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Peer Review

Review of: "Oral Polio Vaccine Is Unsafe for the World and Should Be Replaced with Inactivated Poliovirus Vaccine Globally"

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This is a critical review that highlights author-perceived flaws in the global polio eradication initiative and its progress to date. The author makes a number of important points, including the under-utilisation of IPV as a tool to enhance global polio eradication. This article draws attention to the previous inclusion of only 1 dose of IPV rather than 2 on the recommended immunisation schedule of the WHO. Inadequate upscaling of IPV is the most important contribution of the paper and warrants global discussion. The relative contribution of cost concerns, manufacturing constraints, insufficient immunization coverage, and theoretical factors to the constraints on IPV use are not widely articulated by the WHO or the GPEI.

However, the paper has a number of important omissions that need to be taken into consideration for this to be a balanced and thoroughly researched article. In particular, the following points should be elucidated for the readers:

1. The reason for the sustained use of OPV: While both IPV and OPV have high immunogenicity and work well to ensure that a vaccinated individual will not become paralysed on a future exposure to wild poliovirus, OPV creates intestinal immunity, which is valuable for decreasing the duration of poliovirus shedding if there is a future exposure to wild poliovirus or cVDPV. OPV is therefore valuable to interrupt the transmission of poliovirus within communities. Thus, both vaccines are good for individual protection from disease, but only OPV is good for preventing poliovirus transmission.

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While wider IPV use will be safer for communities than the use of OPV, the utility of IPV depends on coverage, i.e., the number of people immunised. OPV, however, even if used to vaccinate only a proportion of the population, results in individuals who cannot transmit wild poliovirus. (Non-transmitters are distinct and in addition to the concept of individuals inadvertently immunized by acquisition of the vaccine virus itself via contact with vaccinees, who have been correctly described by the authors in the first paragraph of the introduction).

The distinction between individual protection against disease versus effect on transmission of the virus is important. The public health importance of a vaccine depends on how good the vaccine is at preventing disease *transmission* rather than disease *acquisition*. In countries or regions that use IPV-only schedules, any unvaccinated individual remains at risk because any imported wild poliovirus can spread silently among IPV-vaccinated individuals until it reaches the unvaccinated individuals. For references and commentary, see

a. Israel's silent polio epidemic breaks all the rules. Roberts L, Science 342 Nov 2013, News and Analysis.

b. Onorato et al, The Journal of Infectious Diseases, Vol. 163, No. 1 (Jan., 1991), pp. 1-6, available at https://www.jstor.org/stable/30119500

c. Hird and Grassly, PLoS Pathog 8(4): e1002599. doi:10.1371/journal.ppat.1002599

(conflicting data at The Cuba IPV Study Collaborative Group; N Engl J Med 2007;356:1536-44)

2. The suggestion in the abstract that OPV should be withdrawn "country by country" is contentious, even if readers agree that OPV should be withdrawn – do the authors mean "country by country" or "region by region"? Region by region is less contentious, e.g., Africa as a whole or Asia as a whole. If the authors intend that "country by country" is a valid plan, they should argue this point in full. The risk of one country withdrawing OPV while its neighbours use IPV is that any travellers who are recently OPV vaccinated may shed vaccine virus into the population that is only IPV vaccinated and who have no intestinal immunity (mucosal IgA) to prevent prolonged circulation. After many months of circulation, the IPV-only country will be at risk of silent transmission of mutated strains reaching any unvaccinated children.

The point in the abstract also differs from the sentence on page 9 just above the conclusion: to break this vicious cycle, a "globally coordinated and expedited withdrawal of OPV should be pursued, transitioning toward exclusive IPV use".

Globally coordinated withdrawal is part of the Polio Eradication Strategy. Are the authors in agreement? Do they suggest global withdrawal of OPV now, even in Pakistan and Afghanistan, which still have circulating wild poliovirus type 1?

Reference: Polio Eradication Strategy 2022-2026 Delivering on a Promise. WHO, 2021 ISBN 978-92-4-003193-7 (see Figure 8, page 21)

3. The Global Polio Eradication Initiative (GPEI) should be defined as distinct from the WHO. The Global Polio Eradication Initiative is a public-private partnership led by national governments with partners – the World Health Organization (WHO), Rotary International, the US Centers for Disease Control and Prevention (CDC), the United Nations Children's Fund (UNICEF), and more recent partners, the Bill and Melinda Gates Foundation and Gavi, the vaccine alliance.

