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REVIEW

Poliomyelitis is a current challenge: long-term sequelae and circulating vaccine-derived poliovirus

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Abstract For more than 20 years, the World Health Organization Western Pacific Region (WPR) has been polio-free. However, two current challenges are still polio-related. First, around half of poliomyelitis elderly survivors suffer late poliomyelitis sequelae with a substantial impact on daily activities and quality of life, experiencing varying degrees of residual weakness as they age. The post-polio syndrome as well as accelerated aging may be involved. Second, after the worldwide Sabin oral poliovirus (OPV) vaccination, the recent reappearance of strains of vaccine-derived poliovirus (VDPV) circulating in the environment is worrisome and able to persistent person-to-person transmission. Such VDPV strains exhibit atypical genetic characteristics and reversed neurovirulence that can cause paralysis similarly to wild poliovirus, posing a significant obstacle to the elimination of polio. Immunization is essential for preventing paralysis in those who are exposed to the poliovirus. Stress the necessity of maintaining high vaccination rates because declining immunity increases the likelihood of reemergence. If mankind wants to eradicate polio in the near future, measures to raise immunization rates and living conditions in poorer nations are needed, along with strict observation. New oral polio vaccine candidates offer a promissory tool for this goal.

Keywords Poliovirus · OPV · Vaccine-derived poliovirus · Poliomyelitis · Post-polio syndrome · Aging

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Introduction: the poliovirus

Since its identification in 1909, classified as a member of the Picornaviridae family and belonging to Enterovirus group C, the poliovirus (PV) has been the subject of extensive research to better understand its life cycle, restrict its spread, and treat poliomyelitis, a crippling condition it produces. The word poliomyelitis originates from the Greek word "polio" meaning "gray" and "myelon" meaning "marrow" representing the most feared concern.

Picornaviruses are the causative agents of a variety of significant human and animal illnesses, including poliomyelitis, hepatitis A, foot-and-mouth disease, and others. PV is undoubtedly the best-known enterovirus and one of the most studied viruses. PV is a human pathogen that may spread in cultured, non-neural human cells. It not only aided in the creation of polio vaccinations but also significantly aided in the emergence of molecular virology as a distinct field of study. It was the first

animal RNA virus whose entire genome sequence was identified and for which a reverse genetics technique was developed [1, 2].

The PV has a 25–30 nm diameter (Fig. 1). Each of the 60 capsomers that make up its capsid, or outer layer, is made up of the virion proteins VP1, VP2, VP3, and VP4, which are organized in an icosahedral pattern. Eight protein strands are organized in a β sheet array to form a β barrel that makes up each of the four virions. Loops are formed as a result of the mixing of different proteins, and these loops act as antigenic sites to combine with the appropriate antibodies. Three serotypes of PV have been recognized as types 1, 2, and 3. The prototype strains that have been crystallized and studied in detail are Brunhilde and Mahoney strains for type 1, Lansing and MEFI for type 2, and Leon and Saukett for type 3. The PV genome is a single 7.4-kb RNA molecule with positive (mRNA-like) polarity within an icosahedral capsid. The PV genome is organized in a manner like that of other picornaviruses, particularly enteroviruses. It has a single open-reading frame (ORF) and 5' and 3' untranslated regions (UTR), each measuring around 740 and 70 nt in length. The ORF encodes a polyprotein of around 2200 residues, which the viral proteolytic activities eventually convert into 11 "mature" polypeptides, with some of the intermediary stages of the processing acting as discrete functional units. Four of the final polypeptides (VP1–VP4), which correspond to the polyprotein's N-terminus, are structural components of the viral capsid. The remaining polypeptides are involved in viral genome replication, polypeptide proteolytic processing, and a variety of activities directly or indirectly ensuring effective viral progeny generation (Fig. 2). Additionally, viral RNA has a number of cis-acting components. The replicative elements oriL (also referred to as the clover leaf element), oriR, and cre (oriI) in the 5UTR and 3UTR, as well as a translational cis-element called internal ribosome entry site (IRES) in the 5UTR, which is in charge of the cap-independent internal initiation of translation of the viral RNA hijack the cellular translation machinery [3].

