Detection of vaccine-derived poliovirus type-3 in sewage of Kathmandu Valley, Nepal

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ABSTRACT

Enteroviruses include polioviruses, which are classified into three types: type 1, type 2, and type 3. The oral polio vaccine (OPV), which contains attenuated strains of these three types, has been pivotal in reducing polio incidence worldwide. However, OPV can lead to vaccine-derived poliovirus (VDPV) cases, including circulating VDPV1 (cVDPV1), cVDPV2, and cVDPV3. In contrast, the inactivated or 'killed' polio vaccine (IPV), effectively prevents poliomyelitis without the risk of causing cVDPV cases. On 26 May 2024, a novel mutated form of poliovirus was detected in sewage samples from Kathmandu, Nepal, indicating an ongoing risk of poliovirus reintroduction and transmission. This finding highlights the importance of robust surveillance and containment measures. Historically, the Salk vaccine (IPV) and the Sabin vaccine (OPV) have been used against poliovirus, each with its advantages and limitations. Moving forward, it is necessary to replace OPV with genetically modified OPV, or new IPV formulations. Enhanced vaccination strategies and continued surveillance are crucial for achieving complete poliovirus eradication and preventing future outbreaks.

Introduction

Enteroviruses are a diverse genus within the *Picornaviridae* family, and include several different pathogens, including the enteroviruses, coxsackieviruses, rhinoviruses, polioviruses, and echoviruses (Chavda et al., 2023; Sinclair and Omar, 2024). The genus is divided into twelve species with more than 200 serotypes identified within these species. These viruses together are widespread affecting humans globally, and while most infections are self-limiting, they can lead to significant health and economic burdens (Bessaud and Delpeyroux, 2020). Illnesses range from mild such as the common cold to severe conditions such as poliomyelitis and aseptic meningitis. As such, there is a need for ongoing research to better understand these viruses and develop effective preventive and therapeutic measures.

Poliovirus, causative agent of acute polio and poliomyelitis is a member of the *Picornaviridae* family and belongs to the *Enterovirus* species (Sinclair and Omar, 2024). There are 3 distinct serotypes of wild poliovirus each with distinct capsid proteins affecting their infection and antigenic properties. (i) Type 1 (WPV1), the most common and widespread and responsible for most of the polio cases including paralytic poliomyelitis. As of March 2020, WPV1 is the only wild form in circulation localized in Afghanistan and Pakistan, but until it is eradicated, outbreaks can occur. For example, in late 2021 and early 2022, nine individuals in Southeastern Africa contracted WPV1, with the virus linked to the outbreak originating in Pakistan (Davlantes et al., 2023). (ii) Type 2 (WPV2) was declared eradicated globally in September 2015, with the last reported case in India in 1999, and type 3 (WPV3) which was declared eradicated in October 2019, with the last reported case in Nigeria in 2012 (Fig. 1) (Bammeke et al., 2023). Despite this, circulating vaccine-derived poliovirus (cVDPV, or variant poliovirus) of all serotypes is still active in 32 countries as of December 2023 (Geiger et al., 2024).

Vaccines against poliovirus

On April 12, 1955, Jonas Salk introduced the first vaccine against poliovirus. This vaccine, known as the inactivated polio vaccine (IPV), is composed of poliovirus which is killed using formalin and it is injected. It provides protection against all three wild types of polioviruses: WPV1, WPV2, and WPV3. By stimulating a robust immune response, the IPV generates strong anti-polio IgG antibodies with effectiveness of 70 %, 90 %, 90 % against WPV1, WPV2 and WPV3 respectively. These antibodies play a crucial role in preventing the poliovirus from advancing to viremia, a condition where the virus spreads through the bloodstream, and consequently protecting the motor neurons from being damaged. As such, the IPV vaccine's ability to induce a protective immune response against developing paralytic poliomyelitis is approximately 94 % (Sutter et al., 2024). Following mass vaccinations in the United States the annual incidence of polio cases declined from 35,000 in 1953, 5600 in 1957 to 161 in 1961. This significant decline in cases highlighted the vaccine's effectiveness and marks a significant achievement in public health efforts to control and eventually eradicate polio. Despite the vaccine's success, public confidence in its safety waned after the Cutter Incident in April 1955, when 120,000 doses of vaccine contained live poliovirus instead of being inactivated. This led to 40,000 cases of abortive poliomyelitis, 56 cases of paralytic poliomyelitis, and 5 fatalities, causing a significant decline in vaccination rates (Nathanson and Langmuir, 1963).

