oral poliovirus vaccine (OPV).[4] China licensed Sabin IPV in 2015, which helped to mitigate the effect in the country of a global shortfall in Salk IPV supply.[4] Although Sabin strains are infectious, they do not generally cause paralysis unless they can mutate and acquire neurovirulence. Therefore, manufacturing IPV using Sabin strains presents a lower risk if there is a containment breach than using wild poliovirus strains.

Over the past 5 years, despite some setbacks, the Global Polio Eradication Initiative has achieved two commendable milestones: certifying the global eradication of indigenous wild poliovirus types 2 and 3.[5] With the world closer to global polio eradication, there is need to refine poliovirus vaccination schedules. Use of OPV, the principal tool to achieve eradication, would need to stop after the certification of eradication of all wild polioviruses because live polioviruses can have adverse effects. Rarely, Sabin strains cause vaccine-associated paralytic poliomyelitis (VAPP) in vaccine recipients and their close contacts or revert while circulating in under-immunised populations, eventually acquiring

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neurovirulence vaccine-derived poliovirus (VDPV).[6] IPV does not cause VAPP or VDPV because it contains killed polioviruses. However, an important limitation of IPV is its inability to induce mucosal intestinal immunity, which is important to prevent excretion and transmission of polioviruses.

The study by Hanqing Wang and colleagues[7] in *The Lancet Infectious Diseases* provides helpful data on the immunogenicity of Sabin IPV and bivalent OPV when used in a sequential schedule. A sequential schedule is important for several countries, including China, that have no wild poliovirus circulation but face the threat of outbreaks because of endemic poliovirus transmission in neighbouring countries (Pakistan and Afghanistan in the case of China) while continuing to observe VAPP cases because of OPV use. The risk of VAPP is highest with the first OPV dose, so schedules that give only IPV as the first dose lower or eliminate the risk of VAPP. In Hungary, VAPP was not observed after the introduction of a single IPV dose, the first of many countries to introduce a sequential IPV–OPV schedule for VAPP prevention.[6] Hanqing and colleagues[7] report that at least two Sabin IPV doses are needed to achieve at least 90% seroprotection against type 2 poliovirus. The Strategic Advisory Group of Experts on Immunization has recommended achieving at least 90% seroprotection against poliovirus type 1, 2, and 3 after OPV withdrawal, with the first IPV dose at or after 14 weeks of age and a second dose at least 4 months later.[8] Hanqing and colleagues[7] also reported that it is possible to not only achieve 90% seroprotection by 4 months of age but also to do it following a sequential IPV–OPV schedule to mitigate the risk of VAPP.

Although it is clear that at least two IPV doses are essential for adequate humoral immunity, the study is missing data on intestinal immunity. Does one dose of bivalent OPV following two doses of Sabin IPV induce adequate intestinal immunity to type 1 and 3 polioviruses? Previous studies have shown that although one OPV dose induces intestinal immunity in a high proportion of recipients, there is a substantial gain in intestinal immunity with a second OPV dose, whereas a third OPV dose provides little gain in intestinal immunity.[9] Could the solution be to administer both IPV and bivalent OPV at the second immunisation visit, with only IPV given at the first visit and only bOPV given at the third visit?

This study provides further reassuring data that Sabin IPV is safe and effective. A useful next research step would be to compare the intestinal and humoral immunity of different sequential Sabin IPV–OPV schedules. Worldwide, the challenge facing vaccine production lies in reliably increasing production of Sabin IPV, so that its use can be widespread beyond Japan and China.

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