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EDITORIAL

History of polio vaccination

Anda Baicus

Anda Baicus, National Institute of Research and Development for Microbiology and Immunology Cantacuzino, University of Medicine and Pharmacy "Carol Davila", 050096 Bucharest, Romania
Author contributions: Baicus A solely contributed to this paper.
Correspondence to: Anda Baicus, MD, PhD, Lecturer in Microbiology, Head of the National Polio Laboratory, National Institute of Research and Development for Microbiology and Immunology Cantacuzino, University of Medicine and Pharmacy "Carol Davila", 050096 Bucharest, Romania. abaicus@cantacuzino.ro
Telephone: +40-740-213102 Fax: +40-215-287305
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Abstract

Poliomyelitis is an acute paralytic disease caused by three poliovirus (PV) serotypes. Less than 1% of PV infections result in acute flaccid paralysis. The disease was controlled using the formalin-inactivated Salk polio vaccine (IPV) and the Sabin oral polio vaccine (OPV). Global poliomyelitis eradication was proposed in 1988 by the World Health Organization to its member states. The strategic plan established the activities required for polio eradication, certification for regions, OPV cessation phase and post-OPV phase. OPV is the vaccine of choice for the poliomyelitis eradication program because it induces both a systemic and mucosal immune response. The major risks of OPV vaccination are the appearance of Vaccine-Associated Paralytic Poliomyelitis cases (VAPP) and the emergence of Vaccine Derived Polioviruses strains. The supplementary immunization with monovalent strains of OPV type 1 or type 3 or with a new bivalent oral polio vaccine bOPV (containing type 1 and type 3 PV) has been introduced in those regions where the virus has been difficult to control. Most countries have switched the schedule of vaccination by using IPV instead of OPV because it poses no risk of vaccine-related disease. Until 2008, poliomyelitis was controlled in Romania, an Eastern European country, predominantly using OPV. The alternative vaccination schedule (IPV/OPV) was implemented starting in September 2008, while beginning in 2009, the vaccination was IPV only. The risk of VAPP will disappear worldwide with the cessation of use of OPV. The immunization for polio must be maintained for at least 5 to 10 years using IPV.

Key words: Poliomyelitis; Formalin-inactivated polio vaccine; Oral polio vaccine

Peer reviewer: Ian M Mackay, PhD, Qpid Laboratory, Sir Albert Sakzewski Virus Research Centre, Royal Children's Hospital, Herston Road, Herston Q4029, Australia

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INTRODUCTION

Poliovirus (PV), an enterovirus belonging to the Picornaviridae family is the etiological agent of poliomyelitis, an acute paralytic disease. This disease results from lower motor neuron damage and is characterized by asymmetric persisting weakness (flaccid paralysis). The transmission of this virus during ancient times was suggested after the studies on Egyptian mummies, which showed a shortening of a lower limb in a child. In 1789, in the second edition of *A Treatise on Diseases of Children*, Michael Underwood described the disease as "debility of the lower extremities in children"[1]. He did not record any reference to outbreaks of this disease.

Badham[2] described an acute paralysis suggestive of poliomyelitis in four children in 1835. In 1840, Heine[3] published a monograph where poliomyelitis was recognized and defined as infantile spinal paralysis. Duchenne in 1855, then Charcot *et al*[4] in 1870, located the atrophy in the anterior horns of the spinal grey matter. This find-

ing gave rise to the pathological term "poliomyelitis" from the Greek *polios* for "gray" and *myelos* for "spinal cord". In 1875, Erb introduced the term "acute anterior poliomyelitis". Medin first reported the epidemic form of this disease in 1890, after an epidemic of 44 cases in Stockholm in the summer of 1887. He recognized a systemic phase of the disease which often failed to progress to neurological paresis and developed the classification of that. Wickman introduced, in 1907, the eponym "Heine-Medin disease" to honor Medin's contributions. Putnam *et al*[5] recorded the earliest descriptions of epidemic poliomyelitis using basic epidemiological methods in 1893, by Caverly[6] in 1894 in the United States and by Wickman in 1905 in Sweden. By the epidemiological studies conducted between 1910 and 1912 during epidemics in the United States, Frost found a widespread exposure to poliomyelitis but a low incidence of clinical disease to those susceptible to infection. During the epidemic in the north eastern United States in 1916, the role of asymptomatic persons in the spreading of infection was recorded by the Public Health Service. This epidemic caused widespread panic; over 27 000 persons were reported to have been paralyzed, with 6000 deaths.

