



Polio Vaccine: The First 50 Years and Beyond

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Conference Summary

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The purpose of the conference was to bring together regulators, manufacturers, academia and public health authorities to review the standardization and regulatory issues around existing and new polio vaccines.

Session 1: Polio control and eradication through vaccination

Progress with eradication

- Eradication is feasible - the strategies work; where there have been problems with implementation the programme has adapted to overcome these; funding gap remains biggest threat
- Fast progress is currently being made towards eradication and transmission could stop quickly
- The eradication programme is innovating and evolving to respond to achieve the eradication goal
Regulators and manufacturers have been responsive and flexible to the need for new products, and there will be a need for continued flexibility as we move into the OPV cessation phase of the programme

Vision for a polio free world

- Polio eradication includes planning and delivery of OPV cessation products
- Countries, with support from WHO, will be developing OPV cessation policies; a framework for OPV cessation is already in place
- Investments are needed into the post-eradication period to protect the eradication accomplishments

Session 2: Challenges to polio control

Vaccine-derived polioviruses

- VDPVs have occurred and will likely continue to occur whilst OPV use continues
- In one example, based on retrospective studies, introduction of OPV into a small number of vaccines in an underimmunized population may have led to widespread transmission within a population
- Because of this, at least one researcher considers that mOPV use as an emergency response in the post-eradication era will be unacceptable
- Additional research should be encouraged on new vaccines and anti-viral drugs

Long-term excretors

- A small number of long-term excretors have been identified in patients with antibody deficiencies, either through serendipity or through polio surveillance programmes; 1 apparently healthy child also has been documented with longer than usual excretion
- No persistent excretors have been identified in HIV positive patients; perhaps need for additional studies
- Studies to estimate the true rate of long-term excretors suggest the upper bound of the estimate is less than 1% in immunodeficient patients, and in patients with conditions that may be a proxy for immunodeficiency
- 3 long-term excretors are known to be still excreting virus today
- No documented transmissions of viruses from long-term excretors to contacts

Surveillance for polioviruses

- AFP surveillance is and should remain the cornerstone of polio surveillance
- In some situations, supplementary surveillance can be of programmatic benefit, especially environmental surveillance
- Environmental surveillance is labour-intensive and in some countries is difficult or impossible to implement
- Supplementary surveillance is best suited to targeted surveys

Current trends in polio vaccine manufacture and quality control

Risk assessment of wild and attenuated poliovirus strains

- Comprehensive risk assessment conducted to inform development of 3rd edition of WHO global action plan for poliovirus containment
- The poliovirus content of infectious materials, and the infectious dose needed to initiate infection, have been estimated
- Data suggests infective dose after ingestion of wild type virus is about 10 CCID₅₀ and 1000 CCID₅₀ of Sabin viruses
- Data also suggest that some infectious materials, especially cell culture harvest and vaccine harvests are likely to have virus contents that exceed human infectious dose
- Community risk of exposure is highest through infections carried out of facilities as silent infections in workers
- In certain situations, exposure of communities to liquid effluents from vaccine facilities may also pose a community risk
- The risk assessment is one part of a process; a consequence assessment is also needed and under development

Biocontainment of polio vaccine production and quality control facilities

- Based on risk assessment, key occupational medical requirements to protect workers in polio facilities are: to immunise workers with IPV and to demonstrate antibody seropositivity to all 3 serotypes after immunization; and to implement medical surveillance and monitoring of staff
- Thorough biosafety training of workers in the polio facility is critical; proficiency testing in biosafety procedures may be useful; establishing a biosafety culture in a polio facility is essential
- Worker protection procedures can be introduced to protect all skin surfaces, including personal face shield systems
- For wild poliovirus strains, work will need to be conducted in closed systems, under negative air-pressure and with liquid effluent decontamination
- For Sabin strains, a WHO assessment of vaccine manufacturing facilities has been undertaken and WHO guidelines will be developed based on the findings of the group
- Procedures can be introduced into production facilities to decrease risks from contamination of surfaces, such as filling vials under low humidity

