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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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Oral polio vaccine should be replaced with IPV globally

Summary: This is a very interesting paper where the authors discuss why the oral polio vaccine should be replaced by IPV. In their opinion, since the 1960s, when the first VAPP cases were described in the USA, it was clear that IPV should be the best option. The discussion is based on relevant papers that confirm the risks of IPV for individuals and for the community, and recent data showing the emergence and spreading of cVDPVs, which became more and more frequent despite the large use of OPV. cVDPVs are responsible for more AFP cases than the wild polio virus type 1. The references are excellent, making it easier for readers to understand the discussion.

I recommend the approval of this paper and have only a few suggestions:

Title: I suggest reducing the title to "Oral polio vaccine should be replaced with IPV globally," cutting "*is unsafe for the world,*" because this affirmative could contribute to reducing the Vaccine Coverage Rates (VCRs) in countries that did not have access to a full IPV schedule. Additionally, it could reduce confidence in vaccines, giving arguments to "anti-vaccine influencers" that modify a scientific concept to increase vaccine hesitation (now a big challenge in many countries, including the USA).

Abstract: Excellent abstract. I only disagree with the statement that *"VDPVs are essentially wild poliovirus"*. Technically, they can have very few mutations as compared with Sabin strains (0.6% to 1% or more) as described in the text, but they also can cause paralysis. My suggestion is to change it to "cVDPVs can cause acute flaccid paralysis (AFP) that cannot be distinguished from cases caused by wild polio viruses."

doi.org/10.32388/ZVEBOD

I also suggest cutting the word “widely” in line 7 of the abstract, because even in countries where OPV is not used at all, there is the risk of importation of VDPVs originated by OPVs (including nOPV2).

Text

Pg 2 - line 13. Check the year when OPV was introduced into the routine schedule for infants in the USA. I guess that it was in 1962 (not 1966), 1997 mix schedule, two IPV followed by IPV, and after 2000, a full IPV schedule.

Pg 3 - line 18. I suggest adding the risks associated with the silent circulation of WPV1 and VDPVs and the risks of importation from countries using OPV; additionally, it could be interesting to mention the long-term excretion in immunodeficient people, emphasizing that until now there is **no treatment** for polio. (ref Imported vaccine-associated paralytic poliomyelitis--United States, 2005 - PubMed)

Pg 3, line 25. Change “cVPVs are essentially WPV” to the WHO definition of cVDPVs and inform that they can cause disease clinically undistinguished from those caused by WPV (technically, cVDPVs can differ by only 0.6% to 1% from wild polioviruses, so I guess they are not essentially WPVs).

Pg 6 - line 9 – I agree that there is no information about VAPP cases, but as cVDPVs are VDPVs, it should be better to *include also aVDPV and iVPDVs, and discuss the number of polio-compatible cases*, that nobody knows if they are caused or not by polio (information available at AFP/polio data (who.int) Accessed April 19th 2025 (date of last update April 17th 2025*). Since 2017, the number of cVPVs AFP cases has been higher than WPV1 AFP cases: In 2016, there were 32 WPV1 AFP cases and 5 cVDPV AFP cases, and in 2017, 22 WPV1 AFP cases and 96 AFP cVDPV cases. In 2020, there were 140 WPV1 AFP cases and 1,117 cVDPV cases, when WHO recommended the second IPV dose. From 2020 to 2024: 287 AFP cases caused by WPV1 in 4 countries, and 3,519 AFP cases caused by cVDPVs, additionally more than 832 polio-compatible cases. In 2025 (as of April 14th), there were 7 AFP cases caused by WPV1 and 34 AFP cases caused by cVDPVs.)*

Pg 7. Line 2 – include the reference that supports that only *one IPV dose is insufficient to protect against polio* (can be the Vaccines chapter)

Pg 7. Line 15 – I totally agree with this information, but I suggest also that WHO experts should consider the *time for production of IPV and the capacity of the industry to prepare a sufficient supply years before establishing any new recommendation*. When they took the decision to add one IPV dose worldwide in 2016, there was limited supply of IPV. Good planning is key for the success of new recommendations. Nowadays, WHO experts affirm that there is sufficient supply for two IPV doses, but last March 2025, SAGE experts recommended 3 IPV doses. I´m not certain that there is sufficient supply for 3 doses for all