The polio outbreaks gradually became more severe, more frequent and widespread throughout Europe and the United States at the beginning of the 20th century. The epidemiology of PV was gradually understood. The model of polio spread was irregular and many patients had no direct contact with a known source. In 1905, Wickman first recognized that poliomyelitis was an infectious disease. Landsteiner and Popper demonstrated in 1909 that the etiological agent of poliomyelitis was a filterable virus. They transmitted the disease to a Cynocephalus monkey by intraperitoneal injection of neural tissue from a human fatal case. In 1910, Flexner supposed that the PV was strictly neurotropic. He thought that PV entered the human body via respiration[7], a hypothesis that was later disproved. Howe and Bodian considered the possibility of the oral alimentary route of polio infection during the 1930[8]. In the late 1930s, Armstrong produced experimental poliomyelitis in mice. It was an advantage for the study of PV and for the development of a neutralization test in order to measure the antibodies. The assumption that there is more than one type of PV was launched by Burnet and Macnamara in 1931 and confirmed by Paul and Trask by observation in monkey experiments. The three distinct types were identified by a prototype strain, Brunhilde (type Ⅰ), Lansing (type Ⅱ) and Leon (type Ⅲ)[9]. The concept of poliomyelitis as an enteric infection had begun in 1932, when Paul and Trask found the virus in feces and recovered virus over a period of weeks from patients and healthy contacts. In 1936, Sabin and Olitsky reported that PV could be successfully grown *in vitro* in human embryonic neuronal tissue fragments cultivated in glass vessels. By sewage water testing in New York during periods when paralytic polio was prevalent, a ratio of 100 subclinical infections for every paralytic case was estimated[10]. In the 1950s, it was established that PV could be isolated from flies collected during epidemics. By the studies in the laboratory with flies emerging from maggots, no evidence of virus multiplication was recorded[11]. In 1949, Enders, Weller and Robbins successfully cultured the Lansing strain in nonneuronal tissue culture, leading to the capacity to produce the virus safely and in sufficient quantity, thus opening the way for production of viral vaccines. The serological studies about serum antibodies against PVs in underdeveloped countries showed that once exposed and infected, even asymptomatic persons were immunized for life. In developed countries, children living in crowded areas acquired infection at an earlier age than children from higher socioeconomic levels. By 1952, serological studies established that the antibodies against PV were present in the patient shortly after the onset of the disease and increased during convalescence. In 1952, a field trial conducted by Hammon showed that passive immunization by γ globulin administration assured protection against disease for only about 2 to 5 wk. Summer transmission of infection was associated with increased quantities of PV in sewage water. Two phases of disease, the gastrointestinal infection followed by viremia, and CNS invasion were confirmed by laboratory studies.

DEVELOPMENT OF PV VACCINES

In 1935, Brodie tried an inactivated vaccine with 10% formalin suspension of PV taken from infected monkey spinal cord; he tried it first on 20 monkeys, then on 3000 Californian children. The results were poor and additional human studies were never performed. In the same year, Kollmer tried a live attenuated virus consisting of a 4% suspension of PV from infected monkey spinal cord, treated with sodium ricinoleate. He used it on monkeys and then on several thousand children. The acute paralysis occurred in about 1/1000 vaccines shortly after administration and some cases were fatal.

The discovery that the various antigenic strains of PVs could be grouped into three distinct viral types and the propagation of the PV *in vitro* led to the development of the vaccines against poliomyelitis: the formalin-inactivated vaccine (IPV) by Jonas Salk (1953) and the live-attenuated vaccines (OPV) by Albert Sabin (1956)[12].