Production, regulation, standardization and quality control of IPV and IPV containing combination vaccines

- Although IPV vaccines have been used safely and successfully over many years, there are still issues around standardization of assays for IPV
- Development of Sabin-IPV introduces new challenges for assays of IPV
- Choice of reference standards needs careful consideration; the use of an IPV-only reference for control of IPV combination vaccines needs to be validated
- At present there is no worldwide harmonisation of the D antigen ELISA measurements
- the current 40-8-32 D antigen specification for wt IPV gives high levels of seroconversion, especially in combination vaccines, should be re-evaluated
- In house antigenic profiling of IPV by D ELISA is a useful tool to guide product development, and evaluation of product consistency
- The in vivo antibody response in the rat potency assay mirrors the human antibody response
- One current producer of wtIPV is not convinced that a switch to Sabin-IPV is feasible

General discussion

There is a continued need for polio research targeted at the needs of the eradication programme

New developments in polio vaccines

Use of monovalent OPV in the eradication end game and beyond

- mOPV requested by the eradication programme to interrupt final chains of transmission, as a supplement to tOPV campaigns
- Within a very short period mOPV 1, was produced by two companies, licensed in three countries, WHO pre-qualified and introduced into vaccination programmes in two countries
- Also being used in outbreak response in one country, and to rapidly boost type specific population immunity in a country at risk of importations
- Licensure of mOPV 3 is next priority, also to be used to interrupt final chains of transmission; mOPV 2 licensure is needed for the stockpile
- A WHO stockpile project has been initiated, for a stockpile of mOPV of each type, and an investment case prepared for funding
- Use of mOPV will be important in early post-eradication era; further consideration is needed for scenarios 10 or more years after cessation of vaccination
- Re-evaluation of mOPV 3 VAPP data is underway; additional review of the impact of poliovirus reversion rates and duration of replication of mOPV 3 may be needed

Manufacturing and supply of mOPV

- Joint effort between manufacturer, regulators and WHO resulted in quickest ever vaccine development and licensure, and WHO pre-qualification
- Production of mOPV based on existing tOPV but with appropriate change controls to assure the quality of the product, and to distinguish mOPV from tOPV
- Only difference in specifications between tOPV and mOPV was in interim thermal stability specification; due to concerns that mOPV1 may be more thermolabile than tOPV
- Key success factors included clear and careful definition of the project; close collaboration between manufacturer, regulators and WHO; commitment and motivation of staff

Licensing of mOPV

- Accelerated licensure of mOPV required an innovative parallel-track evaluation from regulators not only in country of production but also in receiving country
- Standard package of regulatory data requested and submitted simultaneously to production and recipient countries, and to WHO for pre-qualification purposes
- Main concern of receiving country regulator was thermal stability of the vaccine, since the vaccine will be used in very hot conditions; data from the field suggest that mOPV1 has similar thermal stability to tOPV
- Surveillance for VAPP in the early introducing countries will be important
- Key steps in successful licensure process was close regulatory cooperation between country of manufacture and receiving countries

Development of Sabin-IPV

- Sabin-IPV is an upstream development project underway
- Development of a specific ELISA tests to quantitative the antigen content of S-IPV has been achieved
- The rat potency test has been used to help develop an appropriate formulation for S-IPV; a new formulation that is at least as immunogenic in monkeys as current wtIPV has recently been developed

Technology transfer of Sabin-IPV to new developing countries

- Yields of virus per ml of culture fluid from a wtIPV and from a SIPV production process are very similar
- Yields of vaccine per ml of culture fluid are very similar for wt IPV and S IPV, but both are much less than for OPV; thus switching OPV production to IPV production will result in overall lower vaccine capacity
- Immunogenicity of Sabin IPV is different to wt IPV thus the usual 40-8-32 formulation may not be appropriate
- New manufacturers are approaching existing IPV producers to learn IPV production and QC methods; preferable for new producers to develop Sabin-IPV rather than wt IPV
- Financial backing for new IPV production is difficult to obtain; thus step wise approach being taken

