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Revisión

History and future of poliovaccination, a personal account *

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ABSTRACT

Immunization against poliomyelitis began in the fifties of the previous century, with the development of a formalin-inactivated poliovirus vaccine (IPV). Shortly later, a live attenuated oral poliovirus vaccine (OPV) was developed. It has been shown that both vaccines are very effective, but they achieve success in different ways.

The virus causing the disease, i.e. poliovirus, has been and is still the most extensively studied virus in the world. In the eighties of the previous century, the complete genomes of several poliovirus strains have been sequenced and the capsid structure has been elucidated at the atomic level.

These scientific break-throughs of modern molecular genetics and immunology have opened the way for the development for new or alternative vaccines. Consequently, different innovative approaches were undertaken to develop better vaccines, in order to improve the control of poliomyelitis. Some of these developments, such as the capsid stabilisation of the OPV and the use of subviral particles produced in yeast as an alternative vaccine, will be discussed.

The eradication programme of WHO will be discussed with an open mind to questions such as:

(1) Is eradication possible?
(2) Which vaccine should be used for the eradication?
(3) Can we ever stop poliovaccination?
(4) What is the impact of bioterrorism on poliovaccination policy?

Key words: Poliovirus.—Vaccination.—Eradication.—Vaccin.

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RESUMEN

La inmunización contra la poliomielitis comienza en los años cincuenta del siglo pasado con el desarrollo de la vacuna de la polio inactivada (IPV). Inmediatamente después se desarrolló una vacuna oral polio trivalente (OPV). Se ha demostrado que ambas vacunas son muy efectivas, pero que alcanzan su objetivo de diferentes maneras.

El virus causante de la enfermedad, es decir, el virus de la polio, ha sido y sigue siendo el virus más extensamente estudiado en el mundo. En los años ochenta del siglo anterior se logró secuenciar el genoma completo de varios tipos del virus de la polio, así como la elucidación a nivel atómico de la estructura de su cápside.

Los avances científicos en genética molecular moderna e inmunología han abierto el camino para el desarrollo de nuevas o alternativas vacunas. Una de las consecuencias es el desarrollo de técnicas innovadoras para la creación de vacunas más perfeccionadas con el fin de mejorar el control sobre la poliomielitis. Algunos de estos desarrollos van a ser discutidos como, por ejemplo, la estabilización de la cápside en la OPV o el uso como vacuna alternativa de partículas subvirales producidas en levaduras.

El programa de erradicación de la OMS (Organización Mundial de la Salud) va a ser discutido, prestando una especial atención a preguntas como las siguientes:

— ¿Es posible la erradicación?

— ¿Qué vacuna debería usarse para la erradicación?

— ¿Podremos parar algún día la vacunación contra la polio?

— ¿Cuál es el impacto del bioterrorismo en la política de vacunación de la polio?

Palabras clave: Virus de la polio.—Vacunación.—Erradicación.—Vacuna.

RESUMEN EXTENSO

Vacunación contra la polio, historia y futuro

La poliomielitis es una enfermedad de las células espinales nerviosas causada por una infección del virus de la polio y que puede causar parálisis. La enfermedad puede atacar a personas no inmunes de cualquier edad, pero afecta principalmente a niños menores de tres años. Es una enfermedad de transmisión fecal-oral, el virus se introduce en el organismo a través de la boca y se reproduce en el interior de la garganta e intestinos. En algunos casos (un caso de cada 200 a 1.000 infecciones) el virus penetra en el torrente sanguíneo e invade el sistema nervioso central. Cuando se multiplica, el virus destruye las células nerviosas (neuronas motoras) que activan los músculos. Los músculos de las piernas son afectados en mayor medida que los músculos de los brazos. Los miembros se vuelven débiles y sin vida —condición conocida como parálisis flácida aguda—. Una parálisis más extendida, incluyendo los músculos del tórax y del abdomen, puede conducir a quadriplegía. En los casos más severos, el virus de la polio ataca las neuronas

motoras del tronco cerebral reduciendo la capacidad para respirar y causando dificultades para la deglución y el habla. Sin una asistencia técnica respiratoria adecuada, la polio puede causar la muerte.

El virus de la polio que causa la poliomielitis pertenece a la familia de las Picornaviridae. El genoma del virus de la polio consiste en una molécula de cadena sencilla positiva de RNA que puede ser traducida directamente en un único y gigante polipéptido que tiene que seguir una serie de divisiones postsintéticas sucesivas para constituir proteínas funcionales. El virus de la polio tiene tres tipos distintos de serotipos.

