

the polio pipeline

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

Research underpins new roadmap to a polio-free world

In 2008, alarmed that polio remained entrenched in the four countries which had never stopped transmission of wild poliovirus, the World Health Assembly (WHA) called for the development of a new strategy to complete polio eradication. Since then, the Global Polio Eradication Initiative (GPEI) introduced a major programme of work to help develop new approaches to interrupt the remaining chains of wild poliovirus transmission. Underpinning the finalization of this new Strategic Plan has been an accelerated research agenda to develop and evaluate new tools and approaches that directly tackle the remaining barriers to eradication in the lingering polio endemic areas, that facilitate a swifter, more thorough outbreak response, and that limits renewed international spread of polio.

The accelerated research agenda has focused on a vast array of cross-cutting and country-specific studies. The game-changing bivalent oral polio vaccine (OPV) was evaluated and developed in record time; the Short Interval Additional Dose (SIAD) strategy was introduced in conflict-affected and outbreak settings; social research was conducted to tailor social mobilization strategies in India, Nigeria and Pakistan; trials were held to more clearly assess vaccine efficacy in multiple settings; seroconversion studies focused on validating supplementary immunization activity (SIA) performance in key reservoir areas; and, mathematical modelling and case-control studies were employed to more clearly highlight

areas at particular risk of outbreaks following re-infection. New methods to monitor SIA operations were pioneered to help guide mid-course corrections and new strategies were examined to further boost the efficacy of OPVs and close susceptibility gaps in targeted communities. Finally, supplemental surveillance strategies - including expanding environmental surveillance to key urban reservoir areas - were explored.

All of these new approaches, the implementation of which has already had a significant epidemiological impact, particularly in the traditional reservoir areas of northern India and northern Nigeria, have now been institutionalized in the published *GPEI Strategic Plan 2010-2012*, which was endorsed by the WHA in May. Mr Bill Gates, co-chair of the Bill and Melinda Gates Foundation, told the United States Congress in March 2010 that this new Plan will "strike at the final reservoirs of polio and consign this terrible virus to history".

There has never been a better opportunity to achieve a polio-free world, as the GPEI is now armed with the required insight and knowledge to tackle the remaining challenges. Due to the fact research will play a key role in both monitoring the implementation of the new strategy and in further sensitizing the approaches, this issue of *Polio Pipeline* examines in greater depth the role research has played in developing this new strategy, and how it will contribute to its implementation.

Programmatic benefits of bivalent OPV - 'from bench to bush!'

Following the development and wide utilisation of monovalent oral polio vaccines (OPV) since 2005, transmission of indigenous wild poliovirus type 1 (WPV1) and wild poliovirus type 3 (WPV3) has been restricted to geographically limited areas of four endemic countries: Nigeria, India, Pakistan, and Afghanistan.

However, given the ongoing co-circulation of WPV1 and WPV3 in these areas, in November 2007, the Advisory Committee on Poliomyelitis Eradication (ACPE) recommended that the Global Polio Eradication Initiative (GPEI) exploit an opportunity to obtain clinical data on a bivalent OPV (containing type 1 and 3 serotypes) in a clinical trial.

In 2008-2009, the clinical trial was conducted in India (in Indore, Pune and Chennai), to compare the rate of seroconversion to each serotype in the bivalent OPV with that of the respective monovalent OPV and trivalent OPV. For both types 1 and 3 polio, bivalent OPV was found to be at least 35% more effective than trivalent OPV and almost as good as the monovalent OPVs. The ACPE reviewed the final trial results in November 2009 and concluded that the strategic use of bivalent OPV in supplementary immunization activities (SIAs) could be an important additional tool in polio eradication, in those areas where both serotypes are circulating.

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A worldwide premiere: the new bivalent OPV was used for the first time anywhere in December 2009 in Afghanistan, and has since been administered more than 345 million times.

