



The effect of new schedules of immunisation on humoral and intestinal immunity to poliovirus and implications for the polio end game

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Poliomyelitis became a serious public health issue for higher income countries in the twentieth century. This led to the development of vaccines in the mid-1950s and the eventual control and elimination of the disease by the 1970s. It remained common in lower and middle income countries despite the use of vaccine; this was probably partly to do with the epidemiology and pathogenesis of the disease and partly to problems of delivering vaccines in tropical areas with poor infrastructure. The Global Polio Eradication Initiative began after the development of newer and more effective strategies for vaccinating in tropical countries and as a response to resolution WHA 41-28 of the World Health Assembly in 1988 which committed WHO to eradication. The initial target date was 2000, a deadline that was clearly not met. By 2016 however there were only three member states that had never interrupted endemic transmission (Nigeria, Afghanistan and Pakistan) and the prospects for eradication are very good with less than fifty cases world-wide in 2016. When polio is eradicated enthusiasm for vaccination will disappear, but the situation is complex and arises from the nature of polio vaccines and their production and the pathogenesis of the disease. A key question that is now pressing is how to reduce vaccination against polio safely.

Poliovirus occurs in three serotypes such that immunity to one type does not protect against another. The vaccines used in the past have contained a single strain of each type and vaccine production involves the growth of extremely large amounts of virus; inactivated polio vaccine (IPV) mostly involves growth of wild type viruses that are known to be able

to cause polio while the live attenuated vaccines (oral polio vaccine or OPV) do not cause disease in recipients or their immediate contacts except at very low rates. However they can on rare occasions mutate and acquire the ability to transmit and cause epidemics (circulating vaccine derived polio viruses or cVDPVs) or infect patients unable to mount a humoral immune response who can excrete virus for years (iVDPVs). The vaccines therefore raise concerns and while the priority is obviously to eradicate wild type poliovirus, eradication must include the current vaccines as well. The situation has been brought into sharp focus by the fact that no case of poliomyelitis caused by a naturally circulating wild type 2 virus has been seen since 1999 and that the type 2 component of OPV is most likely to cause disease in recipients, to revert to a cVDPV and is the most highly effective of the three vaccine types, and thus out competes them and reduces the effectiveness of OPV against type 1 and 3. These are excellent reasons for removing the type 2 component from OPV, which was done in 2016, but there are risks.

Most infections with poliovirus, the causative agent of poliomyelitis, are entirely silent being confined to the intestinal tract so that infected individuals cannot be identified easily and can pass the infection to others. Quarantine of cases is therefore ineffective and the only way to eradicate poliomyelitis is to eradicate the virus. Individuals are protected from disease by low levels of serum antibodies but can still be infected and pass the virus on to others. The clinical and epidemiological effects of the two types of vaccine have been hotly contested since they were first developed. OPV is

believed to protect against infection of the gut as it harmlessly imitates natural infection; as it is able to prevent infection of the gut it breaks transmission and wild type virus dies out. OPV has been the main vaccine used in the eradication programme, but IPV eliminated polio from Scandinavia in Europe although it is thought to be less effective than OPV at preventing gut infection. When the type 2 component of OPV was withdrawn it remained possible that type 2 viruses were still in circulation, for example as cVDPVs, so that recipients of the bivalent OPV containing only types 1 and 3 were at risk. The decision was thus to introduce a single dose of IPV to all children in the world. The effectiveness of this strategy on the induction of immune responses expected to protect against disease and secondarily on immunity to infection is the subject of a study published in the *Lancet* by Asturias *et al.* in July 2016 (1) in which five cohorts were challenged with monovalent type 2 OPV after various immunisation schedules. The study was conducted in Latin America (Colombia, the Dominican Republic, Guatemala and Panama) in 2013, before withdrawal of the type 2 component.

Oral polio vaccine was given at weeks 6, 10 and 14 weeks of age; this is a more compact schedule than that in routine use (8, 16 and 24 weeks). One group received trivalent OPV i.e. containing types 1, 2 and 3 OPV and was challenged with monovalent type 2 OPV at 18 weeks. Another group received bivalent OPV (bOPV containing types 1 and 3) and another bivalent OPV and IPV at 14 weeks of age. These three groups compare the effects of giving no type 2 vaccine, type 2 OPV or one dose of trivalent IPV after bOPV. The other two groups compared the effects of giving bOPV with or without two doses of IPV at weeks 24 and 36 serologically and on challenge with monovalent type 2 OPV at week 40.

After two doses of OPV, by week 18 (groups 1, 2 and 4) and 40 (groups 3 and 5) all participants had high titres of antibody against types 1 and 3. All recipients of three doses of tOPV (group 3) also had high titres against type 2 having received three doses of type 2 OPV. The shortened schedule was therefore effective. The titres of participants who had received one dose of IPV were lower and fewer (about 80%) had seroconverted: there was evidence of a more rapid response after the type 2 OPV challenge in this group suggesting that they had been primed and possibly protected.

Group 3 showed good protection against challenge with type 2 OPV as was to be expected with less than 10% shedding virus; the titres of virus shed were also relatively low, of the order of 3.0 log. In contrast about three quarters of the recipients of bOPV shed virus at day 7 and one third at 28 days post challenge, at titres of 4 to 5.7 log. The group that

received one dose of IPV shed virus at marginally lower titres for marginally shorter periods, an effect that was more marked in the group that had received two doses of IPV. More detailed analysis (2) to give a shedding index based on the titre of virus and duration of excretion also demonstrated the effect.

The data reported in this paper are consistent with other recent and historical studies on seroconversion following immunisation with OPV and the effect of IPV on shedding. The study will help with details of immunisation schedules and it is possible that the small but real effect of IPV on shedding could have some epidemiological significance in the end stages where the transmission of all polio viruses in the absence of OPV usage is increasingly important to polio eradication. This remains to be seen. The effects of the withdrawal of type 2 OPV will need to be monitored very carefully but provide a guide to the eventual cessation of OPV vaccination altogether.

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