The poliovirus genome variability

The PV genome's variability is a key characteristic underpinning the evolution of the virus, as well as its pathogenic and epidemiological traits. It is also a key tool for understanding the links between genotype and phenotype. The covalent modifications of the viral RNA are caused by two different sets of processes, replicative and non-replicative. Codified

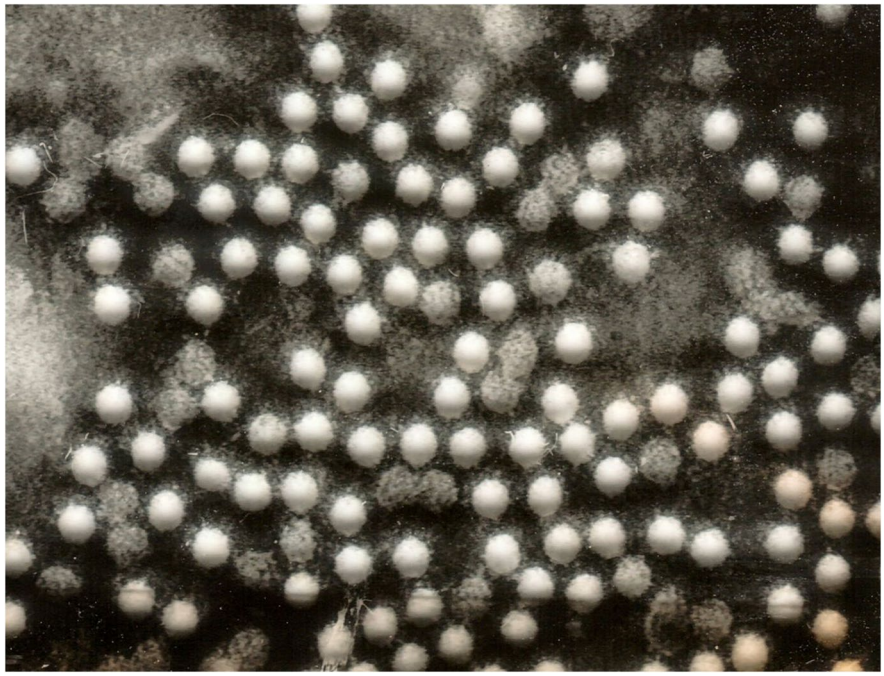

Fig. 1 Transmission electron micrograph of polioviruses. By Dr. Graham Beards at en.wikipedia, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=11575159