countries, even if some use fIPV, but even in India, where fIPV is used, the recommendation already moved to 4 IPV doses! It´s clear that 3 doses for infants can guarantee excellent seroprotection against all polio serotypes, but all studies published until now about the long duration of protection were performed with at least one IPV booster in preschool children or analysed the duration of protection in adults that lived their infancy in a time when wild polio circulated and could offer a "natural booster." They also did not consider that GMTs are lower after fIPV and after vaccination with the hexavalent wP-IPV vaccine. Additionally, in 2023, the VCR for IPV-1 was < 90% in more than 50 countries, and, in some, like Angola, CAR, Papua N Guinea, Somalia, and Yemen, it can be lower than 50%. Some countries only recently introduced the second IPV dose, and the VCR tends to be lower than that for IPV-1, leaving a big gap of children unprotected against polio 2.

Pg 8. Table: include the reference and change in the last column from 2019-2024 to ***2020-2024.*** *I also* suggest adding the most recent information showing that both, *WPV1 and cVDPVs were not eradicated until April 2025*. Polio eradication. Wild Poliovirus count – GPEI (polioeradication.org) Accessed 19 April /2025. 2020-2024 = 287 wPV1 in 4 countries; 2025, as of 14 April 2025 = 7 WPV1 in two endemic countries, showing that the new target for polio eradication possibly needs to be changed again...

Pg 8 Basic lessons of virology and polio vaccinology

Pg 8 I think that the phrase "*VAPP is like Russian Roulette*" is too aggressive considering the number of bullets in a gun and the risks of VAPP caused by OPV. To avoid any risk of giving arguments to anti-vax influencers who are experts in reducing confidence in vaccines and causing lower vaccine acceptation (the risks are high in countries with no access to full IPV schedules, and the reduction in VCR can result in new VDPVs emergencies), my suggestion is to modify it to something like: "*despite the low risk of VAPP associated with OPVs (including nOPV2), the risk is real, and now is considered ethically unacceptable".*

There are also some other interesting topics that could be included in the discussion to support why it's time to move to full IPV schedules:

- The role of **novel OPV 2**, which has been defended by BMG and WHO experts as a "magic bullet" to finish the job, but also can cause paralysis, induce **lower seroconversion** in some countries, and has **low effectiveness vs. IPV**

- The **environmental surveillance** recommended by WHO is not implemented in all countries, and in many others, it was only implemented AFTER the detection of WPV or cVDPV AFP cases.

- The time to detect VDPVs and implement measures to control outbreaks: the example from Israel, where when they introduced the campaign with OPV, it could prevent only 10%.

- The difficulties in achieving high VCR in conflict areas and the recent detection of cVDPV in occupied Palestinian territories.

- The challenges to achieve high VCR after natural disasters.

- The challenges to achieve high VCRs in some religious communities.

- The high rate of population displacement and migration that recently introduced cVDPV even in countries using exclusively IPV, like the UK, USA, Canada, Germany, and Poland.

- The limited duration of intestinal immunity used by WHO as a strong argument to defend OPV, which nowadays we know is limited.

Below, I added some recent references about some of these topics. If you decide to include one or more of these topics in the discussion, but considering that it's very difficult to include all in a limited number of pages, I recommend the approval of this paper with only a few modifications mentioned page by page.

Some interesting references that can provide support if you decide to include some of the new arguments:

1. Immunodeficiency: Mohanty MC, Govindaraj G, Ahmad M, Varose SY, Tatkare M, Shete A, Yadav S, Joshi Y, Yadav P, Sharma D, Kumar A, Verma H, Patil AP, Edavazhipurath A, Dhanasooraj D, Othayoth Kandy S, Puthenpurayil JM, Chakyar K, Melarcode Ramanan K, Madkaikar M. Immunodeficiency-Related Vaccine-Derived Poliovirus (iVDPV) Excretion in an Infant with Severe Combined Immune Deficiency with Spillover to a Parent. Vaccines (Basel). 2024 Jul 9;12(7):759. doi: 10.3390/vaccines12070759. PMID: 39066397; PMCID: PMC11281642.
2. Silent polio circulation – immunization campaign with OPV in Israel after avoided only 10% of infections because of the retard in identification of WPV - Brouwer AF, Eisenberg JNS, Pomeroy CD, Shulman LM, Hindiyeh M, Manor Y, Grotto I, Koopman JS, Eisenberg MC. Epidemiology of the silent polio outbreak in Rahat, Israel, based on modeling of environmental surveillance data. Proc Natl Acad Sci U S A. 2018 Nov 6;115(45):E10625-E10633. doi: 10.1073/pnas.1808798115.
3. Mucosal immunity
    a. Connor RI, Brickley EB, Wieland-Alter WF, Ackerman ME, Weiner JA, Modlin JF, Bandyopadhyay AS, Wright PF. Mucosal Immunol. 2022 Jan;15(1):1-9. doi: 10.1038/s41385-021-00428-0