IPV

The first inactivated polio vaccine (IPV) was produced by Salk using virus grown on monkey kidney cells and inactivated with formalin. In 1954, the inactivated vaccine was tested in a placebo-controlled trial, which enrolled 1.6 million children in Canada, Finland and the United States[13]. In April 1955, Salk's vaccine was adopted throughout the United States. The incidence of paralytic poliomyelitis in the United States decreased from 13.9 cases per 100 000 in 1954 to 0.8 cases per 100 000 in 1961[14]. Some disadvantages of the Salk vaccine in that time were the decrease of the titres of the circulating an-

tibody within a few years of vaccination, the further circulation of wild PV and its implications in outbreaks, and the large number of monkeys (about 1500) needed to be sacrificed to produce every 1 million inactivated doses. The strains of virus used in the vaccine were Mahoney (type l), MEF-I (type 2) and Saukett (type 3). Shortly after the licensing of Salk vaccine, the failure of inactivation of vaccine virus at Cutter Laboratories, Berkeley, was followed by 260 cases of poliomyelitis with PV type 1 and 10 deaths. The supposition was that the virus was resistant to inactivation by formaldehyde because it contained more foreign proteins than optimal or that the virus may have clumped. A second filtration step was introduced in the production process in order to remove aggregates that may have developed during treatment and safety tests were improved. The use of the highly virulent Mahoney strain in vaccine production has been controversial and after the Cutter incident, even more so. In Sweden, the Brunenders strain for type 1 was preferred. In 1980, concentration and purification of polio antigens were introduced into the manufacture of IPV and the immunogenicity of the vaccine was increased. The original IPV contained 20, 2 and 4 D antigen units of PV types 1, 2 and 3. Van Wezel introduced a technology to produce enhanced potency IPV. He decided to concentrate and purify the virus before treatment with formalin. Since this procedure has been introduced, no failure in the inactivation process has been recorded. By the introduction of a new culture technique using cells on microcarrier beads in suspensions cultured in large stainless steel tanks, a more potent IPV containing 40, 8 and 32 D antigen units of types 1, 2 and 3 was produced[15,16]. Trials with this enhanced IPV (eIPV) showed greater than 90% seropositivity against all 3 PV types after one dose and 100% seropositivity after two doses[17]. An enhanced-potency IPV was licensed in the United States in 1987, with a good response to types 1 and 3 for either a 4 or 8 wk interval between doses and after 8 wk to type 2. The recommended schedule of vaccination in different countries contains 4 IPV doses in the primary series received at 2, 4, 6 and 15-18 mo of age[18] and a booster dose at age 4-6 years. For an optimum booster response, a minimum interval of at least 6 mo is needed between dose 4 and 5. In IPV vaccines, pharyngeal infection by PV is inhibited and intestinal excretion is reduced.

OPV

The development of the attenuated PV vaccine starts with passages of PV strains in rats and mice followed by passages in the cell culture. The reduction of the virulence of the PV strains was recorded in 1946 by Theiler, who passaged the Lansing strain in rats and mice more than 50 times and by Enders, Weller and Robins, who passaged the same strain in cell culture.

Candidate strains of attenuated PV suitable for immunizing humans were developed independently in the United States by Koprowski (Wistar Institute, Philadelphia), Cox (Lederle Laboratories) and Sabin (the Children's Hospital Research Foundation).

In 1950, Koprowski began experiments with a rodent-adapted type 2 PV that had been fed to a small group in California. He, Cox and their associates had fed millions throughout the world with the three types of viruses[19]. The isolation of PV with the properties of the Cox strain from the brain tissue of the dead father of a vaccinated child was followed by the withdrawal of this strain[20].

In 1960, Sabin described, in an article published in *JAMA*, *Live, orally given poliovirus vaccine*[21], the results obtained with his newly developed trivalent oral vaccine to 26 033 children from a city of 100 000 people in South America. Because the strains developed by Sabin provided good antibody levels and were less neurotropic for monkeys, they were selected and licensed between 1961 and 1963 in the United States for widespread application. The first nationwide polio vaccination campaign was in Cuba, in 1962[22]. During a meeting in 1956 between Sabin and Chumakov, Sabin provided his experimental results and his strains of polio vaccine to Chumakov, who began to produce it for use in his country. A few million children from Estonia and Lithuania (part of the Soviet Union at that time) received this vaccine by 1959 and it was a success story that contributed to the recommendation for license of the three monovalent strains developed by Sabin[23].