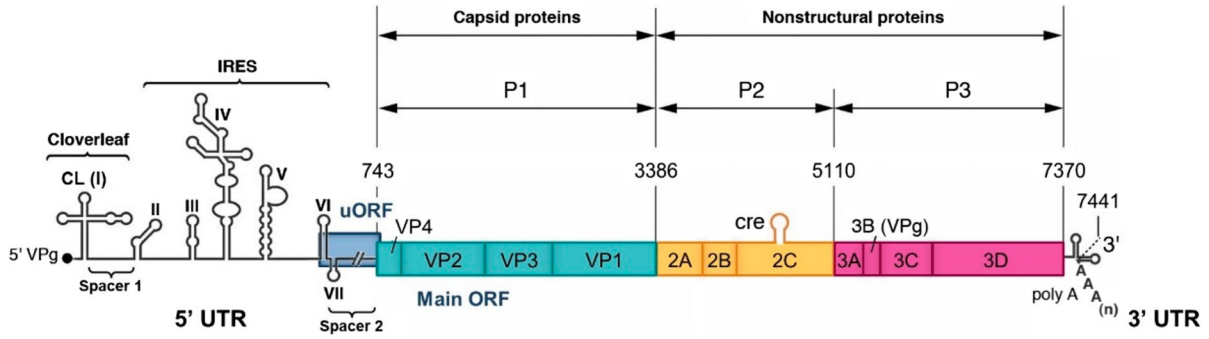

Fig. 2 Organization of the genome of poliovirus type 1 (PV1) Mahoney. The poly-adenylated single positive-strand RNA genome is covalently linked to the viral protein VPg (also named 3B) at the 5′ terminus. In addition to the main large open-reading frame (ORF), the majority of the EV-A, EV-B, and EV-C genomes, and in particular PV1 genome, contain a second upstream overlapping ORF (uORF). However, PV2 and PV3 genomes do not contain an intact uORF. The coding region is flanked by two untranslated regions (5′ and 3′ UTRs). The 5′ UTR (nucleotides 1 to 743) is magnified to indicate the seven stem-loop structures (I to VII) forming two functional units, the cloverleaf (CL, I) and the internal ribosome entry site (IRES, II–VI). The P1 region encodes the capsid proteins (VP1–4) and the P2 and P3 regions encode the non-structural proteins such as the RNA-dependent RNA polymerase 3D. Attribution: By Claire Muslin, Alice Mac Kain, Maël Bessaud, Bruno Blondel, and Francis Delpeyroux — https://www.mdpi.com/1999-4915/11/9/859/htm, CC BY 4.0, https://commons.wikimedia.org/w/index.php?curid=96181686. Obtained from: https://www.mdpi.com/1999-4915/11/9/859/htm

in the 3D gene, the viral RNA-dependent RNA polymerase (RdRP) copies the viral RNA with the aid of other viral and host proteins. Premature termination, which may or not be related to template flipping, and incorporation of erroneous nucleotides are at least two types of errors that the enzyme is innately capable of making. Point mutations are produced by misincorporation, whereas intra- or intermolecular rearrangements can be produced through template swapping. While not extensively documented in the case of poliovirus RdRP, slippage or shuttering, which results in repeated copying of a nucleotide or oligonucleotide, may be added to the list of probable replicative errors. The error frequency values in the range of $5\times10^{-3}-10^{-5}$ were obtained when the degree of nucleotide misincorporation was measured using purified preparations of the enzyme [4–6], with transitions occurring approximately ten times more frequently than transversions. The fact that each progeny RNA molecule produced by the poliovirus RdRP carries, on average, one nucleotide variation from its template is a significant implication of the quantity of diversity that already exists. However, there are fluctuations in the degree of poliovirus RdRP infidelity. Particularly, PV with a more accurate RdRP is more attenuated, less competitive, and less adaptive.

The serial passage of the three major PV strains in nonhuman primates and cultured primate cells resulted in strains with reduced neurovirulence [7, 8]. These are the Sabin strains in the oral polio vaccine (OPV) that have been essential in the global effort to eradicate PV. Since the Global Polio Eradication Initiative (GPEI) was established in 1988, two of the three wild-type PV serotypes (types 2 and 3) have been eradicated in 2015 and 2019, respectively. Wild polio cases have decreased globally by more than 99% since 1988, but the endemic transmission of wild-type 1 remains uninterrupted only in Afghanistan and Pakistan where nine cases were reported during 2022 [9–12]. During 2022, two wild polio cases were reported in Malawi and Mozambique at the Southeast region of Africa (https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON395 and https://polioeradication.org/polio-today/polio-now).

The major genetic determinants of all three Sabin strains have been mapped to mutations in the IRES at the 5′ UTR of the genomic RNA, thus resulting in reduced levels of viral translation [13–15]. Among the six well-identified domains in the poliovirus IRES secondary structure, the binding of canonical eukaryotic initiation factor 4G (eIF4G) to domain V (or others), which is located near the 3′ end of the IRES, is a key step in PV translation (Fig. 2) [16, 17]. Such eIF4G recruits eIF4A (RNA-dependent DEAD-box helicase) and eIF4B for the IRES restructuring thus allowing the ribosome recruitment, thus stimulating

virus translation initiation. In addition, other non-canonical trans-acting cellular RNA-binding factors interact with the viral IRES, also at the domain V. These include polypyrimidine tract–binding protein (PTB), La autoantigen, and poly(rC)-binding protein 2 (PCBP2) [17–23].