La polio no es una enfermedad nueva. En realidad es conocida desde hace más de 3.000 años. Varios ejemplos testifican de la presencia de casos ocasionales de la poliomielitis durante la historia de la humanidad. Pero la enfermedad no aparece a menudo de forma epidémica. La poliomielitis ha sido durante muchos años una enfermedad ocasional de los niños, que pasó a denominarse parálisis infantil —y esta característica se mantiene aún en algunas comunidades con medidas sanitarias primitivas, donde la enfermedad es endémica—. No fue hasta finales del siglo XIX y principios del siglo XX que la poliomielitis se convirtió en una amenaza para la salud humana y llegaron las primeras epidemias de poliomielitis. Aquí describimos detalladamente los factores responsables de este cambio en el comportamiento epidemiológico de la poliomielitis. Aunque difícil de creer: el factor principal conductor de epidemias de poliomielitis es paradójicamente la mejora en la sanidad y en la higiene.

En el año 1952 se detectan 58.000 casos de polio en los Estados Unidos, la mayor cantidad jamás alcanzada. En el continente europeo, una estimación de 28.500 niños eran paralizados anualmente por la poliomielitis. ¡La «histeria de la polio» es un hecho! ¡En esa época, todos los avances terapéuticos usando medicamentos no tuvieron éxito! (y esto se mantuvo durante más de cuarenta años). Al final, se comprobó que el único método útil para parar la amenaza de la poliomielitis sería la creación de una vacuna eficiente. La primera vacuna desarrollada en 1955 por el doctor Jonas Salk fue la vacuna de la polio inactivada (IPV). La vacuna contiene virus neurovirulentos procedentes de tres tipos distintos (o tres tipos de serotipos). La IPV ha de ser inyectada y funciona produciendo anticuerpos protectores en la sangre, previniendo de esa manera la dispersión del virus de la polio a través del sistema nervioso central. Sin embargo, provoca solamente niveles muy bajos del virus de la polio en el intestino. Como resultado, provee una protección individual contra la parálisis de la polio, pero no puede prevenir la dispersión del virus de la polio salvaje. Pocos años después de la creación de la IPV, se dispone de una vacuna oral contra la poliomielitis (OPV). Esta vacuna fue desarrollada por el doctor Albert Sabin. La OPV se toma por vía oral. Esta vacuna contiene virus atenuados o debilitados a partir de tres distintos serotipos. La OPV tiene dos acciones diferenciadas: la OPV provoca anticuerpos en la sangre. De nuevo, esto protegerá al individuo contra la parálisis de la polio evitando la dispersión del virus de la polio al sistema central. Pero la OPV produce también una respuesta local inmune en la membrana mucosa de los intestinos (que es en realidad el lugar primario de la reproducción del virus de la polio). Los anticuerpos limitan la reproducción del virus «salvaje» o «virus neurovirulento» en el interior del intes-

tino, evitando una infección efectiva. Las ventajas y desventajas de ambas vacunas son discutidas en detalle.

Debido a las campañas masivas de inmunización con IPV llevadas a cabo durante la segunda mitad de los años cincuenta del siglo XX en los Estados Unidos y en Europa (y más tarde con la OPV), la incidencia de la poliomielitis en ambas zonas ha disminuido de manera drástica. En los años setenta la poliomielitis no representa ya una amenaza para los países desarrollados. Los años ochenta fueron otra época dorada para la investigación sobre el virus de la polio. Se logró la secuenciación de los genomas completos de varios tipos de virus de la polio, así como la elucidación de la estructura de la cápsida a nivel atómico. Durante ese tiempo, la Organización Mundial de la Salud (OMS), decidió erradicar la polio del mundo. Sin embargo, hubo ciertas dudas sobre la eficacia de la OPV para la erradicación de la poliomielitis. Uno de los problemas principales con la OPV es su termolabilidad. Se necesita una «cadena fría» para transportar la vacuna hasta las personas a las que va destinada. Gracias a nuevos avances científicos en la investigación del virus de la polio, varias vacunas alternativas se desarrollaron en los años ochenta y principios de los noventa. Sin embargo, ninguna de estas vacunas alcanzó el nivel de producción. Algunas de ellas van a ser discutidas aquí.