Since then, bivalent OPV products from four vaccine manufacturers have been pre-qualified by WHO, while a further two applications for pre-qualification are pending. Between December 2009 and May 2010, over 300 million doses have been procured and utilized in nine countries, with a further rapid scale up of utilization expected throughout 2010 (Table 1). This new vaccine complements the existing arsenal of monovalent and trivalent OPVs, but fills a previously key gap by simultaneously generating immunity to both remaining WPV serotypes. The new bivalent OPV has greatly simplified

the logistics of conducting SIAs, and it is anticipated that this tool could greatly accelerate eradication in some settings. The rapid scale-up of the new bivalent OPV is expected to be a cornerstone approach to optimizing SIA strategy during the life of the new GPEI Strategic Plan 2010–2012.

The field evaluation, development and availability of bivalent OPV further reflects the dynamic nature of the GPEI: evidence-based programming, ongoing learning and tactical adjustments to provide the best possible response to field challenges and

Table 1 - Utilization of bivalent OPV, by country, during SIAs

Country	Date of SIA	Number of doses of bivalent OPV used (in millions)
Afghanistan	15 December 2009	4.6
	24 January 2010	0.5
	14 February 2010	4.6
Pakistan	14 March 2010	9.4
	15 February 2010	38.5
	15 March 2010	19.2
Sudan	24 May 2010	19.2
	22 February 2010	8
India	29 March 2010	3.4
	10 January 2010	15.6
Nepal	7 February 2010	40.6
	25 April 2010	44.5
	23 May 2010	39.4
Benin	10 April 2010	5.8
	15 May 2010	5.8
Niger	24 April 2010	3.3
	26 March 2010	5.1
Nigeria	24 April 2010	5.1
	30 January 2010	51.8
Grand total	24 April 2010	18.6
		344.4

requirements (Figure 1). The very rapid process from field test to actual field application of this vaccine was the result of an extraordinary collaboration between WHO, UNICEF, vaccine manufacturers and national regulatory agencies.

Figure 1: 'From bench to bush': timeline of initial evaluation of bivalent OPV to first-time use



Programme evaluation: identifying gaps and providing clear epidemiological picture

As control activities to achieve eradication become more sophisticated by targeting specific poliovirus serotypes with type-specific monovalent oral polio vaccines (OPV) or with the new bivalent OPV containing type 1 and 3 serotypes (particularly where co-circulation of both serotypes exists), there is a concurrent need to better assess the coverage achieved during supplemental immunization activities (SIAs) and to better measure the impact of the SIAs on actual population immunity against polioviruses.

As a supplement to existing monitoring procedures, and to help assess vaccination coverage achieved during SIAs, the Global Polio Eradication Initiative (GPEI) adopted the existing methodology of Lot Quality Assurance Sampling (LQAS) to the specific

needs of the eradication programme. In November 2009, the new cluster LQAS methods were piloted in Nigeria, and applied subsequently over the next six months in Nigeria and other countries in the WHO African Region.

To better measure population immunity, a number of seroprevalence surveys have been conducted or are planned for the next six months, both in Asia (ie India and Pakistan) and Africa (ie Nigeria). These seroprevalence surveys usually focus on very young infants, ages 6–11 months, to provide the most conservative population immunity profiles (immunity in these young infants is lowest since maternally-derived antibodies have waned and they have received relatively fewer doses of polio vaccines than older age groups). At end-2009, the GPEI had already

documented a marked increase in type 1 immunity in northern India, from ~80% in 2007 to >99% in 2009, confirming and validating the corresponding decrease in type 1 poliomyelitis cases in this area.

While both methods provide important data to validate programmatic efforts to refocus the vaccine mix if necessary, or to provide confidence to programme managers that activities are on the right path, these methods are time- and resource intensive, and should only be used to answer specific important questions. Thus, while both methods are unlikely to become standard tools for the GPEI, these methods will be applied in areas where there are questions about programme performance or where case reporting data may conflict with SIAs coverage data.

The importance of optimizing outbreak response

From case investigation to mass campaigns

In April 2010, a wild poliovirus type 1 outbreak was confirmed in Tajikistan, representing the first importation of a wild poliovirus into Europe since the Region was certified polio-free in 2002. This outbreak underscores the

risk ongoing indigenous wild poliovirus transmission continues to pose to polio-free areas everywhere, and of the need to conduct effective outbreak response activities in the event of an importation.

