PREGLED LITERATURE – REVIEW ARTICLE

Our progress against polio - eradication still remains challenge

Napredak u borbi protiv polija - eradikacija jos ostaje izazov

Ivana Đurić-Filipović[1], Đorđe Filipović[2], Milica Tasić[3], Zorica Živković[4,5]

[1]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia
[2]Institute for Emergency Medicine, Belgrade, Serbia
[3]Primary Health Care Center "Dr Simo Milošević" – Čukarica, Belgrade, Serbia
[4]Medical Center „Dr Dragiša Mišović",Children's Hospital for Lung Diseases and Tuberculosis, Belgrade, Serbia
[5]University Business Academy in Novi Sad, Faculty of Pharmacy, Novi Sad, Serbia

Summary Polioviruses are enteroviruses that are transmitted direct from person to person or following excretion in feces or pharyngeal secretions. Because the poliovirus receptor is only expressed on human cells or on cells of few subhuman primate species, eradication is possible. In 1988 the Global Initiative for Polio Eradication (GIPE) at the 41st WHO summit announced that the main goal for 2000 is complete polio eradication. According the CDC reports the aim has not been reached yet, although the incidence of polio cases were decreased from 350,000 cases of wild polio virus in more than 125 endemic countries in 1988 to only 400 cases of polio reported in only 3 endemic countries (Nigeria, Afghanistan and Pakistan) in 2000. The last case of wild polio virus (wPV) was detected in 1997 in Serbia. In order to eradicate polio virus two vaccines are used- inactivated and live-attenuated polio vaccines. According to the studies oral polio vaccine has better efficacy and immunogenicity profile in comparison to inactivated polio vaccines, but due to safety reasons inactivated polio vaccine is now widely used (there is no risk of vaccine associated paralytic polio - VAPP and vaccine derived polio virus- VDPV). Although there are very effective and immunogenic vaccines available all over the world the polio eradication is not a simple project, in undeveloped and developing countries vaccines are not available, whereas in developed countries parents refused to vaccinate their children.

***Keywords**:* children, polio virus, vaccination

Sažetak Polio virusi spadaju u grupu entero virusa, prenose se sa osobe na osobu direktno ili feko-oralnim putem. Kako su ljudi jedini rezervoar polio virusa, eradikacija je vakcinacijom teorijski moguća. 1988. godine na 41. sednici Svetske Zdravstvene Organizacije (SZO) doneta je odluka o Globalnoj Eradikaciji Polija - the Global Initiative for Polio Eradication (GIPE) koja je imala za cilj eradikaciju polija do 2000. Godine. Prema podacima Centra za kontrolu i prevenciju bolesti ovaj cilj još uvek nije ostvaren, iako je incidenca polija značajno smanjena sa 350 hiljada slučajeva u preko 125 endemskih zemalja na svega 400 slučajeva u tri endemske zemlje (Aganistan, Nigerija, Pakistan) 2000. godine. U Srbiji je poslednji slučaj divljeg polija zabeležen 1997. godine. U cilju iskorenjavanja dečije paralize koriste se dve vrste vakcina (inaktivisana i živa). Iako su studije kliničke efikasnosti i imunogensti pokazale prednost žive-oralne polio vakcine, iz bezbednostnih razloga danas se sve više koristi inaktivisana vakcina (nema rizika od vakcinom povezanog poliomijelitisa). I pored dostupnih vakcina i velikih napora, kao i brojnih kampanja u cilju eradikacije polija cilj još uvek nije ostvaren, u nerazvijen zemljama zbog nedostupnosti vakcina, a u razvijenim zemljama zbog sve većeg broja roditelja koji odbijaju vakcinaciju.