Ahora la erradicación del virus de la polio se acerca a su fin, e incluso la OMS espera que se cese la inmunización contra la polio en un futuro próximo. Pero, ¿es esto realizable? ¿Y qué sucede con el terrorismo biológico? Como arma terrorista, el virus de la polio es casi ideal: es altamente contagioso, fácil de distribuir en la alimentación y reservas de agua, y es virtualmente imposible de detectar hasta que el mal ha hecho ya su efecto.

WHAT IS POLIOMYELITIS?

Poliomyelitis is a crippling disease of spinal nerve cells caused by a poliovirus infection. The disease can strike non-immune persons of any age, but affects mainly children under the age of three, and causes paralysis in one case of every 200 to 1,000 infections. It is a faecal-oral transmitted disease, the virus enters humans orally and then multiplies inside the throat and intestines. The incubation period is 4-35 days and the initial symptoms include fever, fatigue, headache, vomiting, constipation, stiffness in the neck, and pain in the limbs. Once established, poliovirus can enter the bloodstream and invade the central nervous system, spreading along the nerve fibres.

As it multiplies, the virus destroys the nerve cells (motor neurons) that activate muscles. These nerve cells cannot be regenerated and

the affected muscles no longer function. The muscles of the legs are affected more than the arm muscles. The limb becomes floppy and lifeless – a condition known as acute flaccid paralysis. More extensive paralysis, involving muscles of the thorax and abdomen, can result in quadriplegia. In the most severe cases, poliovirus attacks the motor neurons of the brain stem – reducing breathing capacity and causing difficulty in swallowing and speaking. Without respiratory support, polio can result in death (1, 2).

POLIOVIRUS

Poliovirus causing poliomyelitis is the type species of the Picornaviridae, a close-knit group of viruses of man and other vertebrates, with small (30nm), unenveloped, spherical virions. The genome consists of one molecule of single-stranded RNA. The RNA is of a positive polarity, meaning that is ready to act as a messenger RNA. The hallmarks of the picornaviruses are the single translation unit, which occupies up to 90% of their RNA and the resulting synthesis of a single, giant polypeptide which has to undergo a cascade of postsynthetic cleavages to functional proteins.

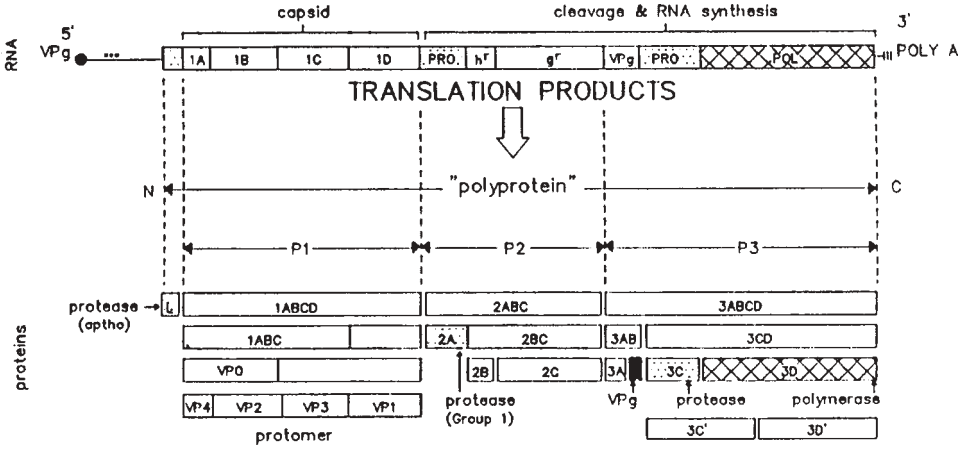

FIGURE 1. *The poliovirus RNA, translation and postsynthetic cleavage (from Rueckert, 1985, with permission).*

The ultimate cleavage products are the four structural proteins (called VP1-4) destined to build the protein capsids of the virions plus half a dozen nonstructural proteins, several which are known to possess enzymatic activities (3).

Poliovirus has three different serotypes and is belonging to the enterovirus genus, one of the six genera of the picornavirus family (4).