Attenuated PV strains contain point mutations in the IRES domain V at nucleotides 480, 481, and 472 that inhibit viral translation in the Sabin 1, Sabin 2, and Sabin 3 strain numbering, respectively [24–26]. These mutations are located in, or directly adjacent to, the reported binding sites of eIF4G and PTB [17, 23], thus impairing their binding and reducing the viral translation and consequently the replication in the brain and spinal cord, thus explaining the attenuated neurovirulence of the PV vaccine strains. Of all three mutants, the Sabin 3 mutant exhibits the most severe translation and initiation factor binding defects [13, 15]. Impaired binding of PTB to the poliovirus Sabin serotype 3 mutant also correlates with translation attenuation [27]. However, it is still not definitively elucidated the reasons that explain the cell type restriction of Sabin mutant attenuation to cells of the central nervous system but not in others such as HeLa cells [28]. In this regard, variations in the intracellular concentration of eIF4G have been proposed as responsible for cell type-specific translation defects of a PV Sabin 3 mutant [16].

Poliovirus pathogenesis

The only known natural hosts of the PV are humans. The fecal–oral pathway is how the sickness spreads. Following localized growth in the tonsils and neck lymph nodes, the PV then spreads to Peyer patches and the small intestine. The virus multiplies in the pharynx and intestine for 1 to 3 weeks. A 2- to 35-day incubation period is typical. The virus is shed in the feces after 3 to 5 days and can also be recovered from throat swabs of exposed patients, according to a theory that the virus may occasionally reach the circulation before subsequently invading the tonsils. Either no symptoms at all or moderate viremic signs may be present throughout this time.

The local immune response often prevents the spread of viruses. Infections are thus either asymptomatic or marked by flu-like symptoms in approximately 95% of cases. Gastroenteritis, respiratory tract infections, and influenza-like illnesses can all have self-limiting episodes. Antibodies may cause the viremia to decline, or it may move to the central nervous system (CNS) through the bloodstream. The virus is excreted most fully in the feces 2 to 3 days before and 1 week after the onset of symptoms. Additionally, according to published research, the virus spreads along the brain's afferent nerve route because it has a specific affinity for the cellular receptor CD155, which facilitates cell entrance and attachment [29]. In humans, CD155 protein was detected on the intestinal epithelium, M cells of Peyer's patches, and in germinal centers within the Peyer's patches [30]. The virus's cytopathic nature largely causes destruction. The spinal cord anterior horn cells have sustained significant damage. Limb paralysis results from this. The posterior horn cells, thalamic motor neurons, and hypothalamus are potential targets for the virus's propagation. Brain stem involvement in the bulbar type of poliomyelitis may be deadly. The damaged brain cells' histological appearance reveals vacuolation and infiltration, along with an accumulation of plasma cells, polymorphonuclear neutrophils, and microglia. Axon degeneration results from macrophage phagocytosis of infected cells. Muscle atrophy spreads widely, resulting in flaccid paralysis. In severe situations, respiratory paralysis typically results in death. Twenty-five to 30 years after the first paralytic episode, post-polio syndrome (PPS) might develop [31]. Progressive muscular atrophy is observed in PPS, most likely as a result of continuous motor neuron degeneration. Another theory postulates that aberrant cytokine levels may be caused by PV persistence in the brain and spinal cord [32, 33].