Albert Sabin developed an attenuated poliovirus vaccine which involves cultivating the poliovirus in non-human cells at low temperatures below physiological levels. As such, cultivation induces spontaneous mutations in the viral genome, reducing the virus's virulence so that it can no longer cause disease but still elicit strong immunity. The Sabin poliovirus vaccine is administered orally (OPV) allowing the virus to replicate in the gastrointestinal tract (and not within nervous system)

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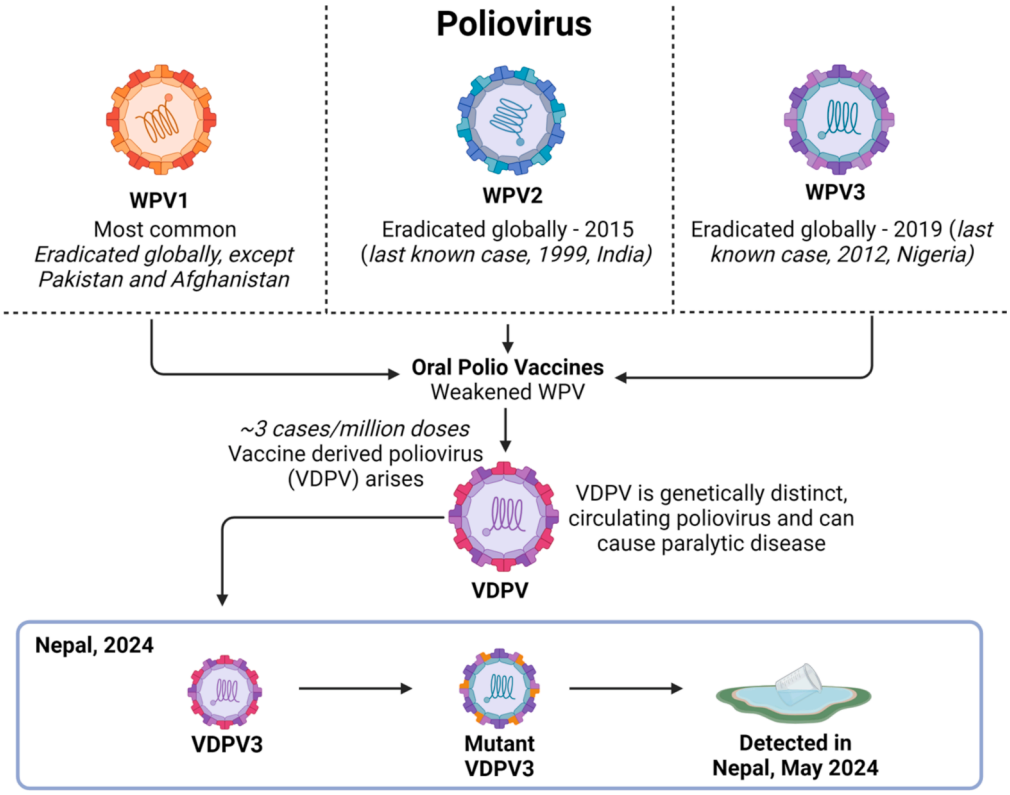

Fig. 1. There are 3 serotypes of wild poliovirus, type 1 (WPV1), WPV2 and WPV3, which have been mostly eliminated due to mass world vaccination programs. Oral polio vaccines consist of a weakend WPV which can result in vaccine derived poliovirus (VDPV / cVDPV), which is genetically distinct from the circulating wild type of poliovirus and can cause paralytic disease. On 26 May 2024 sewage samples were collected and on 13 July 2024, a mutant VDPV3 was reported to have been detected in the samples from Kathmandu Valley, Nepal, suggesting an ongoing risk of reintroduction and transmission.

stimulating immune responses (Sabin et al., 1960). Large-scale human clinical trials were conducted in the Soviet Union in 1957 to early 1960′s which showed immunogenicity and safety (Sabin, 1987), and the vaccine was licensed and chosen for worldwide distribution. This method of vaccine formulation and administration proved effective in reducing the incidence of polio and played a crucial role in global efforts to eradicate the disease. Attenuation causes several nucleotide substitutions in the virus's internal ribosome entry site, of the parent virulent WPV1, WPV2, and WPV3 with 57, 2 and 10 nucleotide substitutions respectively (Kew et al., 2005). These genetic substitutions impair the poliovirus's ability to use its RNA template to produce proteins within host cells. In 1961, types-1 and types-2 OPV monovalent vaccines were licensed, followed by type-3 in 1962. In 1963, trivalent OPV (comprising all attenuated types) was introduced and quickly became the preferred vaccine in the United States, largely replacing the IPV. A subsequent mass immunization campaign, from 1962 to 1965, led to approximate 100 million Americans to receive the Sabin vaccine, leading to a significant drop in poliomyelitis cases, further reducing the incidence beyond the levels achieved with the IPV vaccine (O'Grady and Bruner, 2024; Pearce, 2004).