Sabin's OPV consists of three live attenuated Sabin poliovirus strains, obtained by sequential *in vitro* and *in vivo* passages of the wild strains. The virulent strains P1/Mahoney/41, P2/P712/56 and P3/Leon/37 served as a source for the attenuated Sabin strains: P1/Lsc,2ab, P2/P712,Ch,2ab and P3/Leon,12a$_1$b.

At the beginning, the trivalent OPV contained the three PV types in equal proportions but lower seroconversion rates to types 1 and 3 were recorded. By using a balanced formulation of trivalent OPV which contained 10^6, 10^5 and $10^{5.5}$ TCID50 (50% tissue culture infective dose) of Sabin types 1, 2 and 3, the neutralizing antibodies against all three PV types were detected in almost all persons. Increasing the amount of type 3 virus in the trivalent vaccine improved the immunogenicity[24] and the Expanded Program on Immunization Global Advisory Group recommended a formulation of trivalent OPV which contained 10^6, 10^5, $10^{5,8}$ TCID50 of Sabin types 1, 2 and 3 per dose[25]. The OPV vaccine was easier to administrate and had a herd effect, inducing long-lasting protective systemic, humoral and cellular immunity as well as local mucosal resistance to PV infection. In 1972, Sabin donated his vaccine strains of PV to the World Health Organization (WHO), increasing the availability of this vaccine to developing countries. From 1977 to 1995, the percentage of all children in the world who received the required three doses of OPV in the first years of life increased from 5% to 80%.

The major risks of OPV vaccination are the appearance of Vaccine-Associated Paralytic Poliomyelitis cases (VAPP) and the emergence of Vaccine Derived Polio-

viruses strains (VDPV), the OPV strains having more than 1% nucleotide divergence from the original vaccine strains in the VP1 coding region of the genome. The appearance of VAPP cases is due to the reversion to neurovirulence of the vaccine strains. During replication in intestine, the OPV strains can undergo genetic variation by point mutations at an average frequency of 10^{-4} due to RNA polymerase or through natural recombination. The incidence of VAPP for immunocompetent children receiving their first dose of OPV was estimated at one case per 750 000 doses and one case per 6.9 million subsequent doses[26]. Type 3 was the most common isolate associated with paralysis in vaccine recipients and type 2 was associated with paralysis mostly among contacts of cases. The VDPV strains could be circulant (cVDPV, which can spread in populations with low level of vaccine coverage), could emerge after replication in immunodeficient persons exposed to OPV (iVDPV), or could be ambiguous VDPV (aVDPV, when they are isolated from immunocompetent persons or the environmental source has not been identified). One dose of OPV produces immunity against all three PV serotypes in approximately 50% of recipients; three doses produce immunity in more than 95% of recipients.

MIXED IPV AND OPV

To eliminate the risk of VAPP among OPV vaccine recipients, the sequential schedule IPV/OPV was used in the world. However, the preimmunization of infants with two doses of IPV at 2 and 4 mo followed by two doses of OPV delivered at 18 mo and at 4 to 6 years did not eliminate the risk of VAPP among contacts of vaccines.