Intestinal immune response to the oral polio vaccine

For many years, live attenuated PV vaccines have been the cornerstone of vaccination programs and continue to be essential to the fight to eliminate the wild-type virus. In recipients, the vaccination replicates for an average of 4 weeks, during which time the characteristics of the virus excreted change [34]. The capacity of the oral polio vaccine to establish intestinal immunity and reduce viral shedding following subsequent exposure of patients to live virus sets it apart from other vaccines [35, 36]. Contrarily, Salk

inactivated polio vaccine (IPV) has minimal impact on viral replication in the gut following an OPV challenge in patients who have never been exposed to a live virus, despite producing significant systemic immunity and protecting against paralytic illness [37, 38]. Different studies on mucosal antibody responses after administration of combined bOPV and IPV regimens have reinforced the crucial role of neutralizing antibody responses mediated by IgA in restricting PV replication in the gut. However, boosting serum neutralization by including standard or high-dose IPV in a primary bOPV immunization series does not result in a comparable increase in intestinal immunity upon subsequent exposure to live type 2 PV, thus highlighting polio-specific intestinal immunity, which differs from the serum response and is a key factor in viral shedding [36, 39–42]. Hence, such different studies carried out in Latin American infants have demonstrated a key finding: previous vaccination with the attenuated virus (tOPV or bOPV) develops strain-specific intestinal immunity and significantly reduces viral multiplication upon oral challenge. Such intestinal immunity is not significantly affected by the addition of additional IPV (either standard or high dosage) to a bOPV primary series [43].

The length of time since the last vaccination exposure is linked to a reduction of intestinal PV immunity induced by vaccination. Hence, the mucosal immunity capable of limiting PV reproduction in the gut of older children and adolescents may either fail to develop or steadily decline over time, increasing the chance of virus excretion upon oral re-exposure to the PV, resulting in an immunological gap in later children, adolescents, and adults in the absence of further vaccination doses [44]. The absence of detectable intestinal IgA responses to OPV in older children and adults reveals that induction of mucosal immunity to PV is less robust after infancy despite enteric replication of the virus and strong type-specific serum antibody boosts. Likewise, among elderly adults exposed to OPV, rapid induction of systemic antibody responses was observed, but it was accompanied by a prolonged virus excretion prolonging up to 2 months after the challenge. There are similitudes between the locations of primary PV replication in intestine epithelial cells and in tissues related to the mucosal immune system (such as the adenoid, tonsil, and Peyer's patches) with the anatomic locations being in charge of inducing and expressing mucosal IgA [45, 46]. Such age-dependent decline in intestinal immunity may be related to decreases in enteric IgA production but not in total IgA [47]. The immunologic repertoire including the memory responses is early shaped after exposure to non-commensal microbes through infection or immunization, composed of abundant macrophages and dendritic cells in the lamina propria able to remove pathogens that interrupt the epithelial barrier. A more restricted immune response including the IgA repertoire is observed when the intestinal mucosa is exposed to microbiota, which also depicts a rapid decline in the absence of repeated antigenic exposure. Moreover, even when the IgA response is augmented after successive antigen exposures, it appears different than the systemic prime-boost response [35]. Early childhood vaccination with live attenuated and inactivated polio vaccines during a time of dynamic immunologic development is anticipated to have a major influence on the formation of useful cell-mediated memory responses that can stimulate mucosal IgA and limit viral reproduction in the gut. In addition to raising important questions about the nature of immune regulation of PV replication in the intestine, recent observations of an age-related decline in enteric mucosal IgA and virus neutralizing responses to OPV, associated with sustained virus shedding, have evident consequences for worldwide eradication attempts.

Adult vaccination for polio: how long does the polio vaccine last?