HISTORY OF POLIOLMYELITIS

Polio is not a new disease! Poliomyelitis is in fact known for more than 3,000 years. An Egyptian limestone stele (1350 B.C.) exhibited in the Glyptotek Museum in Copenhagen portrays the priest Rem giving offerings to the Godess Astarte. The man has a thin, withered leg, widely believed have been caused by poliomyelitis. The ancient Greeks were also cognisant of the disease, for instance Hippocrates described paralysis that afflicted patients predominantly in summer and autumn, i.e., the period that has been considered as the «polio season» (6). In archaeological excavations in southern Greenland, 24 skeletons from the 15th century were discovered, which showed bone deformities reminiscent of those typically associated with severe poliomyelitis. These examples ascertain that occasional cases of poliomyelitis have occurred throughout the history of mankind. On the other hand, the scarcity of the reports indicates that the manifestations of poliomyelitis were rare, and that the disease did not often occur in an epidemic form (7).

The epidemiological picture of the disease changed dramatically in the late 19th and, early 20th centuries. The first epidemics occurred in Northern Europe and the U.S.A. These epidemics grew in size, frequency, and severity. In 1889, the first recorded poliomyelitis epidemic has been experienced in Stockholm (Sweden), afflicting 44 persons. By 1916, no fewer than 27,000 cases of poliomyelitis have been recorded in the U.S.A. alone. During the first 3 decades of the 20th century, 80-90% of poliomyelitis victims were under 5 years of age, with the majority of patients afflicted during the first 2 years of life. Therefore, the disease was often termed «infantile paralysis». It became as dreaded as the plagues of the middle ages. In areas which had suffered repeated epidemics, a shift in the age of

incidence occurred, with more children, teenagers and young adults becoming affected (7).

FIGURE 2. *Poliomyelitis, shown on stele for Ruma (or Rem), Egypt, at sanctuary of goddess Astarte at Memphis c. 2000 BC. Major, 43 (with credit to the WHO: http://www.polioeradication.org/features/photos/photogallery.asp).*

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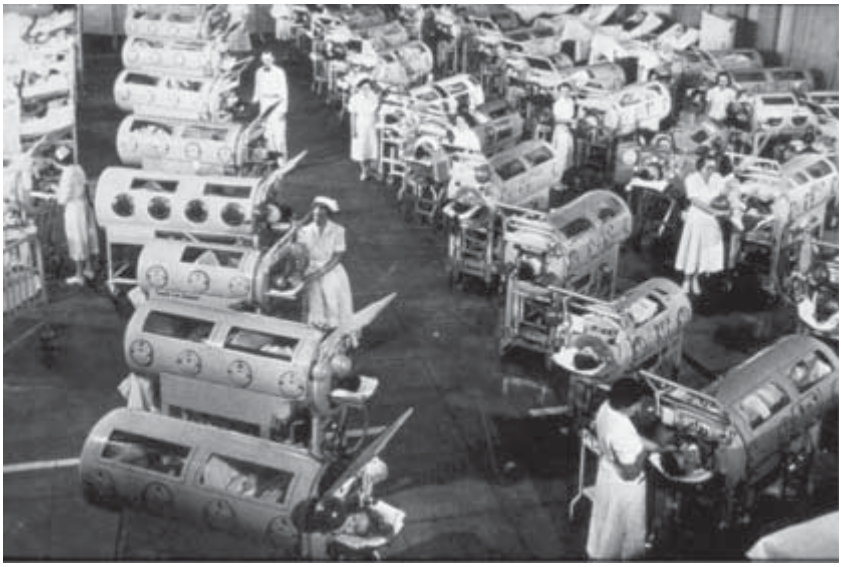


FIGURE. 3. *Polio patients in iron lungs (with credit to the WHO: http://www.polioeradication.org/features/photos/photogallery.asp).*

Meanwhile, the Austrian physicians Karl Landsteiner and Erwin Poppen, made the first hypothesis that poliomyelitis might be caused by a virus. After the second World War, large epidemics occurred all over the world. In 1952, there are 58,000 cases of polio in the U.S.A., the most ever. In the European Region, an estimated 28,500 children were annually paralysed by poliomyelitis. «Polio hysteria» is a fact (2).

THE EMERGENCE OF POLIOEPIDEMICS

As described previously, poliomyelitis was for many years primarily an occasional disease of infants and this pattern is still seen today in communities with primitive sanitation, where the

disease is endemic. It was only by the end of the 19th century and the beginning of the 20th century that poliomyelitis became a threat to human health, and the first polioepidemics occurred.

What are the factors underlying this change in epidemiologic behaviour of poliomyelitis? The main factor inducing polioepidemics is paradoxically the improvement of sanitation and hygiene.