POLIO VACCINATION IN ROMANIA

In Romania, an Eastern European country, between 1927 and 1960 the evolution of poliomyelitis was sporadic and epidemic. The incidence of paralytic poliomyelitis in Romania decreased from 10 cases per 100 000 in 1949 to 0.1 cases per 100 000 by the mid 1980s by using inactivated PV vaccine in 1957 and oral PV vaccine in 1961. Polio vaccination started in 1957, with Lepine vaccine manufactured by the Pasteur Institute of Paris, but did not include the whole infant population (or even the entire contingent of children born in that year) and was followed in 1959 by IPV produced in USSR, with which all babies were vaccinated (two doses at a 2 mo interval). The success of the use of OPV, which determined the elimination of polio epidemics in many countries, led to the decision to use this new type of polio vaccine in Romania. First, the vaccine was bought from USSR and the entire Romanian population under the age of 30 years received this vaccine between 1961 and 1962. Cantacuzino Institute of Bucharest began the production of OPV in 1962, first using the vaccine seed virus received from the Poliomyelitis Research Institute in Moscow and later (since 1967), the vaccine seed virus was received directly from Sabin. Between 1961 and 1963, infants received a first dose of IPV and then OPV. Beginning in 1964, the trivalent oral vaccine stabilized with magnesium chloride prepared by the Cantacuzino Institute was used for widespread immunization in Romania. The administration of oral polio vaccine took place in annual national campaigns from 1961-1978. A few years after OPV was widely used, the incidence of paralytic poliomyelitis declined dramatically but VAPP cases began to appear. In 1974, the WHO approved the Cantacuzino Institute as an OPV production facility. Since 1970, Romania has participated for over 15 years with 11 other states on a WHO collaborative study on the risk of VAPP cases and the risk was the highest in this country. The health authorities from Romania decided in 1978 to stop the use of existing vaccine stocks (prepared with WHO seed viruses received in 1974) and to use a new WHO-B virus seed (Behring). This seed virus was to be available in summer 1978 but due to problems with preparation and especially control of seed, WHO-B viruses were distributed by the WHO only beginning at the end of 1979. Due to this problem, between July 1978 and March 1980, vaccination was only with monovalent OPV type 1 with a single dose administered to children aged 6 wk. During this period, no case of paralytic poliomyelitis was recorded in Romania. The vaccination was resumed with existing vaccine stocks in April-June. The effects of this 2-year disruption were epidemics which occurred during 1980-1982, caused by wild PV type 1 (161 cases) and type 2 (15 cases). The epidemic disappeared in the third quarter of 1982. The spreading of the wild PVs was stopped by an immunization campaign with trivalent OPV (TOPV). The poliomyelitis epidemic in Romania from 1980-1982 allowed an important conclusion: the interruption of TOPV vaccination for 2 years was sufficient to build a contingent of children highly susceptible to infection with PV, allowing re-implantation of wild PVs and their active movements, followed by the emergence of a polio epidemic. In 1983, vaccination campaigns were introduced in spring and fall. The vaccination schedule was designed so that each child should receive 4 doses TOPV in the first 10 years of life; first dose between 2 and 7 mo, second dose between 4 and 9 mo, third dose between 10-15 mo and a booster at 9 years of life. The vaccination coverage with three doses of TOPV at age 2 years was more than 90%. From 1983 to May 1990, no cases of paralytic poliomyelitis caused by wild PV were recorded. The latest outbreak of wild type 1 PV occurred between November 1990 and April 1992. The outbreak involved children from a gypsy community who were unvaccinated or inadequately vaccinated. Four of 13 wild PV cases were infected with HIV[27]. All cases of paralytic polio that occurred in Romania from 1984-1992 occurred in children younger than 5 years, which demonstrated that immunity to the three serotypes of PV was almost 100% for children older than 5 and adults.

The oral PV vaccine administered in Romania until September 1990 was produced by the Cantacuzino Insti-