In November 1987, an enhanced-potency IPV was licensed in the United States, which comprised higher concentration of poliovirus antigens, enhanced stability, immunogenicity and fewer side effects. The enhanced IPV was incorporated into the routine childhood immunization schedule, with doses given shortly after birth, at 4 months, between 6–18 months, and a booster at 4 to 6 years, marking a significant advancement against poliovirus (Atkinson et al., 2008); some countries give a fifth injection in adolescents. In 2002 a pentavalent combination vaccine (Pediarix) was approved in the United States, comprising, the IPV vaccine together with tetanus, diphtheria, and acellular pertussis (DTaP) vaccines, as well as a pediatric dose of the hepatitis B vaccine (DTaP-HBV-IPV) (Pichichero and Stonehocker, 2003; Yeh, 2005). Other combination vaccines of IPV include DTPa (DTaP-IPV, Kinrix), DTPa and Haemophilus influenza-type b (Hib) vaccines (DTPa-IPV/Hib, Pentacel) (Johns and Hutter, 2010). These combination vaccines are generally safe, effective, stimulate strong IgG responses of at least 92.5 % after primary vaccination and reduce the number of required injections (Boisnard et al., 2023; Omenaca et al., 2018).

Global health initiatives

Prior to global health initiatives, polio epidemics from 1900 to 1950 caused severe illness, with approximately 1 in 200 polio cases leading to permanent paralysis and fatalities among children worldwide. By 1988, endemic polio affected 125 countries, with 350,000 reported cases. The Global Polio Eradication Initiative (GPEI) was a comprehensive international effort to eradicate polio globally launched in 1988. By 1994, polio was eliminated in United States, by 2002, Europe was declared polio-free and by 2014 India was declared polio-free. The Mandela declaration on polio eradication in 1996 ('kick polio out of Africa'), secured government/political commitment across Africa to eliminate the disease. Coordinated and extensive vaccine immunization programs and surveillance efforts between governments, health workers, volunteers, the Bill & Melinda Gates Foundation, Rotary International, the WHO, US Centers for Disease Control and Prevention and UNICEF, led to the eradication of polio (WPV1) from the African continent, on 25 August 2020 (Bahl et al., 2018). As of August 2024, only Pakistan and Afghanistan remain worldwide with reported cases of WPV partly due to vaccine resistance and misinformation (Ahmad et al., 2024).

The WHO and other organizations continue to push for high vaccination coverage to prevent outbreaks. There are three-types of vaccines (Cooper et al., 2024; Estivariz et al., 2023; Kalkowska et al., 2024; Montero et al., 2023); (i) the monovalent polio vaccine which targets single poliovirus types (WPV1 or WPV2 or WPV3), often used in

outbreak settings where a specific type is predominant; (ii) the bivalent polio vaccine targets two of the most common poliovirus types (WPV1/WPV3); and (iii) the trivalent vaccines which targets all three types (WPV1/WPV2/WPV3) and provides broad spectrum protection. The choice between mono-, bi-, and tri- valent polio vaccines depend on the specific needs of vaccination programs. Bivalent vaccines are often preferred for their effectiveness in controlling the more prevalent strains and reduces the risk of circulating vaccine-derived poliovirus (cVDPV) (Cooper et al., 2024; Estivariz et al., 2023; Kalkowska et al., 2024; Montero et al., 2023). Poliovirus still poses a threat even after international efforts to eliminate polio have been made, especially in areas with low immunization rates and inadequate sanitation (Wolbert et al., 2024).

