King Saud University

Poliovirus focus on risk in refugees

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1.introduction:

1-1 Nature of the poliovirus :

Poliomyelitis, also known as polio or infantile paralysis, is a disease of the central nervous system. Following primary asymptomatic infection of the alimentary tract, fewer than 1% develop paralytic disease. In developing countries, 65–75% of cases occur in children under 3 years of age and 95% in children under 5 years of age. The resulting paralysis is permanent, although some recovery of function is possible.[1]

In the last 20 years the number of polio cases around the world has reduced. This is largely due to global vaccination programs that aim to immunise people against the poliovirus.[2]

Poliovirus is a member of the enterovirus subgroup, family Picornaviridae. Enteroviruses are transient inhabitants of the gastrointestinal tract, and are stable at acid pH. Picornaviruses are small, ether-insensitive viruses with an RNA genome. There are three poliovirus serotypes (P1, P2, and P3). There is minimal heterotypic immunity between the three serotypes. That is, immunity to one serotype does not produce significant immunity to the other serotypes. The poliovirus is rapidly inactivated by heat, formaldehyde, chlorine, and ultraviolet light. [3]

1-2 The history of poliovirus:

Since 1988 the world has come very close to eradicate polio through global polio eradication initiative . The objective of this initiative was to interrupt wild PVs as soon as possible to achieve certification of Global Polio Eradication and to strengthen the routine immunization and surveillance as well. Since its inception, this initiative has made remarkable headway worldwide and number of cases of poliomyelitis dropped from 35,000 in 1988 to 1650 in 2008.However,Countries such as North and South America, the western Pacific region (including Australia) and Europe are now all polio-free; however cases are still being reported in some parts of Asia and Africa [4] the Indigenous

transmission of wild poliovirus (WPV) has never been interrupted in Afghanistan, Pakistan, India, and Nigeria.

In current study 111 wild type1 poliovirus isolates collected during 2005-2007 from Pakistan and Afghanistan were sequenced for complete VP1 gene to study their genetic diversity and to reveal the indigenous genotype in this region that would be helpful to track the transmission patterns in Pakistan and Afghanistan being a single epidemiological block. [5]

1-3Epidemic :

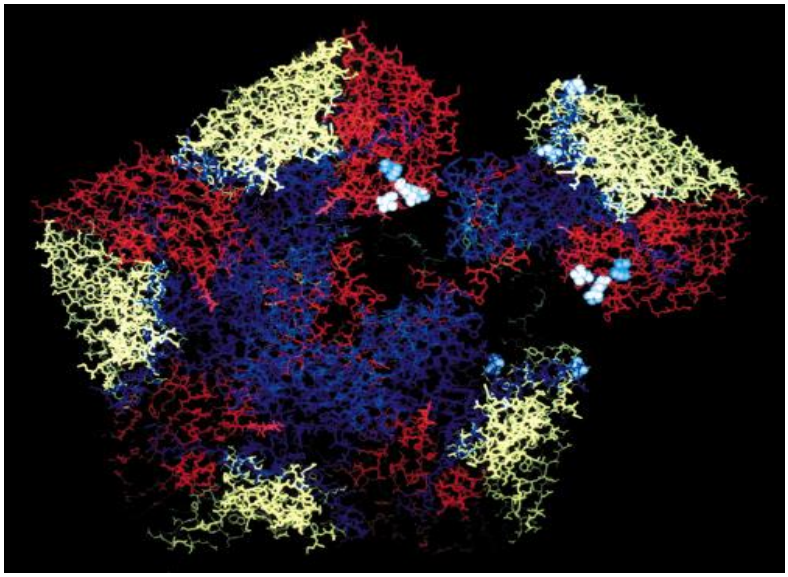
The Global Polio Eradication Initiative (GPEI) has made significant gains since its inception in 1988. From 1988 to 2015 the incidence of wild poliovirus (WPV) cases decreased from 350,000 to 74, and the number of polio-endemic countries decreased from 125 to 3. Wild poliovirus types 2 and 3 have not been detected globally since 1999 and 2012, respectively. [6] However, due to the small but consequential risk of the generation of vaccine-**derived** polioviruses (VDPV) as well as vaccine associated paralytic poliomyelitis (VAPP) cases , the eradication of wild polioviruses must be followed by the global cessation of oral poliovirus vaccine (OPV) use .[1]

2. classification of poliovirus:

[7]

Family	***Picornaviridae***
Order	*Picornavirales*
genus	*Enterovirus*
Species	*poliovirus*