First and foremost, in any outbreak, an effective initial case investigation must be conducted, to enable the subsequent implementation of comprehensive and effective control measures. Following reports of any case or cluster of cases of acute flaccid paralysis (AFP), an investigation should be launched to determine if the AFP case(s) display signs and symptoms consistent with polio. This will be followed by a virological investigation, ensuring collected specimens are processed in a WHO-accredited laboratory, and prioritizing any isolated poliovirus for intra-typic differentiation and genetic sequencing. If polio is confirmed, surveillance needs to be sensitized through active searches for additional AFP cases in the community, and the state of routine immunization coverage assessed to determine overall population immunity levels. Travel information should be collected to determine whether the case(s) (or their

The importance of a thorough case investigation – setting the stage for an effective response

A thorough case investigation will help determine areas and population groups at highest-risk of an outbreak, and will ensure that resources can be targeted in the most effective manner to such areas and groups during the outbreak response. A comprehensive case investigation should be initiated within 48 hours of identification of a suspected outbreak, and consist of:

- determination if AFP cases display signs/symptoms consistent with polio;
- active case search for additional AFP cases in the community;
- evaluation of routine immunization coverage in the immediate area;
- collection of travel information of the case(s) and close contacts; and,
- collection of information on geographical and temporal clustering, age, gender and ethnicity.

Further information on polio outbreak response guidelines, including case investigations, are available at:

<http://www.polioeradication.org/content/publications/outbreakresponse.asp#OUT>

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close contacts) had any connections with polio-endemic countries or areas. Finally, the descriptive epidemiology of the case or cluster being investigated should include information on geographical and temporal clustering, and age, gender and ethnicity.

Surveillance sensitivity should subsequently further assessed, including laboratory quality indicators (non-polio AFP rates, timeliness of stool collection, processing of stool specimens in a WHO-accredited laboratory, proportion of cases pending, geographical distribution of AFP cases, etc) for the area involved during the previous 12 months, to determine the possibility of transmission that might have previously been missed. Retrospective record reviews should be conducted in health facilities in the area of the outbreak and surrounding areas. Provincial surveillance units across the country should be instructed to notify,

by telephone, of the possibility of cases in other provinces.

All of these activities will help lay the ground-work for an effective outbreak response. While the response activities are comprehensively conducted on a large-scale, resources and technical support can be prioritized, as appropriate, to those areas and populations identified during the case investigation to be at highest-risk. The outbreak response should follow the international outbreak response guidelines adopted by the World Health Assembly in 2006 (Resolution WHA59.1), with at least three large-scale immunization campaigns with the respective monovalent oral polio vaccine.

New approaches are now being evaluated to more rapidly and comprehensively build population immunity levels, as part of the outbreak response. The Short Interval Additional Dose (SIAD) approach, to more rapidly boost population immunity levels

by administering subsequent doses of monovalent OPV at intervals of two weeks (rather than the traditional interval of four weeks necessary with trivalent OPV), could prove to be an important new tool in outbreak response. This approach has been successfully employed in outbreak settings in the past (eg Kenya, Somalia) and is now being applied in Tajikistan, and to further validate this approach in outbreak settings, a clinical trial in Egypt later in 2010 will assess SIAD in young infants.

These activities will provide invaluable insight into optimizing outbreak response, and may potentially lead to a revision of internationally-agreed outbreak response guidelines, if appropriate. In the meantime, to minimise the risk and consequences of an importation, it is critical that all polio-free countries maintain high population immunity levels through high vaccination coverage and strong AFP surveillance.

Pre-empting poliovirus: identifying countries at risk of outbreaks

Reinfection of previously polio-free countries and the resulting outbreak response activities cost the Global Polio Eradication Initiative (GPEI) close to US\$1 billion during 2003–2009. Those countries most at risk of an outbreak have historically been close to remaining endemic areas or had significant gaps in immunization coverage. However, historical patterns are not always a good indicator for future risk. In 2008–2009, polio cases were reported across Africa in a series of outbreaks on an unprecedented scale¹. Many of these countries experienced their first polio outbreak after stopping indigenous wild poliovirus transmission.