Ključne reči: deca, polio virus, vakcinacija

Viruses, vaccines and disease

Polioviruses are enteroviruses that are transmitted from person to person following excretion in feces and pharyngeal secretions, mainly via the hand-to-hand-to-mouth route. Because the poliovirus receptor is only expressed on human cells or on cells of few subhuman primate species,there are no known extrahuman reservoirs (1, 2). After the infection, the virus replicates in the gastrointestinal tract and may cause viremia (3,4)

Following , the virus then spread into the central nervous system and destroys lower motor neurons, causing a clinically distinctive flaccid paralysis without permanent sensory loss (5). The average incubation period for paralysis is approximately 10 days (range 5–25 days) (6, 7). Fortunately only 1 in 150 primary poliovirus infections causes paralytic poliomyelitis; since mostinfections are subclinical, paralytic cases represent only the ''tip of the epidemiologic iceberg'' (8). According to antigenic types polioviruses can be sorted into 3 different categories (types 1, 2, and 3). The classification is based on viruses' ability to

induce protection against second paralytic attacks (9) and is confirmed by neutralization tests (10).As humans are the only natural reservoir of polio virus and the virus is very sensitive outside, the availability of good vaccines can make the polio eradication possible. In 1988 the Global Initiative for Polio Eradication (GIPE) at the 41st WHO summit announced that the main goal for 2000 is complete polio eradication. The project was supported by the UNICEF, CDC (Centre for Disease Control) and Rotary International (11,12,13).

At the annual Rotary International Convention, held in Seoul (late May 2016), the Secretary General of the UN welcomed the significant contribution of the Rotary association to the global fight against polio. The Rotarians gave finical support of more than 1,2 billion dollars for polio eradication all around the world and made influence to the governments to relocate 6 billion dollars additional to this cause. UN, UNICEF and Rotary have been working for almost 30 years on polio eradication. We can acknowledge Rotary for excellent results in polio eradication. From thousands of cases each year to less than 30 cases in 2016 polio eradication represents one of the most important preventive. Today poli cases are only present in two endemic countries of Afghanistan and Pakistan. The main aim of the organization is "zero case" and total polio eradication.

The goal is reached only in developed countries. According to the epidemiological data the last case of wPV (wild polio virus) is reported in 1993. in the USA (United States of America) while the last case of wPV in west Pacific is reported four years later. In the rest of the undeveloped and developing countries the goal of polio eradication is not reached and the main obstacles for that are: due to civil war in certain areas (usually where the wild polio virus can be still detected in population) the vaccines are not available (Nigeria, Pakistan, etc.). On the other side mostly in developed countries parents refused to vaccinate their children; in countries where the coverage rate is still very low vaccine derivate polio virus can cause epidemics. According the CDC reports in 1988 there were 350,000 cases of wild polio virus in more than 125 endemic countries while 25 years laterthere were only 400 cases of polio reported in only 3 endemic countries (Nigeria, Afghanistan and Pakistan) (14) Poor control of acute flaccid paralysis (AFP) leads to the increase of a number of paralytic cases from 2001, long term excretion of virulent serotypes from immunocompromised patients and import and spread of wild polio virus in the countries certificated as "polio free". In March 2016 WHO reported 10 cases of polio (7 cases of wild polio and 3 cases of cVDPV) in two endemic countries. (15) According to Serbian Report on Immunization Practice published in 2012, 30 cases (24 cases of wPV and 6 cases of VAPP) of polio were reported between 1996 and 2012. Since 1997 there have been no wild polio isolated from the feces of infected patients (16).

Polio vaccination

Two vaccines are used in routine polio vaccination: live attenuated oral polio vaccine (OPV) and inactivated poliovirus vaccine (IPV). In 121 countries (17),OPV is used instead of IPV for several reasons: OPV costs substantially less than IPV or more) [3]; primary immunization with OPV induces superior intestinal immunity compared with IPV and thus has the potential to better prevent transmission of wild viruses; OPV confers contact immunity through passive immunization of unvaccinated persons from viruses shed by vaccines; and OPV is administered in oral drops, which are easier to administer than IPV injections and easier to store and transport. (Table 1)