tute. Because of a high rate of vaccine associated paralytic poliomyelitis reported from 1970-1984, beginning in November 1990, an oral vaccine approved by the WHO was imported and replaced the Romanian produced vaccine[28]. However, a case-control study demonstrated that the cause of elevated risk of vaccine associated paralytic poliomyelitis in Romania was not the PV vaccine manufacturer but the administration of multiple intramuscular injections of antibiotics within 30 d of receipt of OPV, which increased the risk of paralysis by a factor of 2 to 10 fold[29]. A decrease of the risk of VAPP was obtained by a reduction of parenteral treatment in recipients of OPV and by the change of the administration schedule of oral polio vaccine from 2 campaigns of two rounds, to throughout the year vaccination since April 1995. From 1992-1994, a project of the Ministry of Health supported by the Marcel Merieux Foundation demonstrated the feasibility, safety and high immunogenicity of sequential use of enhanced-potency IPV followed by OPV in 1 of the 41 counties in Romania[30]. Until 2008, poliomyelitis was controlled in Romania by predominantly using OPV administered at 2, 4, 6, 12 mo and a booster at 9 years of life; the alternative vaccination schedule (IPV/OPV) was implemented starting in September 2008 and at the beginning of 2009, vaccination with IPV only was decided[31]. The reported vaccination coverage with 4 doses of TOPV in the first 14 mo of life has been more than 90% since 1980. The risk of VAPP decreased from less than 2 VAPP cases per year in 1995-2006, to 0 VAPP cases since 2007[32]. In 2002, 1 mo after Certification of European region as polio free, a type 1 PV strain, aVDPV recombinant Sabin1/Sabin2/Sabin1 was isolated from a VAPP case not vaccinated against poliomyelitis and from 8 healthy contacts considered to be at risk[33]. In 2008, we studied the circulation and the biodiversity of enteroviruses in a group of children from a minority population with low anti-polio vaccination coverage from the same area where in 2002 a VDPV strain was isolated. Evidence of inter-human circulation of Sabin strains was found[34] but no VDPV strain was isolated. The surveillance of at risk populations from at risk areas and maintenance of complete vaccine coverage in the population are important objectives in the framework of global polio eradication.

CONCLUSION

With the development and use of vaccines, the complete eradication of poliomyelitis became an objective. In 1988, the WHO proposed the worldwide poliomyelitis eradication to its member states. The Global Polio Eradication Initiative (GPEI) Strategic Plan established the activities required for polio eradication, certification for regions, OPV cessation phase and post-OPV phase. At the beginning, this plan was based on maintaining of a high vaccination coverage (> 80%) among children, the application of supplementary vaccine doses during national vaccination days (NVD), mopping up vaccination and implementing effective PV infection surveillance systems and containment activities. The presence of susceptible subgroups with gaps in immunization favors the introduction of wild PV strains in a vaccinated population. The OPV strains have become the main instrument for the wild-type PV eradication program because it induces both a systemic and mucosal immune response. Most countries have switched the schedule of vaccination against polio by using IPV instead of OPV. The advantage of using IPV is that it poses no risk of vaccine-related disease. The disadvantages for the global introduction of IPV are its cost, the intramuscular administration, its inability to produce optimal intestinal immunity and the biocontainment required for its production. In 2011, 23 years after the decision of the WHO to globally eradicate poliomyelitis, the wild PV (type 1 and 3) is still endemic in only four countries: Afghanistan, India, Nigeria and Pakistan. The type 2 wild PV strain has been eradicated globally since 1999, while a type 2 circulating vaccine-derived PV (cVDPV) has persisted in northern Nigeria since 2006[35]. A plan for the cessation of routine OPV immunization against type 2 PVs must be devised[36]. In those regions where the virus has been difficult to control, supplementary immunization with monovalent strains of OPV type 1[37] or type 3[38], or with new bivalent oral polio vaccine bOPV (containing type 1 and type 3 PV) has been introduced[39]. In 2008, the GPEI plan was updated in order to overcome barriers to interruption of wild PV transmission. The objectives for 2010-2012 are: interrupting wild PV transmission in Asia and Africa; enhancing PV surveillance and outbreak response; and strengthening immunization systems. In 2010, an outbreak of wild PV type 1 cases genetically related to wild PV circulating in 2009 in India was recorded in Tajikistan, part of the WHO European Region certified polio-free in 2002[40]. This episode demonstrated that if a region is polio free, the risk of wild PV importation from endemic regions remains present until polio is globally eradicated. Because most VDPV strains implicated in poliomyelitis outbreaks worldwide are recombinants between OPV strains and non polio enterovirus strains of Human enterovirus species C[41], increasing the surveillance of co-circulation and evolution of polio and non-polio enteroviruses must be achieved. The risk of VAPP will disappear with the cessation of use of OPV. Some research programs are initiated by WHO for obtaining an affordable IPV by reduction of the necessary antigen dose by intradermal administration[42,43], by using adjuvants[44] and by introduction of Sabin strains as seed[45,46]. In the first 5 to 10 years after global cessation of OPV administration, the maintenance of immunity to polio by IPV use must be assured[47].

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