To understand the factors that put a country at risk of a polio outbreak a team from the World Health Organization (WHO) and Imperial College London studied polio surveillance and demographic information, including movement data from across Africa. Regression models showed that poor routine immunization coverage with three doses of oral polio vaccine (OPV), high levels of exposure to poliovirus from Nigeria through population movement and a young population were all independently associated with a larger number of polio outbreaks. Periodic supplementary immunization activities were implemented in some countries to protect against outbreaks, but were of variable quality over the period of analysis and no strong protective effect was observed.

Country-specific forecasts of outbreak risk six months ahead of time can be produced using routinely reported data on the risk factors that were identified by the regression analysis. These forecasts were found to have a reasonably good predictive ability and identified countries newly at risk in advance of an outbreak, and accurately described the increased number of outbreaks in 2008–2009 and show a reduced risk in 2010 as a result of the recent decline in the number of polio cases reported in Nigeria. Continued use of these forecasts will help optimize resource allocation in Africa to minimize the number of polio outbreaks during 2010–2012.

1 Resurgence of wild poliovirus types 1 and 3 in 15 African countries, January 2008–March 2009. *Weekly Epidemiological Record*. No. 16, 2009, 84, 133–140.

Call for recruitment

*Senior Programme Officer –
New Vaccines Introduction,
Bill and Melinda Gates
Foundation*

Brief job description:

The Global Health Delivery group at the Bill and Melinda Gates Foundation is looking for a Senior Programme Officer (SPO) for its New Vaccines Introduction team. The SPO will be primarily responsible for the development and management of product development and launch strategies to ensure fast, broad, and appropriate access to the technologies being developed by the Bill and Melinda Gates Foundation's grantees. Initial focus will be on vaccines for pneumonia and diarrheal diseases.

Requirements:

The ideal candidate will bring depth and breadth of experience and knowledge in business strategy, project management skills, and product introduction planning for new health technologies, particularly in developing countries. The candidate will have at least 12 years of experience in international public health, global development and/or pharmaceutical and healthcare industries. S/he must either have experience working with global partners such as WHO or GAVI Alliance on global product/vaccine introduction or have strategic planning expertise in marketing and/or product launches. The position is based in Seattle, USA. To view the full job description, please visit www.gatesfoundation.org/jobs

Outcomes of the Polio Research Committee (PRC)

The fifth meeting of the Polio Research Committee (PRC) was convened at the World Health Organization (WHO) in Geneva, Switzerland in June 2010, to review current research projects, unmet research needs and evaluate new research proposals.

The PRC reviewed the current status of the global polio eradication programme and ongoing research projects to support the pre-eradication era (eg outbreak investigation, laboratory methods, cost-effectiveness, operational and social research) and post-eradication era (eg antivirals, monoclonal antibody, adjuvant and Sabin IPV development).

The PRC subsequently reviewed more than 20 proposals and endorsed seven new projects (worth a total of US\$2.5 million). The new projects include two communication research projects, two seroprevalence studies, a case-control study on mucosal immunity, an alternate seed-strain development project and an intradermal device development project.

Now that many research questions are being addressed by existing projects and the priorities are shifting rapidly as polio epidemiology is evolving, the PRC is in the process of updating a list of research priorities, which will be published later in 2010.

Assessing the role of IPV in pre- and post-eradication eras

As progress continues towards the interruption of wild poliovirus transmission globally, a substantial programme of work is ongoing to better understand the role inactivated polio vaccine (IPV) could play in both the pre- and post-eradication eras.

On 4 June 2010, WHO published² new guidance to Member States on the use of polio vaccines (including IPV) and polio immunization in the pre-eradication era. Developed with guidance from the Strategic Advisory Group of Experts on immunization (SAGE) and the SAGE Working Group on IPV, the new WHO Position Paper assists countries with decision-making on polio vaccination schedules and vaccines, given their risk of poliovirus importations and the probable transmission potential for polioviruses in their country.

