Winter 2009
Issue 3

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the poliopipeline

A quarterly update of ongoing research in the Global Polio Eradication Initiative

Polio research: helping secure a lasting polio-free world

Following an overview of research to support countries' polio eradication efforts in Issue 2 (available at www.polioeradication.org), this edition of the Polio Pipeline examines the research activities to help set the stage for the post-eradication era.

The *intensified polio eradication effort* launched in February 2007 by the stakeholders of the Global Polio Eradication Initiative (GPEI) saw renewed innovation to address the remaining technical and operational barriers to polio eradication. Recently-developed tools and tailored eradication tactics – including monovalent oral polio vaccines (mOPVs) – have been evaluated and rolled-out in key polio-infected areas. Bold new initiatives to further optimise the efficacy of polio vaccination – including bivalent OPV - are being field-tested.

The identification, development and evaluation of new tools and tailored tactics to more rapidly interrupt wild poliovirus transmission globally has been a key strategic objective of an extensive programme of research. This work is coordinated by the Research and Product Development team at the World Health Organization (WHO). Strategically guided by the independent Polio Research Committee (PRC), and in close cooperation with the US Centers for Disease Control and Prevention (CDC), this programme of research involves an expanding number of private and public institutions.

This coordinated programme of research is also scaling up its activities to meet its second objective: to broaden and deepen the knowledge-base necessary for policy decisions associated with the post-eradication era, and thereby ensuring that the long-term risks of polio are minimised and appropriately managed.

This second objective focuses broadly on three areas:

1. fully characterizing the long-term polio risks, relating primarily to vaccine-derived polioviruses (VDPVs) as a result of the continued re-introduction into the human population of the attenuated polioviruses contained in OPV;
2. managing the VDPV risks, including through the cessation of OPV use in routine immunization programmes as soon as possible after certification of wild poliovirus eradication; and,
3. internationally coordinating the strategies for the management of the long-term polio risks, the containment of wild and Sabin polioviruses, internationally-agreed processes for the use of OPV in response to new outbreaks of polio and clearing of immunodeficiency-associated excretion of poliovirus.

Polio Research Committee outcomes

The second meeting of the Polio Research Committee (PRC) took place in Geneva, Switzerland, on 10-11 November 2008.

In this meeting, the PRC reviewed submitted research proposals by external researchers and endorsed the following proposals for funding:

1. **Alternative poliovirus seed strains for inactivated poliovirus vaccine - IPV (three proposals)**
   Four proposals focus on developing alternative seed strains, which would allow safe production of IPV in developing countries in the post-eradication era with the ultimate aim to reduce the bio-containment levels for production.
2. **Conducting additional mathematical modelling work (one proposal)**
   This proposal is to develop an "agent-based" model, which would answer critical questions, such as risk of undetected circulation of wild poliovirus, optimal timing to cease routine OPV use, evaluation of outbreak response options and role of antivirals as an adjunct to other control measures in outbreaks.
3. **Seroprevalence survey (one proposal)**
   This proposal focuses on a seroprevalence survey to determine the immunity profile of infants in high-risk reservoir areas in Pakistan to assess programme performance and vaccine efficacy in that area.

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PRC Call for Research Proposals

Submission guidelines

The Polio Research Committee (PRC) is currently soliciting research proposals, especially on topics outlined in Table 1. Proposals will be reviewed at the next PRC meeting, to be held in June 2009 in Geneva, Switzerland.

Researchers are invited to submit proposals by 15 April 2009 to Dr Hiro Okayasu, Research and Product Development, Global Polio Eradication Initiative, WHO Geneva, email: okayasuhi@who.int. The standard research proposal form is available in downloadable format at www.polioeradication.org/content/fixed/opvcessation/opvc_researchproposals.asp.

All research proposals should include the following information:

1. **Research question/objectives** (e.g., clarity of questions, reference to published literature and cutting edge science, description of how the results will be utilized).
2. **Qualification of investigators and collaborators** (e.g., track record of researchers, capability of laboratory, necessary contractual arrangements).
3. **Budget request** (e.g., appropriate for work anticipated).
4. **Study design and methodology** (e.g., clarity of activities, availability of institutions, feasibility of methods, compliance with Good Clinical Practice guidelines, plans for ethical and regulatory approvals).