Table 1. Characteristics of oral and inactivated polio vaccines

OPV
live attenuated oral polio vaccine
Sabin OPV strains
Induce systemic immunity
Induce better intestinal immunity
Contact immunity via passive immunization
Collective immunity
Risk of VAPP
Risk od VDPV
Contraindicated in immunocompromised persons
Oral drops
More sensitive to high temperature
IPV
inactivated poliovirus vaccine
Inactivated wild poliovirus
Induce systemic immunity
No induction of intestinal immunity
No contact immunity
Collective immunity
No risk of VAPP
No risk of VDPV
Only polio vaccine registered in immunocompromised persons
IPV injections
More sensitive to low temperature

Adverse events associated with polio vaccination

In early 1990s, the Institute of Medicine reviewed adverse events associated with childhood vaccines, including poliovirus vaccines. The most important adverse event associated with OPV is Vaccine Associated Paralytic Polio - VAPP. According to epidemiological studies 395 cases of acute persisting spinal paralysis were reported from 13 countries with the total population of 547 million. The risk of VAPP in recipients or contacts of recipients was less than 0,3 cases per 3,3 million doses and the average annual incidence of VAPP was 0,14 per 1 million people. The following evidence support vaccine virus causative:

Clinical syndromes are typical of poliomyelitis.

- Vaccine virus is frequently isolated from cases.
- History of exposure to vaccine is often obtained.
- Recipient and contact cases cluster after receipt of the first dose of OPV. (One would expect virtually equal numbers of cases after each dose if there were other etiologic agents causing the illnesses.)
- Shed viruses have been shown to have mutated toward neurovirulence.
- The incidence of VAPP is highest in immunodeficientpeople with B-cell deficiencies, a group also at higher risk of poliomyelitis from wild poliovirus. The completeness of reporting of VAPP cases to the Centers for Disease Control and Prevention (CDC) was estimated to be 81%.

Between 1990 and 2003, a total of 61 cases classified as VAPP were reported in the United States, including 27 (44%) among immunologically normal vaccine recipients, 10 (16%) among immunologically normal contacts of vaccine recipients, 6 (10%) among immunologically normal nonhousehold contacts, 16 (26%) among immunologically compromised OPV recipients or contacts of OPV recipients, 1 indeterminate case (2%), and 1 imported case (2%) (18). The risk of VAPP is highest after the first dose ofOPV. Recipients of the first dose and their contacts had a 6.6-foldhigher risk of VAPP than did recipients of subsequent doses andtheir contacts. People with immunodeficiency disorders are athighest risk for VAPP. The risk of VAPP among immunocompromised people is elevated to more than 3,200 times the risk for immunocompetent people. Almost all cases occurred in people with congenital or acquired immunodeficiency. Immunodeficient people with VAPP primarily had abnormalities affecting the B-cell system (humoral immunity), with agammaglobulinemia or hypogammaglobulinemia most frequently associated with VAPP. With the exception of one VAPP case with immunodeficiency disorder, in all other cases, the precipitating event for the diagnosis of immunodeficiency was the onset of paralytic disease. Poliovirus type 3 is the virus most frequently isolated from immunocompetent people with VAPP. In contrast, poliovirus type 2 is the most common virus detected in immunodeficient people with VAPP. Poliovirus type 1 is rarely isolated from cases with VAPP(19, 20, 21). For the historical point of view Salk was the first one who created inactivated polio vaccines that was registered in the USA in 1955, and used until 1961 when the OPV was launched in the USA as a more effective and immunogenic vaccine. OPV succeed in polio elimination in the USA in the following more than 30 years but with 6-9 cases of vaccine associated paralytic polio (VAPP) per year. Effectives and immunogenic profile of OPV was very high but the safety profile was under question. In 1997 USA National Calendar of Immunization included combine schedule with both OPV and IPV, and finally in 2000 they switched completely to IPV. There were three types of oral polio vaccines (trivalent – the most common used until April 2016), bivalent (type 1 and type 3) approved from 2009 and the only vaccine that is now registered in countries where there is OPV in National Immunization Programme and monovalent (used in endemic countries). OPV is proved to be effective and immunogenic (as vaccine is administered via oral route which is the natural route of transmission it has both influence on humoral and systemic immunity). Oral administration is very simple and can be performed without well trained health care providers. From the economic point of view the price of OPV is very low so these kinds of vaccines are comfortable for undeveloped and developing countries. The main disadvantages of OPV are two very serious side effects vaccines associated paralytic polio (VAPP) and vaccine derive polio virus (VDPV) (21).