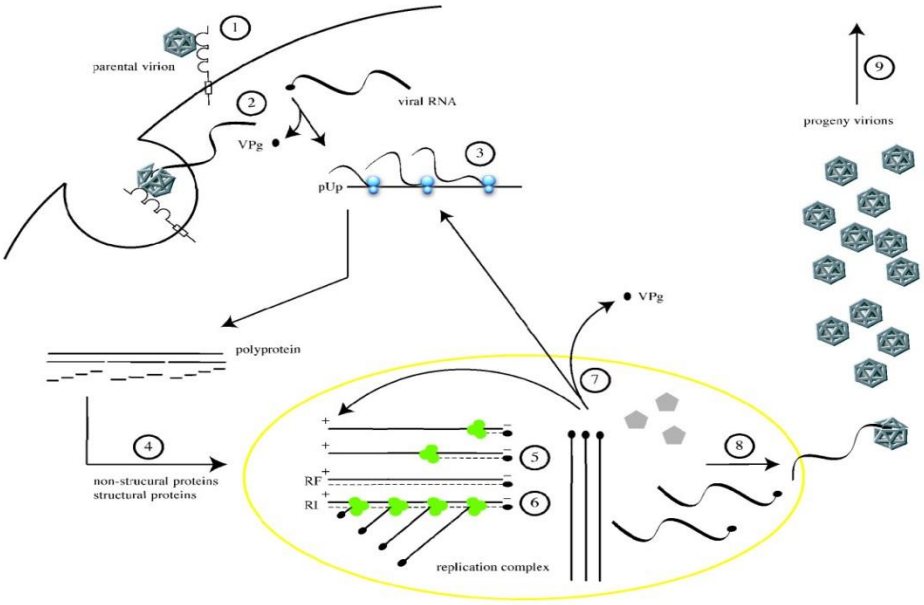
3. protein Structure:



Pentamer of the poliovirus capsid showing VP1 (blue), VP2 (yellow), VP3 (red) and VP4 (green). One protomer has been moved to show the locations of the attenuating mutation at residue 91 of VP3 (pale blue) and suppressors (white) in VP2 (residues 215 and 265) and VP3 (residues 108, 175 and 178) which lie at the interface between adjacentprotomers .[8]

4. Transmission and Target Organ:

Poliovirus is transmitted from one person to another by oral contact with secretions or faecal material from an infected person. Once viral reproduction is established in the mucosal surfaces of the nasopharynx, poliovirus can multiply in specialized cells in the intestines and enter the blood stream to invade the central nervous system, where it spreads along nerve fibres. When it multiplies in the nervous system, the virus can destroy nerve cells (motor neurons) which activate skeletal muscles.[1]



The cellular life cycle of poliovirus.

1. It is initiated by binding of a poliovirion to the cell surface macromolecule CD155, which functions as the receptor .
2. Uncoating of the viral RNA is mediated by receptor-dependent destabilization of the virus capsid .
3. Cleavage of the viral protein VPg is performed by a cellular phosphodiesterase, and translation of the viral RNA occurs by a cap-independent (IRES-mediated) mechanism .
4. Proteolytic processing of the viral polyprotein yields mature structural and non-structural proteins .
5. The positive-sense RNA serves as template for complementary negative-strand synthesis, thereby producing a double-stranded RNA (replicative form, RF) .
6. Initiation of many positive strands from a single negative strand produces the partially single-stranded replicative intermediate (RI) .
7. The newly synthesized positive-sense RNA molecules can serve as templates for translation .
8. or associate with capsid precursors to undergo encapsidation and induce the maturation cleavage of VP0 .

9. which ultimately generates progeny virions. Lysis of the infected cell results in release of infectious progeny virions.[9]

6. Symptoms and signs:

Most people infected with the poliovirus will have no symptoms. Ten per cent of infected people may experience flu-like symptoms such as:

fever

fatigue

nausea

vomiting

headache

occasionally neck and back stiffness – referred to as non-paralytic aseptic meningitis (inflammation of the lining of the brain and spinal cord).

Less than 1% of people infected with poliovirus develop severe muscle weakness (acute flaccid paralysis) affecting the limbs, diaphragm muscle (essential for breathing), and the head and neck muscles.

The risk of permanent limb paralysis is less than 1%. Death occurs in 2 to 5% of children and 15 to 30% of adults with paralytic polio.[10]

7. Diagnostic Methods :

Poliovirus can be detected in specimens from the throat, and feces (stool), and occasionally cerebrospinal fluid (CSF), by isolating the virus in cell culture or by detecting the virus by polymerase chain reaction (PCR).

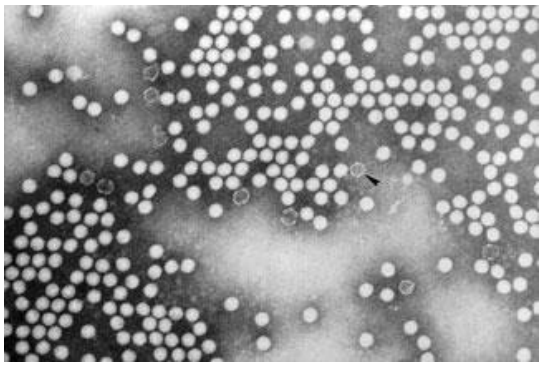
CDC laboratories conduct testing for poliovirus including:

•Culture

•Intratypic differentiation

•Genome sequencing

•Serology



Electron micrograph of the poliovirus

7-1Virus Isolation:

Virus isolation in culture is the most sensitive method to diagnose poliovirus infection. Poliovirus is most likely to be isolated from stool specimens. It may also be isolated from pharyngeal swabs. Isolation is less likely from blood or CSF.