Circulating vaccine-derived poliovirus (cVDPV)

Whilst WPV cases have decreased globally, an increase in cases of cVDPV has emerged. As the OPV vaccine comprises an attenuated poliovirus, with nucleotide substitutions (mutations), over time the attenuated/weakend virus can further mutate as it replicates in vaccinated individuals, to lead to a new version of poliovirus (Fig. 1) including a neurovirulent form. These new mutant versions can cause paralysis especially in those with poor immune systems and can spread to others particularly in areas with low vaccination rates. Further, as OPV is excreted in feces it can be further spread especially in areas of poor sanitation posing a risk like that of WPV (Mohanty et al., 2023). Despite its risks, OPV remains the preferred vaccine due to its cost-effectiveness, ease of administration, and lack of need for special medical equipment or prior training. It can induce community immunity by spreading the virus through excretions from vaccinated individuals. Administered orally, OPV also induces intestinal mucosal immunity, which helps protect against future infections and offers long-term, lifelong protection against poliovirus (Mohanty et al., 2023). Even though IPV, which is inactive does not have the risks of inducing cVDPV, it is more expensive, logistically challenging and does not provide community immunity.

Vaccines against all three WPV (WPV1, WPV2, WPV3) strains have given rise to strains of cVDPV, with type-2 (cVDPV2) being most prominent. As such, in 2016, global eradication efforts transitioned from using the trivalent OPV to the bivalent OPV, which does not include WPV2 (Bassey et al., 2018). The monovalent oral WPV2 vaccine is now only used in specific areas experiencing outbreaks of cVDPV2 (Cooper et al., 2024; Estivariz et al., 2023; Kalkowska et al., 2024; Montero et al., 2023). From 2016 to 2022 there were 121 cases of cVDPV1 in 11 countries, 2667 cases of cVDPV2 in 46 countries and, 8 cases of cVDPV3 in 2 countries (WHO. World Health Organization. Global Circulating vaccine-derived poliovirus (cVDPV). https://polioeradication.org/wp-content/uploads/, 2024). In 2023, 524 cVDPV cases were reported in 32 countries, of which 390 were cVDPV2 and 134 were cVDPV1 (Rajbongshi et al., 2024). In 2024 thus far, 158 cVDPV cases have been reported in 16 countries, of which 152 are of cVDPV2 in 15 countries (Angola, Benin, Chad, Democratic Republic of the Congo, Ethiopia, Guinea, Indonesia, Liberia, Mali, Mozambique, Niger, Nigeria, Palestine, Somalia, South Sudan, Yemen) and 6 of cVDPV1 in 2 countries (Democratic Republic of the Congo, Mozambique) (Initiative, 2024).

Detection of a novel strain (cVDPV3) of poliovirus in Nepal

In July 2024, health authorities reported the detection of a novel mutated form of WPV3 (cVDPV3) in sewage samples collected from Kathmandu, Nepal (Highly contagious poliovirus foundin Kathmandu sewage., 2024). This finding as it suggests that the mutated virus is actively circulating in the environment, posing a potential risk of reintroduction and transmission of poliovirus in the region. This discovery follows Nepal's declaration as polio-free by the WHO on 27 March 2014, after reporting no human cases of polio since 2010 (World Health Oganization (WHO). Staying polio-free. 27 March, 2014). This new detection emphasizes the persistent challenge of eradicating poliovirus and the need for ongoing surveillance, robust vaccination efforts (D'Amelio et al., 2016; Hajj Hussein et al., 2015), and swift action to prevent outbreaks and prevent resurgence.

The detection of this novel strain of cVDPV3 in Nepal has triggered significant global concern (Fig. 1). The national Public Health laboratory conducted environmental surveillance for poliovirus by collecting and testing sewage samples from Tukucha and Bagmati rivers in Kathmandu, on 26 May 2024 (Highly contagious poliovirus foundin Kathmandu sewage., 2024). On 13 July 2024, a mutated form of cVDPV3 was reported, which is considerably different to WPV3 in the polio vaccine. The mutations are suggested to possibly increase the risk of spread among children due to immune evasion. The risk of the virus spreading has risen due to the increased presence of the mutated virus in the environment. This virus, being new and not previously seen elsewhere, suggests it may have originated within Nepal's environment. As such, the WHO advised Nepal to immediately launch a vaccination campaign for all children in nearby regions; with Kathmandu, Lalitupr and Bhaktapur administering the bivalent WPV1/WPV3 oral polio vaccine to all children on 24–28 July 2024 and to be completed within 2 weeks. By increasing the vaccine immunization coverage in these areas should enhance the chances of interrupting virus transmission and reducing the paralytic burden.

Previously, cVDPV3 was reported in March 2022, in Jerusalem Israel in an unvaccinated 3 year old child with acute flacid paralysis, where the virus had shown 17 nucleotide changes (different to that identified in Nepal) from the OPV WPV3 vaccine (Initiative, 2024), and 7 cases in Somalia in 2018. Several environmental VDPV3 cases reported in Israel and Palestine (2021n = 12 and 2022n = 34); and n = 1 in 2021 in China (Initiative, 2024).