- Standardization of D antigen assays needed
- Regulatory issues around Sabin-IPV needs further consideration - especially needs for neurovirulence testing

Licensing issues for new IPV vaccines

- Direct efficacy studies of new IPV vaccines will not be possible; surrogate endpoints will be needed
- Licensure will also need to be supported by a range of nonclinical tests
- Regulatory research has been undertaken to develop innovative approaches to characterise new IPV vaccines
- Use of new methods, both in vitro and in immunization/challenge experiments in transgenic mice, suggests that Sabin-IPV shows differences from wt IPV
- Non-inferiority human clinical studies against existing products will be needed, using neutralizing antibody response as primary endpoint - consensus on the virus strains to be used as challenge in neutralizing antibody tests will be helpful

Poliovirus as a viral vector

- Modified polioviruses are under development as oncolytic therapy for brain tumours; expectation that the modified viruses will enter clinical trial in 2006
- Potential transmissibility of modified poliovirus after direct inoculation into brain is not known
- Impact of pre-existing antibodies on efficacy is likely to be limited since there appear to be antibodies in CSF of glioma patients
- New attenuating mutation in non-coding region of poliovirus identified by studies in tg mice
- Poliovirus can never be considered extinct, since complete sequence of poliovirus is in public domain and poliovirus can be synthesized in vitro

Gaps in scientific knowledge for the post-eradication world

- IPV - need for careful evaluation of candidate vaccine strains; clear need for standards to assay the D antigen content for S-IPV
- Immunodeficients - what are the risk factors for long-term infections
- Safety of OPV - will the safety profile of OPV change in the post-eradication future, if the vaccine is used in a population that is immunologically naive
- Cessation of poliovirus excretion - what are the mechanisms; what interventions would limit/stop infections in the infected host?
- How will we know when all poliovirus circulation has ceased?
- Can we stop OPV in a sequential serotype manner?
- Methods to quickly identify VDPVs after OPV cessation; also need for improved understanding of factors which favour the emergence of VDPVs

Post-eradication stockpile regulatory considerations

- A WHO stockpile of mOPV types 1, 2 and 3 will be built of prequalified vaccine
- Active stock management and active regulatory oversight will be needed

Antivirals against poliovirus

- Currently there are no antivirals designed specifically for treatment of poliovirus infections
- However candidate lead compounds have been developed that are substantially more efficacious than any compounds that are currently available
- A meeting is planned to review the current state of the art and to identify ways to accelerate the development of promising candidates compounds

Use of OPV and IPV in post-eradication outbreaks

- Is a new more concentrated killed polio vaccine needed to respond to outbreaks?
- Current IPV manufacturers are increasing their production capacities; it is expected that there will be increased competition between vaccine producers for IPV supply
- Should countries switch to routine IPV, in combination vaccines, after OPV cessation?
- Can IPV be used to ring fence a country if polio reemerges?

- In immediate post-eradication era, use of mOPV would be ideal to contain any outbreak
- In post-OPV era, will IPV interrupt a post-eradication outbreak? Yes, in industrialised countries.
- Limited data suggest IPV has a herd effect in developing country

- From global public health perspective, a range of scenarios need to be considered for outbreak responses after OPV cessation
- A number of prerequisites for OPV cessation have been defined, and a timeline is defined
- Future outbreaks may occur in different epidemiological settings, which will influence the most appropriate outbreak response, depending on the force of infection in the population where the virus occurs
- mOPV gives good type specific mucosal immunity after 1 dose; risk of cVDPV will change depending on elapsed time since OPV cessation
- IPV is slower and requires more doses, but no risk of cVDPV or VAPP
- Need to be able to respond quickly to an outbreak in post-eradication era
- For tropical countries, mOPV first choice for outbreak control; in middle income countries, conditional on post OPV cessation policies; for high income countries, IPV may be vaccine of choice

- Outbreak responses in communities that refuse vaccination may need special considerations