Poliovirus is in fact not so highly neurotropic as has been supposed. The infection is primarily an inapparent one, involving the alimentary tract and consequently poliomyelitis is actually a relatively uncommon complication (poliomyelitis causes paralysis in one case of every 200 to 1,000 infections). The shedding of the virus from the throat and intestinal tract by asymptomatic persons (clinically unrecognised cases) serves as the main source of spread of the infection, and explains why a history of contact between patients is usually lacking. Dissemination of the virus is facilitated by crowding and poor standards of hygiene and sanitation (example: tropical developing countries). Under these conditions, there is a continuous circulation of the virus, immunizing infections early in childhood are universal, sporadic paralytic cases are confined to the youngest age group and consequently there are no epidemics. The disease remains endemic, which has been the case for at least 3,000 years.

In contrast (and before vaccination became possible), in countries with high standards of hygiene and sanitation, and practically always with high socioeconomic levels, circulation of the virus was intermittent and children were protected from exposure early in life. As a consequence, large numbers of susceptible individuals built up, and when virulent strains were introduced in a community, this resulted in progressively more devastating epidemics that involved increasingly older age groups. Moreover, there is a clear evidence for a higher frequency of paralytic disease when infections occur in susceptible older children and young adults (paralytic disease in one case of every 75 infections) as compared with young children (paralytic disease in one case of every 1,000 infections). Also this fact substantially contributed to the emergence of severe outbreaks and epidemics (8).

Although, it is now clear why polioepidemics occurred so late in history, there are still a lot of questions to answer: (1) what are the

factors involved in limiting the infection to a systemic, inapparent one, primarily involving the oropharynx and the intestinal tract; (2) what interactions spell progression to disease of the central nervous system and paralysis; and (3) why is there a difference in frequency of paralytic disease when infection occurs between younger and older children?

THE AGE OF VACCINATION

In 1916, the worst polioepidemic known in history was spreading throughout the U.S.A., afflicting more than 27,000 persons with a fatal progress in 6,000 cases, in New York alone. Little was known at this time about the pathogenicity of poliomyelitis. This 1916 U.S.A. epidemic gave great impetus to polio research, particularly in the U.S.A. Additional psychological backing for polio research came from an episode, which started in 1921, when the great Franklin D. Roosevelt contracted poliomyelitis. Roosevelt supported all measures that had hope of leading to a healing or prevention of the disease. Yet even in the twenties and thirties of the 20th century, promising results from polio research were very meager. The early therapeutic approaches using drugs were the cause of much frustration. This in contrast to the enormous success in the therapy of bacterial infections with antibiotics, following the discovery of penicillin by A. Flemming in 1928. Many drugs or chemicals were tested in the laboratories, none proved to be of any therapeutic value. Finally, it became clear that the only hopeful method to conquer the threat of poliomyelitis would be the development of an efficient vaccine (7). However, one has to realise that vaccinology was even in the mid fifties of the 20th century a very young discipline, and that at that time the knowledge on poliovirus and poliomyelitis was mainly clinical.

One of the main problems in developing a vaccine against poliomyelitis was the necessity to have a susceptible tissue, in which sufficiently large quantities of virus could be grown. At the end of the fourties of the 20th century, a landmark in the development of a vaccine came when Enders, Weller and Robbins (9) showed that poliovirus could be isolated and readily propagated in cell cultures of non-neuronal human or monkey tissue.

Another break-through was the result of a collaborative effort of many investigators (Committee on Typing of National Foundation of Infantile paralysis, 1951). This study showed that polioviruses belong to only three distinct serological types (type 1 to 3).

Due to this new knowledge on poliovirus and poliovirus replication, the fifties (of the 20th century) evolved into the golden age of poliovaccin development. Two different kinds of vaccine became available. Describing the detailed history of the development of both vaccines could be the subject of another topic. Therefore, only the vaccines will be described, together with their advantages and disadvantages.

The first vaccine developed in 1955 by Dr. Jonas Salk (10, 11), was a formalin inactivated (killed) poliovaccine (IPV). The vaccine contains neurovirulent virus from three different strains (of three different serotypes), originally grown on primary cells of monkeys. After sufficient growth, the virus is concentrated, purified and inactivated with formaldehyde. Each dose of vaccine contains 40 D antigen units of type 1, eight D antigen units of type 2 and 32 D antigen units of type 3. Trace amounts of antibiotics are also found in the vaccines (neomycin, streptomycin, etc.). Some manufacturers use 2-phenoxyethanol as a preservative (12).