PRC outcomes - continued

4. **Environmental surveillance (one proposal)**
   This proposal focuses on environmental surveillance to enhance the sensitivity of poliovirus surveillance in Pakistan.
5. **Antiviral development (one proposal)**
   The proposal is to identify new antiviral compounds against polioviruses through screening of candidate compounds and evaluation of lead compounds in mouse infection models.
6. **Use of adjuvant for IPV (one proposal)**
   Adjuvants would offer the opportunity to save IPV production costs by reducing requirements of antigenic content. The proposal is to evaluate the use of Immunositumulatory Particles (IStP) and other novel and traditional adjuvants for IPV.

The PRC also reviewed the current research projects and discussed unmet needs. A summary of the current unmet research needs is available in Table 1. The PRC is soliciting proposals, focusing especially on those identified research topics.

TABLE 1: UNMET RESEARCH NEEDS

Category	Objectives	Unmet needs
Pre-eradication		
Assessment of emerging polio risks	Minimizing VDPV risks and circulation	- Evaluation of risk factors for VDPV emergence - Outbreak investigation for cVDPV in Nigeria - Evaluation of VDPV burden using real-time PCR
Accelerate eradication	Evaluating program performance	- Evaluation of the impact of IPV use in India (e.g., logistic, coverage and acceptance) - Estimation of efficacy of mOPV3 in India - Evaluation of vaccine efficacy at sub-region level in India
	Improving vaccine efficacy	- Operational lessons learned from implementation of short-interval campaigns - Evaluation of roles of older persons (>5 yrs) in wild poliovirus (WPV) circulation - Development of surrogate test to measure mucosal immunity - Studying the cause of vaccine failures (e.g., epidemiologic, immunologic assessment)
	Overcoming failure to vaccinate	- Development and evaluation of new intervention approaches (e.g., incentives) to address inadequate coverage
	Enhancing surveillance	- Expansion of environmental sampling to increase the sensitivity of detection and surveillance coverage in high-risk areas - Evaluation of alternative approaches to evaluate surveillance in low-performance areas - Operations research on the effectiveness of reverse cold-chain for AFP surveillance specimen transport in Nigeria
Containment		
Long-term containment	Ensuring polio virus is properly contained	- Polio-specific biosafety research (e.g., rapid technique for validating disinfection, alternative methods for poliovirus disinfection, utility of low humidity as a disinfection method) - Determining barriers to achieving containment - Evaluation of containment implementation status
Post-eradication		
Long-term surveillance and response	Preparing response for potential outbreak	- Evaluation of alternative surveillance strategies in post-eradication era - Evaluation of block-ELISA to measure antibody profile (e.g., IPV, OPV, wild virus)
Safer and more affordable IPV	Developing a better protection in post-eradication era	- Evaluation of operational and technical feasibility of IPV use to control cVDPV outbreak - IPV pilot introduction project in Africa
Options for OPV cessation	Developing and selecting OPV cessation option	- Evaluation of stopping strategies in Cuba and other countries switching from OPV to IPV

Upcoming and available publications

- Avellón A, Cabrerizo M, de Miguel T, Pérez-Breña P, Tenorio A, Pérez JL, Martínez de Aragón MV, Trallero G. 'Paralysis Case and Contact Spread of Recombinant Vaccine–derived Poliovirus, Spain.' *Emerg Infect Dis.* 2008 Nov;14(11).
- Chumakov K, Ehrenfeld E. 'New generation of inactivated poliovirus vaccines for universal immunization after eradication poliomyelitis.' *Clin Infect Dis.* 2008 Dec15;47 (12):1587-92.
- Wringe A, Fine PEM, Sutter RW, Kew OM. 'Estimating the Extent of Vaccine-Derived Poliovirus Infection.' *PLoS ONE.* 2008 3(10).
- Nathanson N. 'The pathogenesis of poliomyelitis: what we don't know.' *Adv Virus Res.* 2008;71:1-50.