Surveillance and containment measures

A combination of containment measures for managing the poliovirus detected in sewage and intensifying immunization campaigns among children at risk of contact with the virus is essential to prevent ongoing transmission and potential spread of vaccine-derived polioviruses. The following strategies should be considered:

- Strengthening the surveillance of acute flaccid paralysis with thorough case investigations to expedite the discovery of any new polio cases and conducting a thorough study to assess how long the virus has been circulating to guide public health interventions on when and where the transmission and shedding of the poliovirus began.
- Intensification of supplementary immunization among all children residing in densely populated urban centers and suburban communities in the time span of one or two weeks, and then again at four or five weeks after the first dose due to waning immunity in the vaccinated population.
- Enhanced surveillance for environmental poliovirus circulation in selected regions of neighboring countries (for example, in northern India) to undertake prompt and synchronized precautionary supplementary immunization activities.
- Locally, individuals should adhere to public health measures of hygiene, and a unique identification system for the vaccinated population can be utilized to detect any new cases associated with this specific virus.

Conclusion

The detection of VDPV3 in the sewage of Kathmandu Valley is symptomatic of the possible sustained circulation of VDPV3 around this region, which could potentially cause outbreaks of paralytic poliomyelitis in healthy populations. Therefore, along with targeting the affected individuals, possibilities of continuing and reinforcing oral

polio vaccination programs and monitoring the properties of cVDPV3 strains are essential. The complete genetic characterization of VDPV3 and frequent monitoring for changes in nucleotide sequences as well as serotype of the virus is necessary to understand the affectivity of the existing status of polio vaccination programs in Nepal and initiating periphery-based vaccination strategies 3 months prior to cessation of immunization if necessary. Failure to take these future steps may reverse the global efforts to eradicate the endemic wild-type poliovirus and return to a time of a high number of cases of poliomyelitis due to the spread of VDPVs from an emergence origin.

Moving forward

The surveillance of acute flaccid paralysis in a region is important in polio control programs and is useful for documenting the spread and the genetic characteristics of the virus. Understanding the genetic variability reveals the information on several key aspects of VDPV including its geographic origin, duration of circulation of these viruses and the step of evolution of any VDPVs that were associated with an acute paralytic case. Vaccination with trivalent oral poliovirus vaccine against all 3 subtypes (WPV1, WPV2, WPV3) can result in the appearance of revertants of highly evolved virus that are excreted in the stool of some vaccinated children. These viruses have the potential of continued transmission and to cause paralytic disease in settings of low individual or population immunity.

Re-evaluation of polio vaccination strategies in Nepal and other countries is critical, and IPV vaccines should be re-introduced as the vaccine of choice (Saud and Adhikari, 2024). In fact, by June 2018, 39/47 African countries had changed OPV to IPV in routine immunization programs (Ming et al., 2020; WHO. World Health Organization. Framework for certification of polio eradication in the African Region: Report of the Secretariat. Regional Office for Africa. https://apps.who.int/iris/handle/, 2024), and several other countries also changed to IPV. In addition, fractional IPV could be utilized which includes a lesser dose of the standard IPV where limited vaccine supplies are available to improve coverage, especially in resource-constrained settings. Studies show that fractional IPV remains effective in providing protection against poliovirus, though additional doses may be needed for optimal immunity (Snider et al., 2023). Further, in December 2023, a novel genetically stabilized OPV received full licensing. This novel OPV includes modifications to, (i) the 5′ untranslated region to stabilize attenuation determinants, (ii) 2C coding region to inhibit recombination, and (iii) 3D polymerase to reduce viral adaptability was to reduce the risk of developing cVDPV2 received full licensing (Yeh et al., 2020); other similar vaccines targeting type-1 and type-3 are currently in human clinical trials. To achieve eradication, OPV will eventually need to be phased out in favor of IPV even though they are more costly and challenging to administer, and do not induce contact immunity, they do not carry the risk of generating cVDPV. Moreover, it is important to explore and advance a range of innovative vaccine formulations. This includes developing subunit protein-based vaccines, mRNA vaccines, and DNA vaccines, with or without the use of carriers and adjuvants to enhance their effectiveness. By focusing on these advanced vaccine technologies, we can improve strategies for poliovirus eradication and ensure robust and long-lasting immunity without the development of cVDPV variants. Continued research and development in these areas will be crucial for overcoming challenges related to poliovirus and achieving global health goals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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