b. Saleem AF, Kazi ZU, Zehra SM, Parkar S, Macklin G, Sifontes G, Mainou BA, Alam M, Lopez Cavestany R, Mach O. Mucosal immunity to poliovirus in children 0-15 years of age: A community-based study in Karachi, Pakistan in 2019. J Infect Dis. 2024 Jan 9:jiae006. doi: 10.1093/infdis/jiae006.

c. Habib MA, Soofi SB, Hussain I, Ahmed I, Hussain Z, Tahir R, Anwar S, Cousens S, Bhutta ZA. Does IPV Boost Intestinal Immunity among Children under Five Years of Age? An Experience from Pakistan. Vaccines (Basel). 2023 Sep 1;11(9):1444. doi: 10.3390/vaccines11091444.

4. Bandyopadhyay AS, Lopez Cavestany R, Blake IM, Macklin G, Cooper L, Grassly N, Nery ALMDS, Mach O. Use of inactivated poliovirus vaccine for poliovirus outbreak response. Lancet Infect Dis. 2024 May;24(5):e328-e342. doi: 10.1016/S1473-3099(23)00505-4. Epub 2023 Nov 25. Erratum in: Lancet Infect Dis. 2024 Feb;24(2):e83. doi: 10.1016/S1473-3099(23)00760-0. PMID: 38012892.
5. Devaux CA, Pontarotti P, Levasseur A, Colson P, Raoult D. Is it time to switch to a formulation other than the live attenuated poliovirus vaccine to prevent poliomyelitis? Front Public Health. 2024 Jan 8;11:1284337. doi: 10.3389/fpubh.2023.1284337.
6. Kennedy SB, Macklin GR, Mason Ross G, Lopez Cavestany R, Moukom RA, Jones KAV, Mainou BA, Massaquoi MBF, Kieh MWS, Mach O. Poliovirus antibodies following two rounds of campaigns with a type 2 novel oral poliovirus vaccine in Liberia: a clustered, population-based seroprevalence survey. Lancet Glob Health. 2023 Jun;11(6):e917-e923. doi: 10.1016/S2214-109X(23)00116-X.
7. Cooper LV, Erbeto TB, Danzomo AA, Abdullahi HW, Boateng K, Adamu US, Shuaib F, Modjirom N, Gray EJ, Bandyopadhyay AS, Zipursky S, Okiror SO, Grassly NC, Blake IM. Effectiveness of poliovirus vaccines against circulating vaccine-derived type 2 poliomyelitis in Nigeria between 2017 and 2022: a case-control study. Lancet Infect Dis. 2024 Apr;24(4):427-436. doi: 10.1016/S1473-3099(23)00688-6.
8. Ivanova, O.E.; Eremeeva, T.P.; Baykova, O.Y.; Krasota, A.Y.; Yakovchuk, E.V.; Shustova, E.Y.; Malyshkina, L.P.; Mustafina, A.N.-I.; Mikhailova, Y.M.; Chirova, A.V.; et al. Detection of Polioviruses Type 2 among Migrant Children Arriving to the Russian Federation from a Country with a Registered Poliomyelitis Outbreak. *Vaccines* 2024, *12*, 718. https://doi.org/10.3390/vaccines12070718
9. Sutter RW, Eisenhawer M, Molodecky NA, Verma H, Okayasu H. Inactivated Poliovirus Vaccine: Recent Developments and the Tortuous Path to Global Acceptance. Pathogens. 2024 Mar 4;13(3):224. doi: 10.3390/pathogens13030224. PMID: 38535567; PMCID: PMC10974833.

I´d like to congratulate the authors who brilliantly defended the full IPV schedule for all infants, not only for those who live in high-income countries.

All physicians should remember Hippocrates' advice: First, do no harm, especially when we are working with healthy babies. If a baby develops VAPP, who and how will you convince the mother that the OPV´s risks are very rare and can be acceptable? And who is to do it?

Declarations

Potential competing interests: LFB is employee of Sanofi and may hold shares and/stock option in the company. I did not receive any payment to review this article, and the suggestions/opinions are personal not involving the company.