Upcoming Events

- April 7-9 2009: Strategic Advisory Group of Experts on Immunization (SAGE): Geneva, Switzerland
- May 12-14 2009: Regional Certification Committee for the Eastern Mediterranean: Cairo, Egypt
- May 18-27 2009: 62nd World Health Assembly (WHA): Geneva, Switzerland
- June 2-3 2009: Polio Research Committee (PRC): Geneva, Switzerland
- June 3-4 2009: SAGE IPV Working Group: Geneva Switzerland (tbc)
- June 23-25 2009: 15th Consultation of the Global Polio Laboratory Network (GPLN): Geneva, Switzerland

Update on Improving IPV

This is an update to the article entitled "Improving IPV" published in the first issue of the *Polio Pipeline* (Issue 1, Summer 2008). The aim of this project is to make inactivated poliovirus vaccine (IPV) affordable to countries which may choose to use it after oral poliovirus vaccine (OPV) cessation. A five-pronged strategy is being pursued:

1) **Schedule and dose-reduction:** a number of studies have shown that a routine schedule with IPV given at 2, 4, and 6 months of age provides immunity in >90% of children, also in developing countries. A 2-dose schedule provided at 2 and 4 months is suboptimal (<90% seroconversion to at least some serotypes). Recently, a decision was made to conduct a new 2-dose trial in 2009-2010 to evaluate whether >90% seroconversion could be achieved if the first IPV dose is delayed to later in life (e.g. 4 months) and the interval between the two IPV doses is extended (e.g. by 4 months).

   In terms of dose reduction, preliminary results are available from two fractional-dose trials: Cuba and Oman. In both trials, a needle-free device - Biojector®2000 - was used to administer the intradermal fractional doses (1/5th of a full dose). The results are excellent for the 2, 4, and 6-month schedule in Oman, where >95% of children seroconverted to all three poliovirus serotypes. The results in Cuba provides additional evidence that IPV at 6, 10, and 14 weeks is suboptimal in inducing adequate immunity, and furthermore, with this early schedule, the intradermal arm performed substantially inferior compared with the intramuscular arm. Nevertheless, the data are extremely encouraging and suggest that the fractional dose strategy may provide a viable option for decreasing costs without loss of immunity. Trial results will be submitted for publication in the second quarter of 2009.

2) **Adjuvant to decrease antigen requirement per dose:** a number of research groups have evaluated traditional adjuvants for IPV and have reported that a 3 to 5-fold reduction in antigen content may be feasible. Recently, the Infectious Disease Research Institute (IDRI) in Seattle, USA, with funding provided through the Polio Research Committee (PRC), has been examining newer adjuvants which could lead to further decreases in antigen needs, including oil and water emulsion. The results of this study should be forthcoming in the first quarter of 2009.

3) **Alternative inactivation agents:** given that formalin is quite abrasive to poliovirus and may destroy some of the antigenic sites on the capsid of the virus, a collaboration has been established with the Netherlands Vaccine Institute (NVI) to examine β-propriolactone as an alternative inactivation agent for the inactivation of poliovirus strains used in the IPV. Since β-propriolactone is used to inactivate rabies virus, there is a body of evidence already available for this agent. In addition, a preliminary study suggested that IPV inactivated by β-propriolactone is substantially more immunogenic than IPV inactivated by formalin. The results of this work should be available in 2010.

4) **Optimizing production processes:** production processes have been established first in the 1950s (Salk) and then in the 1960s (van Wezel). Since then few improvements were noted. However, increasing the cell densities in the bioreactors to grow poliovirus or examining suspended cells increase the antigen yield, and potentially lower the production costs.

5) **Production in developing country settings:** because of the stringent containment requirements after polio has been eradicated, the production of IPV in developing countries must be based on Sabin or other strains. Because of this, WHO has established a collaboration with NVI to develop a Sabin-based IPV. The pharmaceutical development of this product has nearly been completed, and the focus is now on the clinical development of this new vaccine over the next 3 to 5 years. Preliminary results suggest that the immunogenicity of Sabin virus is superior for type 1 polio, inferior for type 2 polio, and roughly equivalent for type 3 polio. Ultimately, through technology transfer, developing country manufacturers should be in a position to produce Sabin-IPV.

Frequently asked questions

Q: Why not continue OPV indefinitely in the post-eradication era?