IPV needs to be injected and works by producing protective antibodies in the blood (serum immunity) – thus, in fact, preventing the spread of poliovirus to the central nervous system. However, it induces only very limited levels of poliovirus inside the gut. As a result, it provides individual protection against polio paralysis but, unlike OPV, cannot prevent the spread of wild poliovirus.

There are several advantages of using IPV: (1) IPV is not a «live» vaccine, consequently IPV carries no risk of vaccine-associated polio paralysis, (2) it is more heat stable than OPV, and (3) immunization with IPV triggers an excellent response of the immune system in most IPV recipients.

TABLE 1. *Advantages and disadvantages of IPV and OPV*

Advantage	Disadventage
IPV	
— killed→ no mutation — heat-stable — no vaccine-associated infections	— parenteral administration — expensive — inactivation-procedure — no intestinal immunity
OPV	
— cheap — oral administration — humoral and intestinal immunity	— mutation! — heat labile — virus shedding — vaccine-associated infections

There are also some disadvantages in using IPV: (1) unlike OPV, IPV confers only very little immunity in the intestinal tract. Consequently, in a person vaccinated with IPV, virulent virus can still multiply inside the intestines and can be shed in stools. Hereby risking continued circulation, (2) IPV is expensive. A higher dosis of antigen is required (compared to OPV). There is the cost of the syringe and moreover the need for trained health workers to administer the vaccine using sterile procedures (13).

A few years after IPV, a live attenuated (weakened) oral polio vaccine (OPV) became available. This vaccine was developed by Dr. Albert Sabin. OPV is given orally (14, 15). This vaccine contains attenuated or weakened virus from three different serotypes (the so-called Sabin strains). This non-neurovirulent virus was also originally grown on primary monkey kidney cells and after growth, the virus is concentrated (and less purified than the IPV). The live virus of three serotypes is then blended as follows: 10^6 $TCID_{50}$ for type 1, 10^5 $TCID_{50}$ for type 2 and $10^{5.7}$ $TCID_{50}$ for type 3. Each dose of OPV contains residual amounts of antibiotics. Because OPV is very thermolabile, stabilisers are added. This can be sucrose or $MgCl_2$ (16).

The action of OPV is two-pronged : OPV induces antibodies in the blood (serum immunity). Again, this will protect the individual against polio paralysis by preventing the spread of poliovirus to the

nervous system. But, OPV also produces a local immune response in the mucous membrane of the intestines (which is in fact the primary site for poliovirus multiplication). The antibodies limit the multiplication of «wild» or «neurovirulent» virus inside the gut, preventing effective infection. This intestinal immune response to OPV is probably the main reason why mass campaigns with OPV can rapidly stop person-to-person transmission of wild virus.

What are the main advantages of OPV? (1) OPV is a cheap vaccine. This is due to the fact that it is an orally applicable vaccine. It can be given by volunteers (see National Vaccination Days) and —unlike most other vaccines— does not require sterile injection equipment. (2) The short-term shedding of vaccine virus in the stools of recently immunized children, means that in areas where hygiene and sanitation are poor —and the incidence of poliovirus is likely to be high— immunization with OPV can result in the «passive» immunization of persons with close contact. As discussed above, the unique ability of OPV to induce intestinal immunity is probably responsible for the extraordinary effect of OPV mass campaigns interrupting wild poliovirus transmission.

OPV has also some disadvantages: (1) although OPV is safe and effective, it can induce poliovirus paralysis, the so-called vaccine-associated infection in approximately 1 in every 2.5 million doses.

THE CONTROL OF POLIOMYELITIS

Due to mass immunization campaigns with IPV in the second half of the fifties of the 20th century in the U.S.A. and in Europe, the incidence of poliomyelitis in both regions dropped dramatically. In 1962, IPV is replaced by OPV in much countries. OPV is shown to be superior in terms of ease of administration, but also provides longer-lasting immunization. Using OPV, several countries appear to interrupt transmission of poliovirus after introducing OPV. But also in countries where IPV is used, such as Sweden, Finland and the Netherlands, the potential of IPV for controlling poliomyelitis is amply illustrated. By the 1970s poliomyelitis is no longer a threat in most developed countries (1, 8).