Following three doses of either IPV or OPV, serologic tests have demonstrated that seroconversion rates are approximately 100% for all three viruses. While the World Health Organization (WHO) reported strong scientific evidence for the long-term (> 5–10 years) persistence of protective antibodies in about 80% of the population vaccinated with about 3–4 doses of OPV, the duration of immunity conferred by IPV was recently evaluated and neutralizing against PV1, PV2, and PV3 antibodies in blood samples which were present in more than 90% of the study participants and persisted for at least 18 years after administration of the last dose [48]. According to the Centers for Diseases Control and Prevention in the USA, people who have already finished their polio immunization series during childhood but are "at elevated risk of exposure

to poliovirus" (i.e., those who are visiting countries where they are more likely to contract polio, unvaccinated or incompletely vaccinated adult whose children will be receiving oral poliovirus vaccine, or living or working in a community where poliovirus is circulating, anyone handling samples that may contain polioviruses while working in a lab, healthcare professionals who deal with patients who may have polio or who come into close touch with a poliovirus carrier) can get three doses or a single lifetime booster dose of the IPV, according to previous immunization status.

Accelerated aging and post-polio syndrome are long-term effects of early poliomyelitis

Despite the fact that there are currently only two polio-endemic countries (Afghanistan and Pakistan, having never interrupted the transmission of wild PV1), the large number of polio survivors has led to estimates of the number of people affected by post-polio syndrome (PPS) at roughly 250,000 in Europe and 20 million globally [49]. One-third of patients with prior poliomyelitis had PPS [50]. More than 7000 individuals in Israel have had poliomyelitis, the majority occurring between 1949 and 1956 when the disease was rife and mostly struck children. After being clinically stable for a long time, these people, most of whom are now in their 60 s and 70 s, have begun to experience a worsening of their disease, which is detrimental to their overall health and functioning. PPS, which negatively affects patients' quality of life and function, is one of the potential causes of this decrease. PPS has been diagnosed using a variety of methods, the majority of which are based on muscle atrophy or dysfunction. People with late poliomyelitis sequelae see a substantial impact on their independence and quality of life as they age [51]. Additionally, people from Denmark with a history of poliomyelitis can have a wide variety of symptoms in their later years (muscle symptoms, pain, neuropathic sensory symptoms, and bulbar signs), including symptoms that are associated with areas in the central nervous system other than the anterior horn of the spinal cord. Also, reported PPS rather than early symptoms of the acute stage of poliomyelitis appears to be the connection between late symptoms. This most recent discovery lends credence to the idea that aging is not the sole cause of PPS [52]. Pathologic processes associated with the chronic stress of damaged motor units that occurs in persons with prior poliomyelitis may contribute to the pathogenesis of PPS. PPS is negatively correlated with older age upon poliomyelitis start. The relationship with other illnesses may suggest that persistent physical stress, especially in already weakened motor units, might lead to the emergence of PPS symptoms [50].

A faster-aging process in this group has been suggested as another cause for late functional detriment [53]. Several studies have shown that patients with late effects of poliomyelitis exhibit an increased risk of age-related chronic diseases and health conditions, such as diabetes, high blood pressure, ischemic heart disease, cardiac arrhythmias, chronic obstructive pulmonary disease, osteoporosis, and obesity cardiovascular disease, hypertension, diabetes, breast cancer, and chronic pain than the general population. Patients with PPS have decreased independence in their ambulatory capacity indoors and outdoors and in their daily activities [52, 54–57]. Two consecutive studies, 10 years separated, reported by I. Schwartz and her group at the Hebrew University of Jerusalem (Israel) offer evidence of an early aging process of people with late effects of poliomyelitis, similar to that of other individuals disabled at a young age because of congenital or acquired etiologies [51, 58]. The phenomenon of accelerated aging in people with disabilities may be driven by the attrition phenomena connected to ongoing psychological, biological, and social constraints imposed by the lifetime endeavor to maintain homeostasis [59]. The relevance of both post-polio syndrome and early-onset age-related chronic illnesses resides in their capacity to hasten aging and result in secondary impairments [60–63].