Vaccine-derived polioviruses

Almost all isolated polio viruses related to OPV strains are vaccine-derived polioviruses (VDPVs). However all Sabin OPV strains can be classified in two general categories: “OPV-like” isolates that have close sequence relationships (> 99% VP1 sequence identity) to the original strains and VDPV isolates that have sequence properties (< 99% VP1 sequence identity from the parental Sabin strains) indicative of prolonged replication of the vaccine virus. The VDPV isolates can be, on the other side subdivided into three categories: immunodeficient VDPV (iVDPVs), isolated from immunocompromised patients chronically infected after OPV administration, circulating VDPV (cVDPV) require evidence of transmission and neurovirulence (at least 2 cases with acute flaccid paralysis-AFP) and arise usually in areas with inadequate OPV coverage and ambiguous VDPV not known to be associated with AFP outbreaks or with immunodeficienceis (22). VDPV is developed by replication of live attenuated vaccine serotype of polio virus and recombination of OPV2 and OPV3, and rarely OPV 1 in the gastrointestinal tract of vaccinated person or recombination of OPV with enteroviruses in the gastrointestinal tract of the recipient. VDPV can circulate in human population and the risk factor for spreading the infectious is the same as for wPV: low or inadequate polio vaccination, poor hygiene and sanitary conditions, over crowed areas and tropical climate conditions (22-25).

Aseptic meningitis/encephalitis

On rare occasions, particularly in immunodeficient infants (hypogammaglobulinaemia), aseptic meningitis and encephalitis have been reported after OPV (26-28).

Other vaccine safety concerns

Guillain–Barré syndrome (GBS)

Current data do not indicate an increased risk of GBS following receipt of OPV (29). Kinnuen and co-authors had suggested an increased incidence of GBS following mass OPV vaccination in Finland. (30,31,32) Since the findings which led the US Institute of Medicine to conclude that there was an association between OPV and GBS (33), the Finland results have been reanalysed and other factors

have been identified as having contributed to the increase in the incidence of GBS. These factors include an influenza epidemic and widespread circulation of wild type-3 poliovirus (30). During this time period, another observational study was also completed in the United Stateswhich did not support a causal relationship between OPV and GBS (28-30).

Transverse myelitis (TM)

There are cases reports of transverse myelitis reported after OPV, but occurred following the administration of multiple vaccines. TM was not observed in the clinical trials that occurred prior to licensure of the polio vaccine and no other controlled studies have been conducted. Therefore, the data is inadequate to determine whether a causal relationship exists between OPV and TM (33).

Simultaneous administration

OPV can be administered with other vaccines, with no evidence of increased rates of adverse events nor reduced immunogenicity. OPV is frequently administered simultaneously with diphtheria–tetanus–pertussis (DPT) vaccines and therefore side effects from the latter may often be falsely attributed to OPV. Rotavirus vaccines when administered simultaneously have not affected immune responses to OPV. However in general, the immune responses (i.e., antibody levels) to rotavirus vaccination were lower when rotavirus vaccines were co-administered with OPV. This is particularly greater after the first dose of OPV (22).

Provocation poliomyelitis

In persons incubating wild poliovirus infection, intramuscular injections (e.g. DTP) may provoke paralysis in the injected limb (34, 35).

Conclusion

Although there are very effective and immunogenic vaccines available all over the world the polio eradication is not a simple project. It considers huge finical costs, the support from national government and citizens, as well as a good coordination between these two parts, the organization of global and national campaigns, education of local health care providers and general population about the importance of vaccination, and continuous fight against anti-vaccinators.

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Primljeno/Received: 26. 05. 2016.
Prihvaćeno/Accepted: 21. 08. 2016.

Correspondance to:
dr Ivana Đurić-Filipović,
[1]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Sebia
34000 Kragujevac
Svetozara Markovi'a 64
email. drivanica@yahoo.com