4. Improved clarity regarding the terminology of VAPP and VDPV.

While the authors correctly describe VAPP as a vaccine side effect – the term VAPP predates the terms VDPV and cVDPV. VAPP was used to describe side effects of vaccination in otherwise healthy vaccine recipients or their contacts. The authors should not distinguish between VDPV and cVDPV unless also referring to iVDPV and aVDPV. The term VDPV is a laboratory diagnosis, based on the number of mutations, as correctly described by the authors. Further classification is an epidemiological one depending on available data – if the case has a primary immune deficiency (inborn error of immunity such as agammaglobulinemia), the VDPV is an immune-deficiency associated VDPV (iVDPV). If there is more than one linked case or detections in more than one household (or various other definitions suggesting circulation), the virus is a circulating VDPV (cVDPV). Where there is insufficient data, e.g., one environmental isolate or one case where inborn errors of immunity have not been excluded, the case is an ambiguous VDPV (aVDPV).

a) Therefore, in the abstract, the sentence – "For the community, the increasing risk has been genetic reversal of live vaccine viruses to neurovirulent VDPVs which cause polio more frequently than VAPP and to cvdpvs that are essentially wild poliovirues" is saying the same thing twice. Suggest rephrase, e.g.,

For the community, the increasing risk has been genetic reversal of live vaccine viruses to neurovirulent cVDPVs which cause polio more frequently than VAPP and are essentially wild polioviruses.

b) The sentence on page 5, "in 2000 after over seven years of the absence of WPV in the Caribbean and with the continued use of OPV, an outbreak of VAPP occurred in the Dominican Republic" – incorrect use of the phrase VAPP. This should be cVDPV. An outbreak is caused by a virus – in this case, genetically

identified as cVDPV by the number of mutations away from Sabin. The paralyzed cases were not those who received OPV drops. The term VAPP should be kept for adverse events following immunization itself, i.e., paralysis in an individual vaccinated with the Sabin strain virus that has not accumulated mutations.

c) Similarly, “VAPP used to be sporadic but then it became epidemic”.

The term VAPP was used prior to sequencing information being available.

d) The sentence on page 6: “Thus since 2000, GPEI has been reporting polio due to WPV and cVDPV in various documents but not polio due to vaccine poliovirus and VDPV”.

VDPV is an umbrella term and does not make sense in this sentence.

The “VDPV” should be replaced with “not polio due to iVDPV or ambiguous vDPV”. The comment is valid, as ambiguous VDPVs are often single events and may have significance, but were not reported on the GPEI public dashboard until after 2020.

e) Page 6 – Iatrogenic polio in the twenty-first century - the sentence “however GPEI does not divulge the numbes of VAPP or polio caused by VDPV’s” should be replaced with “aVDPVs”. Note that reporting does now include aVDPV’s – see “other sources environmental” and “other sources human” on the website of GPEI https://polioeradication.org/circulating-vaccine-derived-poliovirus-count/

f) Page 9: the sentence: How many children have developed VAPP since 20212? After Vaccine poliovurs-3 is known as the commonest cause of VAPP.

This sentence actually refers to how many children have developed paralysis from circulating VDPV3 (cVDPV3), which is data available on the website of the GPEI. (The term VAPP is not correct in this context as the cases would have been unvaccinated children who acquired a cVDPV3 from the community, while vaccinated children would have been protected from paralysis).

The sentence “GPEI has not been countring, choosing instead to label VAPP as non-polio, contrary to science and medical ethics” is emotive and factually inaccurate. The authors′ point that the type 3 component of tOPV should have been removed at the same time as the type 2 component of bOPV has merit and should be stated.

5. Novel OPV vaccines – these are exciting technological innovations developed for the exact reasons outlined by the authors in this paper to address deficiencies of Sabin OPV and Salk IPV. Novel OPV vaccine development and deployment should be mentioned earlier, together with the disappointing finding that despite the intentional design of novel OPV to be more stable against reversion than Sabin OPV, they have still seeded new cVDPV outbreaks.

6. In the Introduction: the sentence “low take rate meant vaccine poliovirus transmission would also be far less frequent in LMIC than in the USA, an insight apparently missed by many” is inaccurate. “Low take rate” should be defined. If we assume “low take rate” as low immunogenicity, i.e., low proportions of vaccinated individuals developing serum poliovirus IgG, then vaccine poliovirus transmission is more likely in the scenario of poor immunogenicity of the vaccine.

7. In the introduction, page 3, the sentence “however WHO seems to have neither analyzed the nuances of the USA’s experience nor investigated if vaccine poliovirus transmission enhanced vaccine effectiveness beyond the low VE in LMICs” is long, unclear, and unfair.

a. The sentence is too long and therefore unclear and difficult to understand.
b. I think the authors are referring to whether herd immunity is increased by transmission of the vaccine virus to unvaccinated individuals, thereby vaccinating them. Clearer phrasing would clarify this.
c. The sentence does not give credit for the correct understanding that the OPV-vaccinated individuals themselves have superior immunity (gut immunity) compared to IPV-vaccinated individuals for preventing transmission of any future imported virus to unvaccinated individuals.

8. In the introduction, page 3,

The paragraph “Despite Herculean efforts, we must point out that community-wide distribution of 20 and more doses per child was an unprecedented experimental product. Today we know if it was not a safe procedure for the community at large as mass campaigns with OPV led to polio outbreaks by cVDPV

This paragraph seems to imply that multiple OPV doses to one child are unsafe. The point the authors make about OPV having community risks is correct, but the risk stems from OPV given to non-immune children in whom the vaccine can replicate and therefore mutate. The outbreaks were due to cVDPV and were not related to the number of doses per vaccinated child.