A second publication³ summarizes the findings of a study that was commissioned

by the Bill and Melinda Gates Foundation in collaboration with WHO to assess the supply landscape and economics of IPV-containing combination vaccines that would be affordable and appropriate for use in low- and low-middle income countries in the post-eradication era. This study, conducted by the international management consulting firm Oliver Wyman, also identifies and explores the range and feasibility of innovations needed to achieve IPV-containing hexavalent products that could approach the break-even price for future pentavalent products and stand-alone IPV in low-income settings.

A report⁴ by PATH and Working in Tandem Ltd gives an overview of an economic model, which calculated the costs involved in delivering IPV intradermally (ID), including with new delivery methods such as needle-free jet injection or ID adaptors (to control the depth and angle

2 Polio vaccines and polio immunization in the pre-eradication era: WHO position paper. Weekly Epidemiological Record. No. 23, 2010, 85, 213-228.

3 The supply landscape and economics of IPV-containing combination vaccines: key findings. Commissioned by the Bill and Melinda Gates Foundation. Prepared by Oliver Wyman, May 2010. Available at www.polioeradication.org.

4 Improving the affordability of inactivated poliovirus vaccines (IPV) for use in low- and middle-income countries - an economic analysis of strategies to reduce the cost of routine IPV immunization. PATH and Working in Tandem Ltd. April 2010. Available at www.polioeradication.org.

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.

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of the ID injection), at reduced volumes of vaccine per dose; use of adjuvants to allow a reduced antigen content per dose; and, reduced number of doses per IPV immunization schedule. The report suggests such delivery methods could result in per-dose savings of 71-83% compared with the current, standard IPV dose delivered intramuscularly using a needle and syringe. The report concludes that as there are still substantial

development risks with each approach, all three strategy options should be pursued given the potential cost savings which could be achieved.

The insights and conclusions from these and other studies and assessments will help further elucidate polio immunization policy. For more information, please see section 6 (Post-wild poliovirus eradication planning) of the new GPEI Strategic Plan 2010-2012.

Available and upcoming publications

- Fractional Doses of Inactivated Poliovirus Vaccine in Oman. Mohammed AJ, et al. *N Engl J Med* 2010;362:2351-9.
- Implications of a Circulating Vaccine-Derived Poliovirus in Nigeria. Jenkins HE, et al. *N Engl J Med* 2010;362:2360-9.
- Randomized Controlled Clinical Trial of Fractional Doses of Inactivated Poliovirus Vaccine Administered Intradermally by Needle-free Device in Cuba. Resik S, et al. *The Journal of Infectious Diseases* 2010: 201(9):1344-1352.
- Polio vaccines and polio immunization in the pre-eradication era: WHO position paper. *Weekly Epidemiological Record*. No. 23, 2010, 85, 213-228.
- Meeting of the Strategic Advisory Group of Experts on immunization, April 2010 – conclusions and recommendations. *Weekly Epidemiological Record*. No. 22, 2010, 85, 197-212.
- Poliomyelitis in Tajikistan: first importation since Europe certified polio-free. *Weekly Epidemiological Record*. No. 18, 2010, 85, 157-164.
- Progress towards eradicating poliomyelitis in Afghanistan and Pakistan, 2009. *Weekly Epidemiological Record*. No. 11, 2010, 85, 93-108.
- The supply landscape and economics of IPV-containing combination vaccines: key findings. Commissioned by the Bill and Melinda Gates Foundation. Prepared by Oliver Wyman, May 2010. Available at www.polioeradication.org.
- Improving the affordability of inactivated poliovirus vaccines (IPV) for use in low- and middle-income countries – an economic analysis of strategies to reduce the cost of routine IPV immunization. PATH and Working in Tandem Ltd. April 2010. Available at www.polioeradication.org.
- Meeting of the Strategic Advisory Group of Experts on immunization, April 2010 – conclusions and recommendations. *Weekly Epidemiological Record*. No. 22, 2010, 85, 197-212

Upcoming events

- June 28: Regional Certification Commission (RCC) for the WHO European Region. Copenhagen, Denmark.
- July: India Expert Advisory Group on Polio Eradication (IEAG). India.
- July 28-29: Chad Technical Advisory Group (TAG). N'Djamena, Chad.
- September 22-24: 16th Informal Consultation of the Global Polio Laboratory Network. Geneva, Switzerland.