Reversion to virulence of vaccine-attenuated poliovirus strains

A low incidence of vaccine-associated poliomyelitis, either in vaccination recipients or their close contacts, is linked to immunization with the Sabin vaccine strains. One in every 750,000 people who receive main immunizations develops paralysis due to the vaccine [64, 65]. This vaccine-derived PV appears periodically elsewhere, particularly in Africa and Asia, but since the middle of 2019, more

than 20 countries worldwide have reported cases of vaccine-derived polio. The changes that bestow the attenuation phenotype on the viral genome revert mainly in domain V (nucleotides 468–535) of the 5′ UTR, resulting in vaccine-associated poliomyelitis. For instance, viruses recovered from cases of vaccine-associated poliomyelitis caused by Sabin type 3 (VDPV3) show a nucleotide U472C reversion in the domain V of the IRES or, alternatively, genetic reversions in domains IV (U398C) and V (A481G) of the IRES and in amino acid 143 of VP1 capsid protein, leading to the evolution of Sabin-2 into VDPV2 [66–70]. Most people who received the Sabin vaccination strains appear to have such reversion episodes in their digestive tract [71]. The fact that the Sabin vaccination produces vaccine-associated illness in so few patients is consequently perplexing. One explanation is that the replication of the Sabin strains is still sufficiently delayed in most hosts even with the selection of revertants in the alimentary canal to allow containment by the immune response. Vaccine-associated poliomyelitis may be brought on by a faulty IFNα/β response, which enables revertant viruses to grow unchecked in extraneural tissues before infecting the central nervous system and resulting in paralytic illness [72].

In 2016, the type 2 component of trivalent OPV (tOPV) was removed, and a worldwide coordinated conversion from tOPV to bOPV (types 1 and 3) was made subsequent to the certified eradication of wild-type PV (WPV) type 2 in 2015 [73–75]. These changes were made in response to concerns about the safety of OPV following rare incidences of vaccine-associated paralytic polio (VAPP), which are predominantly caused by the type 2 component of the vaccine and the introduction of vaccine-derived polioviruses (VDPV2) into regions with low population immunity [76–78]. Along with this modification, it was advised to incorporate at least one dose of IPV into vaccination plans in order to increase community immunity against all three serotypes and to prepare people for potential contact with type 2 PV [79].

In Ukraine, polio vaccine coverage declined from 91% in 2008 to 15% by mid-2015. In 2015, two unrelated children were paralyzed by a highly divergent vaccine-derived poliovirus type 1 (VDPV1) isolates exhibiting 20 and 26 nucleotide divergent from prototype Sabin strain [80]. In Yemen, more than a hundred cases of acute flaccid paralysis were diagnosed in 2020. Among them, thirty VDPV1 isolates, differing from the attenuated Sabin 1 type by 17–30 VP1 gene nucleotides, were detected in mostly unvaccinated children in a context of a profound humanitarian crisis since the start of the war in 2015 [81].

The number of acute flaccid paralysis cases associated with VDPV2 has enlarged from two in two countries in 2016, to 366 in 16 countries in 2019, and then to over 1000 in 24 countries in 2020 (https://polioeradication.org/polio-today/polio-now). Last July 2022, vaccine-derived poliovirus type 2 (VDPV2) was detected in stool specimens from an unvaccinated immunocompetent young adult from New York, who was experiencing acute flaccid weakness [82]. The PV has continued to spread in sewage, according to wastewater surveillance in London, New York, and Jerusalem [83, 84]. This has spurred an investigation of additional preventative measures, such as the deployment of a new oral vaccination that is anticipated to gain emergency permission.