To increase the probability of isolating poliovirus, collect at least two stool specimens 24 hours apart from patients with suspected poliomyelitis. These should be collected as early in the course of disease as possible (ideally within 14 days after onset).

Real-time reverse transcription PCR is used to differentiate possible wild strains from vaccine-like strains ("intratypic differentiation"), using virus isolated in culture as the starting material.

Partial genome sequencing is used to confirm the poliovirus genotype and determine its likely geographic origin.

7-2 Serologic testing:

Serology may be helpful in supporting the diagnosis of paralytic poliomyelitis, particularly if a patient is known or suspected to not be vaccinated. An acute serum

specimen should be obtained as early in the course of disease as possible, and a convalescent specimen should be obtained at least three weeks later.

7-3 CSF analysis:

Detection of poliovirus in CSF is uncommon. CSF usually contains an increased number of leukocytes [from 10 to 200 cells/mm3 (primarily lymphocytes)] and a mildly elevated protein (from 40 to 50 mg/100 ml). These findings are nonspecific and may result from a variety of infectious and noninfectious conditions.[11]

8.control of virus:

As recently as 2012, Nigeria accounted for more than half of all polio cases worldwide. Since then, a concerted effort by all levels of government, civil society, religious leaders and tens of thousands of dedicated health workers have resulted in Nigeria successfully stopping polio. More than 200 000 volunteers across the country repeatedly immunized more than 45 million children under the age of 5 years, to ensure that no child would suffer from this paralysing disease. Innovative approaches, such as increased community involvement and the establishment of Emergency Operations Centres at the national and state level, have also been pivotal to Nigeria's success.

Polio, which can cause lifelong paralysis, has now been stopped nearly everywhere in the world following a 25-year concerted international effort. Polio remains endemic in only 2 countries – Pakistan and Afghanistan.

Nigeria has made remarkable progress against polio, but continued vigilance is needed to protect these gains and ensure that polio does not return. Immunization and surveillance activities must continue to rapidly detect a potential re-introduction or re-emergence of the virus. After 3 years have passed without a case of wild poliovirus on the continent, official 'certification' of polio eradication will be conducted at the regional level in Africa. [1]

9.Treatment :

9-1 vaccine :

In 1980, the authors reported preliminary results of large-scale production of inactivated poliovirus vaccine in which virus was produced in Vero cell culture on a microcarrier. For this first stage of development, ISO-litertanks were used. The virus is now produced in 1,000-liter tanks. The main point concerning the quality of Vero cells, namely the absence of tumorigenicity, has been demonstrated, qualifying them for use in the InstitutMerieux cell bank. The purity of the cell line has also been determined by checking for the absence of bacteria, fungi, mycoplasmas, and viruses. The search for oncornavirus and for reverse transcriptase activity was carried out, and the results were negative but are not described in this paper. The quality of the purification process was checked by a search for residual cellular DNA in concentrated, purified, and inactivated vaccine. With use of a molecular hybridization procedure, a specific probe was prepared to detect ~50 pg of DNA per filter. The preliminary results show that the purification procedure fulfills the World Health Organization's requirements. TI oligonucleotide mapping has also shown the identity of poliovirus RNA extracted from virus grown on Vero cells and that from primary monkey kidney cells. These data have led to the awarding of a license by the French government to the InstitutMerieux for production of this new, reassessed, inactivated poliovirus vaccine. [(12)]

9-2 Medication :

There is no cure for polio, only treatment to alleviate the symptoms. Heat and physical therapy is used to stimulate the muscles and antispasmodic drugs are given to relax the muscles. While this can improve mobility, it cannot reverse permanent polio paralysis.

Polio can be prevented through immunization. Polio vaccine, given multiple times, almost always protects a child for life.[(6)]

10. New about Poliovirus:

A Brief Background About PVS-RIPO.

PVS-RIPO is a genetically engineered poliovirus that is being investigated as a new anti-cancer agent at the Preston Robert Tisch Brain Tumor Center at Duke. The idea of targeting cancer with viruses has been around for at least 100 years. However, valid strategies of using 'oncolytic' (cancer-fighting) viruses emerged only recently. This is mostly due to technological advances in genetic engineering of viruses.

How Does PVS-RIPO work?

PVS-RIPO is infused directly into a patients' tumor (e.g. in the brain). This assures that the maximal amount of virus is delivered directly to the tumor. Once inside the tumor, PVS-RIPO infects and kills tumor cells. Although this tumor cell killing alone may have tumor-fighting results, the likely key to therapy with PVS-RIPO is its ability to recruit the patients' immune response against the cancer. There are many events following PVS-RIPO infusion into the tumor that can contribute to such an outcome. The human immune system is trained to recognize virus infections and, thus, responds vigorously to the infected tumor. Unraveling why and how the immune system attacks tumors that were infused with PVS-RIPO is a major research goal in the Gromeier Laboratory.[13]

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