THE GOLDEN AGE OF POLIOVIRUS RESEARCH

The 1980s were another golden decade for poliovirus research. The complete genomes of several poliovirus strains have been sequenced (17, 18) and the capsid structure has been elucidated at the atomic level (19). By preparing escape mutants, selected by murine monoclonal antibodies, the four neutralising antigenic sites of poliovirus could be identified (20, 21). These neutralizing antigenic sites provoke antibodies in man, protecting us against the disease. It was found that these neutralising sites were also present on subviral particles (22), and that these subviral particles could be the active principle of alternative, new vaccines (23). These particles could even be cloned in a Saccharomyces cerevisiae inducible expression system and empty capsids purified from this expression system were shown to have the same immunogenicity as poliovirus virions (24, 25). However, none of these alternative vaccines has been further developed.

THE GLOBAL POLIO ERADICATION INITIATIVE

In may 1988, at its annual meeting in Geneva, the World Health Assembly, the governing body of the World Health Organization (WHO), resolved to eradicate polio from the world. After smallpox, poliomyelitis would be the next disease to be targeted for global eradication. The global eradication of polio has two components: (i) halting the incidence of the disease and (ii) the worldwide eradication of poliovirus. There is only a limited number of diseases that can be eradicated. Most diseases can only be controlled. The rationale for polio eradication is:

(1) polio only affects humans, and there is no animal reservoir

(2) an effective, inexpensive vaccine exists (OPV)

(3) immunity is life-long, and

(4) the virus can only survive for a very short time in the environment.

The polio eradication strategy is based on the premise that poliovirus will die out when it is deprived of its human host through

immunization. The strategy is similar to that used for smallpox eradication in 1977.

The strategy developed by WHO and its partners (Rotary, UNICEF) to eradicate polio has 4 components:

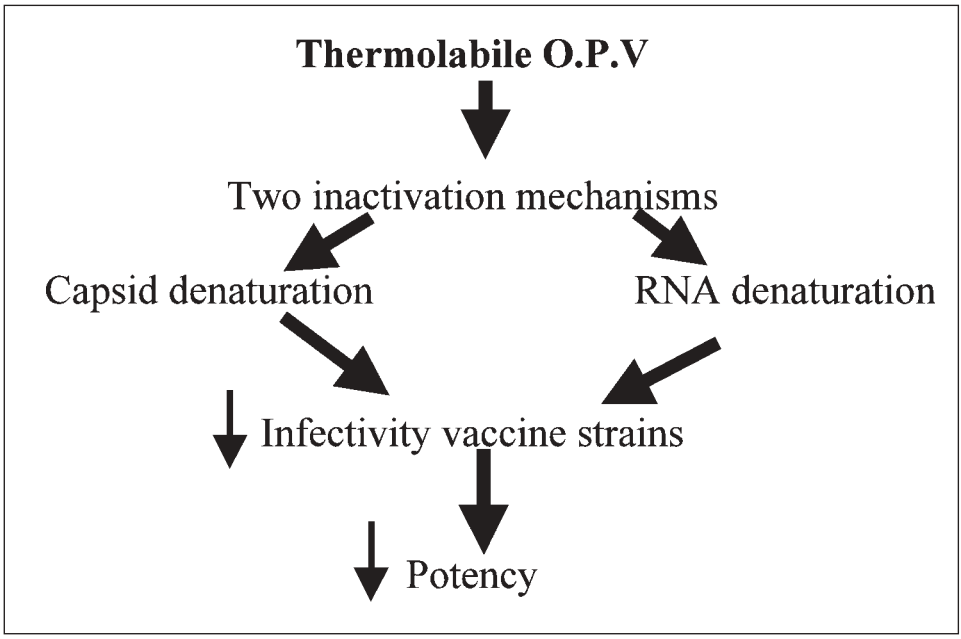
(1) High routine infant immunization with OPV. OPV is one of the six antigens provided by the national routine immunization programme during the first year of life. Routine coverage of at least 90% with three doses of OPV is the foundation for establishing the level of population immunity needed to eradicate polio.

(2) Supplemental mass immunization (National Immunization days). In order to ensure that all children have been adequately immunized with OPV and interrupt the circulation of wild poliovirus, it is necessary to conduct supplemental immunization campaigns.