A: Polio eradication requires the eventual cessation of OPV use in routine immunization programmes. Otherwise, the continued reintroduction of the attenuated polioviruses of OPV into a polio-free world will result in polio cases due to vaccine-associated paralytic polio (VAPP), and polio outbreaks due to circulating vaccine-derived polioviruses (cVDPVs). The cVDPVs could re-seed the world with poliovirus, and thus negate the achievement of eradication. Thus, OPV cessation is the cornerstone to secure polio eradication.

Q: What is the role of IPV following OPV cessation?

A: The role of IPV following OPV cessation is still being evaluated. At a minimum, IPV will be needed in all countries that elect to retain poliovirus stocks. For countries which are not retaining poliovirus after eradication, but perceive the long-term poliovirus risks warrant continued routine immunization, IPV will be the only option with which to do this. Recognizing that current costs of IPV are substantially higher than OPV, the GPEI is evaluating a range of approaches to establish affordable strategies for IPV-use, to achieve immunity at a cost similar to that achieved through OPV. (See 'Update on Improving IPV' on page 3).

What about YOU?

Polio research is happening at many partner institutions, therefore **WE NEED YOUR HELP** to stay thoroughly informed. If you know of a project that is not included here or at www.polioeradication.org, please contact us at polioresearch@who.int.

The Poliovirus Antivirals Initiative

In February 2006, the National Research Council (NRC) of the (US) National Academies issued the report: *Exploring the role of Antiviral Drugs in the Eradication of Polio*. The report concluded that "...it would be prudent to develop at least one, but preferably two, polio antiviral drugs as a supplement... for the control of poliomyelitis outbreaks in the post eradication era." The report further recommended forming a drug development team to guide the effort.

Antivirals – a key tool in a post-polio world?

Antiviral treatment could play an important role in protecting a polio-free world following eradication. The GPEI is exploring its uses as treatment for chronic excretion of the virus, and in outbreak settings in the post-eradication era.

In response to the NRC recommendations, The Task Force for Child Survival and Development (TF) in Atlanta, USA, established the Poliovirus Antivirals Initiative (PAI), in partnership with the World Health Organization (WHO), the US Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institute for Allergy and Infectious Disease (NIAID). A multidisciplinary Steering Team consisting of five independent experts coordinates the efforts of drug sponsors.

Currently there are two drug sponsors: ViroDefense, Inc. (capsid inhibitor) and Pfizer, Inc. (protease inhibitor). Both drug candidates are in early stages of development.

There are three situations anticipated for polio antiviral drug use:

(1) for immunodeficient individuals chronically shedding poliovirus;

(2) for persons exposed to poliovirus (e.g., through unintentional laboratory exposure); and,

(3) (likely in conjunction with inactivated polio vaccine – IPV) for communities exposed to a circulating vaccine-derived poliovirus (cVDPV) in the post-eradication era.

The immediate PAI goal is to determine if a candidate compound is safe and has the capacity to prevent, reduce, or stop virus shedding when administered to adult volunteers before or after OPV challenge. If successful, these "proof-of-concept" results should permit the opportunity to apply for a compassionate use investigational new drug (IND) for treatment of persons chronically shedding poliovirus (situation 1) and individuals exposed in a laboratory incident (situation 2). Proof-of-concept results will also permit assessment of the drug's practical utility for community outbreaks (situation 3) and allow "go-no-go" decisions for further development.

About this Newsletter:
At the annual meeting of the Advisory Committee on Poliomyelitis Eradication (ACPE) in November 2007, dozens of ongoing or pending research trials and multiple potential new products were discussed. Many of these studies were being managed by the Research and Product Development team at WHO, but a large number of important studies in the overall strategy of GPEI research are being conducted in conjunction with partner organizations such as the US Centers for Disease Control and Prevention (CDC) and UNICEF, as well as collaborators in industry and academics. This increased complexity has made it difficult for the global polio eradication scientific community to remain apprised of the overall research strategy and the ongoing projects within the research agenda. For this reason the ACPE recommended that WHO develop a GPEI research newsletter for the scientific community. This will be integrated with broader inclusion on www.polioeradication.org.

Design & Layout: www.paprika-annecy.com