Novel oral poliovirus vaccine type 2 (nOPV2) candidates

In order to minimize the sporadic occurrence of illness and outbreaks linked to the genetic instability of the Sabin vaccine strains, novel oral poliovirus vaccine type 2 (nOPV2) candidates are being developed. A novel vaccine PV strain candidate exhibits a genetically stabilized domain V known as "S15." The possibility of thermodynamically strengthening the RNA structure via point mutations was reduced since it does not include U–G base pairs, but it preserves the virulence attenuation to a level equivalent to that of the Sabin strains while preventing the likelihood of virulence reversion due to single-nucleotide alterations [85]. Then, another novel OPV2 candidate 1 (nOPV2-c1) introduced two additional modifications to diminish the risk of reversion at the "S15" domain V being replaced by a single recombination event. First, the cis-acting replication element (cre) was relocated to the 5UTR of the virus genome, and second two changes to the 3D polymerase decrease the number of recombination events and increase replication fidelity [86]. A novel OPV2 candidate 2 (nOPV2-c2) supplements the S15 domain V with codon deoptimization of the capsid region to further attenuate the strain [87]. These two nOPV2c1 and c2

candidates have recently been analyzed through phase 1 and 2 clinical studies with the goal of providing similar protection as mOPV2 but with reduced risk of loss of attenuation. Two related clinical investigations including children aged 1 to 5 years were conducted to compare standard Sabin OPV type 2 (mOPV2) to nOPV2 for safety, immunogenicity, shedding rates, and characteristics of the shed virus [88–90].

To further evaluate the genetic (mutations and recombinations) and phenotypic (neurovirulence) stability of shed virus following administration of Sabin monovalent OPV2 (mOPV2) or nOPV2 candidates, stool samples were collected from 1-to-5-year-old children that have varying levels of baseline intestinal immunity, during phase 4 and phase 2 trials. All Sabin-2 recipients continue to shed the virus more than 7 days after immunization and quickly showed the known A481G reversion in the primary attenuation site (domain V in the 5UTR) to be associated with increased mouse paralysis. In contrast, nOPV2-c1 and nOVP2-c2 exhibited a modest increase in fitness and virulence after many weeks of replication in the human gut, occurring genetic changes leading to amino acid substitutions at VP1-143, a U459C polymorphism in nOPV2-c1 or U398C in nOPV2-c2, both in domain IV, and polymorphisms that strengthen or extend the relocated cis-acting replication element (cre), without any evidence of nOPV2 recombinant viruses in these samples. Nevertheless, the stabilized domain V in the candidate viruses did not show polymorphisms consistent with reversion to neurovirulence as measured using paralysis in the transgenic mouse model, thus confirming a superior genetic and phenotypic stability of shed nOPV2 strains and suggesting that nOPV2 should be associated with a lower risk of seeding new outbreaks [91].

Concluding remarks

In the twentieth century, before the polio vaccine was created, poliomyelitis was a significant threat to public health. According to the WHO, there are currently 10–20 million poliomyelitis survivors worldwide most of whom are now in their 60 s and 70 s, who may experience its late consequences, experiencing a worsening of their illness, probably due to the post-polio syndrome, and the population's hastened aging process.

The increase in VDPV transmission raises a challenge for the elimination of polio worldwide. The total cessation of transmission is necessary for the eradication of both wild polioviruses and VDPVs; this is predicated on the use of the Sabin oral poliovirus vaccine to induce strong mucosal immunity. But until OPV usage is stopped, VDPV interruption cannot be finished. The creation of more genetically stable oral poliovirus vaccine strains, which are less prone to developing into VDPVs, might provide a solution to this conundrum. Indeed, the WHO gave emergency use listing status to a new OPV-2 (nOPV2) vaccine in 2020, and it has since been widely used in cVDPV2 epidemic scenarios. Surveillance data shows a high chance of success without the same danger of development of cVDPV2 as with normal OPV-2 vaccines.

Elderly people with late sequelae of poliomyelitis have substantial loss of independence and quality of life as they age, highlighting the necessity for targeted rehabilitation programs to stop this population's condition from getting worse. Additionally, in light of the recent detection of VDPV2 in high-income nations, immediate action is required, including higher immunization rates and poliovirus surveillance worldwide. Building momentum to fully fund the implementation of the polio eradication strategy will be essential to permanently end polio transmission and the risk of paralysis globally. Polio eradication efforts are in danger unless this is done correctly.

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Declarations

Conflict of interest The author declares no competing interests.

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