(3) Epidemiological and laboratory surveillance for Acute Flaccid Paralysis. A sensitive surveillance system for acute flaccid paralysis is necessary to identify paths of continuing transmission of wild poliovirus and to provide evidence to allow for the certification of polio-free status and subsequent cessation of immunization.

(4) «Mopping-up» immunization. «Mopping-up» immunization activities are most important in the later stages of the eradication effort, when areas that are at high risk based on continued circulation of the wild poliovirus, can be targeted. During this phase, OPV is administered in a house-to-house campaign (2).

TABLE 2. *Inactivation mechanisms of thermolabile OPV*



One of the main problems with OPV (already discussed in a previous section) is its thermolability. OPV is the least thermostable vaccine of the six antigens provided by the nationale routine immunization. A «cold chain» is required to bring the vaccine to the vaccinees. This «cold chain» might be a problem to realize in developing tropical and subtropical countries. The final step of the eradication of poliovirus, the «mopping-up» component will be more difficult to realize if the vaccine must be strictly maintained within narrow temperature limits. Therefore, WHO prepared in 1989 a request for proposals in order to enhance the thermostability of OPV. Research as an answer to this request, revealed that the thermolability of the vaccine is due to two different inactivation mechanisms: (i) denaturation of the viral capsid and, (ii) degradation of the viral RNA within the capsid (26, 27) and that chemical tools are available to stabilize both mechanisms (27, 28). However, a few years later, WHO decided to abandon all work on new or improved vaccines. After the succes of eradication polio in the Americas, WHO made the decision to globally eradicate poliovirus with OPV.

IS POLIOMYELITIS ERADICATION FEASIBLE?

In the original Global Polio Eradication Initiative (document of WHO) from 1988, poliomyelitis should be eradicated by the year 2000. However, this date was too optimistic. Since the creation of the Global Polio Eradication Initiative, the global toll of polio paralysis dropped from an estimated 350,000 (per year) to fewer than 1,000 in 2004. The Americas had their last case of polio in 1991, they were certified polio-free in 1994. In 2000, the Western Pacific Region, including China, was declared polio-free. The European region, including parts of the former Soviet Union, is on track to be certified in 2002. The world awaits the end of polio in just 10 countries in Africa and South Asia (29). In other words: the «polio endgame» is going on. Global certification of polio eradication is now scheduled for the year 2005.

TABLE 3. *Polio eradication: quick facts*

- There are 20 million polio survivors worldwide, including one million in the U.S.
- Five million children have been prevented from contracting polio since the effort began.
- Polio will be only the second disease ever to be eradicated by mankind.
- The world has reduced polio by a staggering 99%. But it's the last 1% that's the hardest to overcome – that is what our film focuses on.
- In 1988, there were 350,000 new cases of polio a year. In 2004, there were 1,000.
- If polio returns to the pre-eradication level, 1,000 new cases a day could appear.
- The global polio eradication effort is the largest public health initiative in history.
- Many health workers and volunteers risk their lives to immunize children.
- The cost of the oral polio vaccine (OPV) is $0.11 per dose.

An important question to answer is: Will it be possible to cease immunization? The ultimate benefits of polio eradication, including the estimated global savings of • 1.5 billion annually, will be gained only after the cessation of polio immunization. Before polio immunizations can be stopped, all laboratory polioviruses must be destroyed or transferred to maximum biosafety containment facilities.

The WHO plan to cease immunization is based on the model used to fight smallpox. Unfortunately, the two viruses differ

dramatically in both biology and history. The vaccinia virus, used in the smallpox vaccine is not directly derived from a wild virus. There is no way it can mutate back into a pathogenic form and cause an outbreak. OPV, on the other hand, contains three attenuated viruses and can reverse into a wild-type virus. OPV can induce vaccine-associated infections (discussed earlier). That is the reason that as of January 1, 2000, IPV is exclusively used in the U.S.A. for routine childhood poliovaccination. This decision was taken to eliminate the risk for vaccine-associated paralytic poliomyelitis. However, using IPV is also a problem: IPV would not provide the same type of immunity as OPV; individuals vaccinated in this way would still be able to act as carriers (no gut immunity). So, if we are willing to cease vaccination, only a combination of an IPV/OPV protocol would be advisible in the «polio endgame».

However, is cessation of immunization a good idea? What about biological terrorism? As a terrorist weapon, poliovirus is nearly ideal: it is highly contagious, easily released into food and water supplies, and virtually impossible to detect until the damage has already been done.

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