Polio endgame complexity: updating expectations for nOPV2

Lancet Infect Dis 2023
Published Online
May 10, 2023
https://doi.org/10.1016/S1473-3099(23)00133-0
See Online/Articles
https://doi.org/10.1016/S1473-3099(23)00139-1

In 2022, poliomyelitis cases caused by transmission of wild poliovirus type 1 and all three types (1, 2, and 3) of circulating vaccine-derived polioviruses (cVDPVs) were reported in 26 countries, with transmission detected without cases in eight additional countries.[1,2] Notably, these cases included a type 2 cVDPV (cVDPV2) case in an unvaccinated 20-year-old in New York State, USA,[3] which provided a sobering reminder that all unvaccinated individuals remain at risk, even in countries that use only inactivated poliovirus vaccine and maintain very high average immunisation coverage.[4] Similar to recent years,[5] polioviruses paralysed hundreds of African children in 2022 as countries chose to delay outbreak responses to wait for novel type 2 oral poliovirus vaccine (nOPV2), instead of preventing these cases using available Sabin monovalent type 2 oral poliovirus vaccine (mOPV2).[2,6]

Why wait? The accelerated development of nOPV2 came with many hopes, including non-inferior immunogenicity and greater genetic stability for nOPV2 compared with mOPV2, which promised similar individual and population immunity while reducing the risks of recombination and reversion to neurovirulence that might result in new cVDPV2s.[7] Studies conducted to support nOPV2 development, its November 2020 emergency use listing, and initial use show non-inferior individual immunity, lower rates of reversion to neurovirulence, and lower faecal shedding compared with mOPV2 in single antigen clinical trials with historical controls.[7] Field experience reported in 2022 showed that nOPV2 could shut down the cVDPV2 outbreak in Tajikistan, albeit with some questions about its field effectiveness.[8] The consequences of selecting the low-titre formulation for nOPV2 and its genetically engineered reduced fitness in secondary transmission imply lower population immunity benefits than mOPV2[6,8] and potentially a different pattern of interference between types of oral polioviruses when administered concurrently. As the delayed, small, and low-coverage outbreak responses to cVDPV2s allowed these viruses to continue to spread,[9] some countries increasingly face the challenge of responding to outbreaks of cocirculating poliovirus types 1 and 2.[1,2] With the Global Polio Eradication Initiative committed to ending the use of mOPV2 and shifting to nOPV2,[7] cumulative delivery of nOPV2 reached nearly 700 million doses by the end of 2022 (figure[10]). With this shift, questions about nOPV2 performance when administered concurrently with bivalent OPV (bOPV; containing types 1 and 3) become high priorities for research, particularly for countries with outbreaks of cocirculating types who are unwilling or unable to use the best option[11] of trivalent OPV (tOPV; containing types 1, 2, and 3).

Amanda L Wilkinson and colleagues report on the first open label, randomised clinical trial (NCT04579510) to test the concurrent delivery of nOPV2 with bOPV in a population of immunologically naive infants.[12] The February–September, 2021 study (figure) enrolled 736 participants from two sites in Dhaka, Bangladesh, with random assignment of 244 participants to group A (nOPV2 only), 246 to group B (concurrent nOPV2 and bOPV), and 246 to group C (bOPV only).[12] The study participants received three doses of the oral polioviruses for their group at 6, 10, and 14 weeks old, with serum samples collected before dosing at each visit and at 18 weeks old.[12] After two doses (at 14 weeks old), the cumulative immune response for type 2 poliovirus differed significantly, with protection in 209 (86%) of 244 in group A, 159 (65%) of 246 in group B, and 5 (2%) of 246 in group C, and 95% CI of 81–90% (group A),

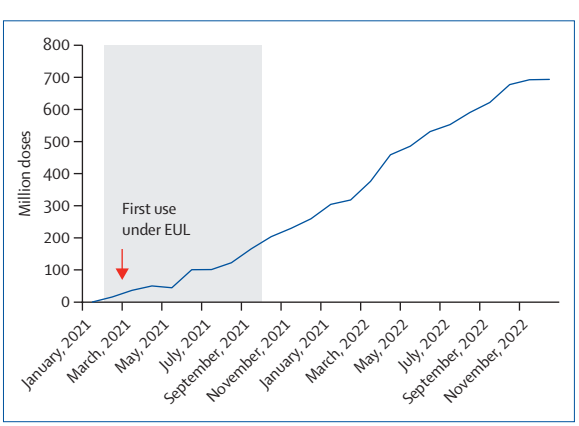

Figure: **Cumulative deliveries of novel oral poliovirus type 2**
Data from UNICEF.[10] Grey box shows the timing of Amanda L Wilkinson et al.[12] EUL=emergency use listing.

58–70% (group B), and 1–5% (group C).[12] The study could not reject the null hypothesis of non-inferiority by a margin of 10% for the concurrent administration of nOPV2 and bOPV compared with the administration of nOPV2 alone, and non-inferiority persisted after three doses.[12] The low level of type 2 immune response in group C reflects the absence of any nOPV2 delivered, and probably indicates some low-level community transmission of nOPV2.[12] The study found essentially no differences in the results for the cumulative immune responses for poliovirus types 1 and 3 for groups B and C, and rejected non-inferiority by a margin of 10% for poliovirus types 1 and 3 for concurrent administration of nOPV2 and bOPV compared with the administration of bOPV alone.[12]

Wilkinson and colleagues[12] confirm that multivalent oral poliovirus administration (Sabin or novel) must account for the trade-offs in both individual and population immunity that come with interference between the types in the actual formulations used. This study[12] should help national, regional, and global polio decision makers manage their expectations about the performance of nOPV2 when used for outbreak response in areas with cocirculating polioviruses and if ever used for preventive immunisation. These results[12] hint at the probable need to achieve higher coverage (or to perform more campaign rounds) using nOPV2 than needed using mOPV2 to induce the same level of population immunity,[8] and imply that nOPV2 use comes with real trade-offs that increase the complexity of an already complicated polio endgame. One repeated lesson with each innovation in poliovirus vaccines: delivering on the promise of polio eradication requires overcoming the failure to vaccinate.[11] This study[12] and experience with nOPV2 to date (including recent demonstration of the ability of nOPV2 to seed new cVDPV2 outbreaks[13]) provide a powerful reminder that accelerated vaccine roll-out for public health emergencies[7] comes at the real cost of needing to manage expectations following post-hoc demonstration of trade-offs reported only after the commitment of substantial resources.

I declare no competing interests.

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