The sentence about 20 or more doses per child is not relevant and should be removed.

9. “Repeated mass campaigns have also raised suspicions about the motives of international actors and resistance from parents and communities, especially in Afghanistan and Pakistan.” This sentence should be made more explicit. The sentence does not relate to repeated mass campaigns but could be rephrased as: “Political use of vaccinators by the American Central Intelligence Agency during the hunt for Osama Bin Laden in 2011 heightened vaccine hesitancy among parents and communities in Pakistan and Afghanistan.” For references, see

a. BMJ 2011, 343 d4580 doi: https://doi.org/10.1136/bmj.d4580

b. Gostin, The Milbank Quarterly, Vol. 92, No. 3, 2014 (pp. 413-417)

10. “The purpose of this paper is to elaborate on such problems caused by the continued use of OPV in LMIC and on the logic of our assertion that global polio eradication is contingent upon the transition from OPV to IPV in all LMI."

This is a valid assertion and is in agreement with the consensus view – the plan to switch to IPV is articulated in recent WHO strategic plans. What is contentious is whether to wait for the global eradication of wild poliovirus type 1 before the removal of bOPV. The authors are advocating to remove bOPV prior to the eradication of wild poliovirus 1 rather than after, which differs from the WHO strategic plan. The aspects of the authors' argument that are in agreement with the strategic plan and those that differ from the strategic plan should be clearly stated.

References:

a. Outbreak and at-risk in Delivering on a Promise: Polio Eradication Strategy 2022–2026. WHO 2021 (See Fig. 8, Goal two milestones for interrupting cVDPV transmission)

b. Responding to a Poliovirus Event or Outbreak version 3.1 WHO 2020 ISBN 978-92-4-000299-9

11. In October 2020, SAGE recommended a routine second dose of IPV to be included in all countries

World Health Organization (2020). Meeting of the Strategic Advisory Group of Experts on Immunization, October 2020 – conclusions and recommendations

https://iris.who.int/handle/10665/337109

and The WHO routine EPI schedule now recommends at least 2 doses of IPV

https://www.who.int/publications/m/item/table1-summary-of-who-position-papers-recommendations-for-routine-immunization

12. The author also makes no mention of other critical voices:

Also consider reading viewpoints such as

- Evaluation of the 2016 switch from tOPV to bOPV: lessons learned and implications for anticipated bOPV cessation. Switch Evaluation Team, Strategy Committee of the Global Polio Eradication Initiative, September 2024.

- Suchard MS, Tomori O and Blumberg L. Extra Time and Penalties in the Polio End Game. Journal of Infectious Diseases, January 2020 https://doi.org/10.1016/j.ijid.2019.12.009

13. Overall, the paper is too long and would attract greater readership if it were shortened. Certain aspects are repetitive and can be removed to shorten the manuscript. I recommend removing the following paragraphs:

a. Benefit-risk balance of OPV in the EPI
b. The consequences of continuing OPV beyond 1999
c. In Iatrogenic polio in the twenty-first century, page 6 – second paragraph – historic description of various outbreaks in the Philippines, Madagascar, Hispaniola – unnecessary
d. Next paragraph – during the decade starting from 2000 – also unnecessary.
e. Page 7 paragraph: Lessons from the one crucial experiment, conducted in Byelorussia in the mid-1960s – this paragraph can be removed. Firstly, it seems to contradict the author's point and strengthen the WHO viewpoint – that if OPV is prematurely withdrawn, the absence of gut immunity allows free circulation of any remaining or imported wild viruses or cVDPVs.
f. The following table on page 8 should be removed – it is not central to the author's argument.
g. Page 9: the paragraph: During 2008-2023, for every case of WPV polio… is emotive rather than factual and doesn't add much to the author's argument.

14. Conclusion should be reworded:

Twin risks: sporadic and epidemic polio – the meaning of "sporadic" is not clear. Do the authors mean VAPP, the adverse event following immunization? VAPP as a side effect of immunization has such a low incidence rate that it is not considered of public health importance. Does epidemic polio mean wildtype 1 or cVDPV, or both? The authors likely mean the risk of cVDPV, which should be clearly stated.

Emotive, non-scientific phrases such as "duty" and "sacrosanct" should be removed.

Acknowledgment should be given that GPEI is being dissolved. The responsibility is no longer that of the GPEI but of all WHO-member states' individual governments.

The decrease in funding availability for the GPEI, leading to "transition planning" to integrate polio immunization and surveillance functions within country budgets rather than as a vertical programme, is a major factor in global polio planning and should be mentioned.

Ref: Polio transition strategic framework: global vision to use polio investments to build strong, resilient, and equitable health systems. WHO 2024. ISBN 978-92-4-010063-3

Declarations

Potential competing interests: No potential competing interests to declare.