The conduct of a vaccine study with a novel live attenuated polio vaccine, under containment

Centrum voor de Evaluatie van Vaccinaties
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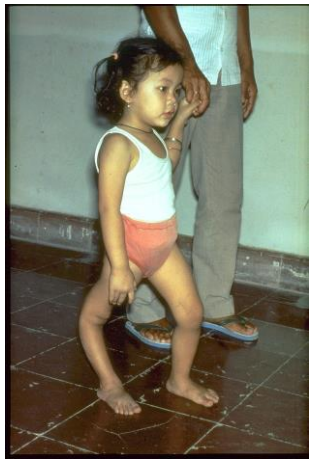
Poliomyelitis (polio) – a highly infectious viral disease mainly affecting young children

- Enterovirus (family Picornaviridae)
- 3 serotypes (I, II, and III)
- Person-to-person spread mainly through the faecal-oral route
- Virus multiplies in the intestine from where it can invade the CNS and cause paralysis
- Symptoms
  - most infected people (90%) have no symptoms and go unrecognized
  - For others initial symptoms incl fever, headache, neck stiffness, pain in the limbs
  - <1% of all polio infections in children result in flaccid paralysis
- Death-to-case ratio:
  - 2-5% among children
  - 15-30% for adults



Polio can be prevented through vaccination

Two types of vaccines to stop polio transmission

1. Inactivated polio vaccine: IPV (developed in 1955 by Jonas Salk)
   - protects against poliovirus types 1, 2 and 3

2. Attenuated polio vaccine: OPV (developed in the 60's by A. Sabin)
   - trivalent oral polio vaccine (tOPV), protects against poliovirus types 1, 2 and 3

     following the "OPV switch" in April 2016, tOPV is no longer in use
   - bivalent oral polio vaccine (bOPV), protects against poliovirus types 1 and 3
   - monovalent oral polio vaccines (mOPV1, mOPV2 and mOPV3) – protect against each individual type of poliovirus

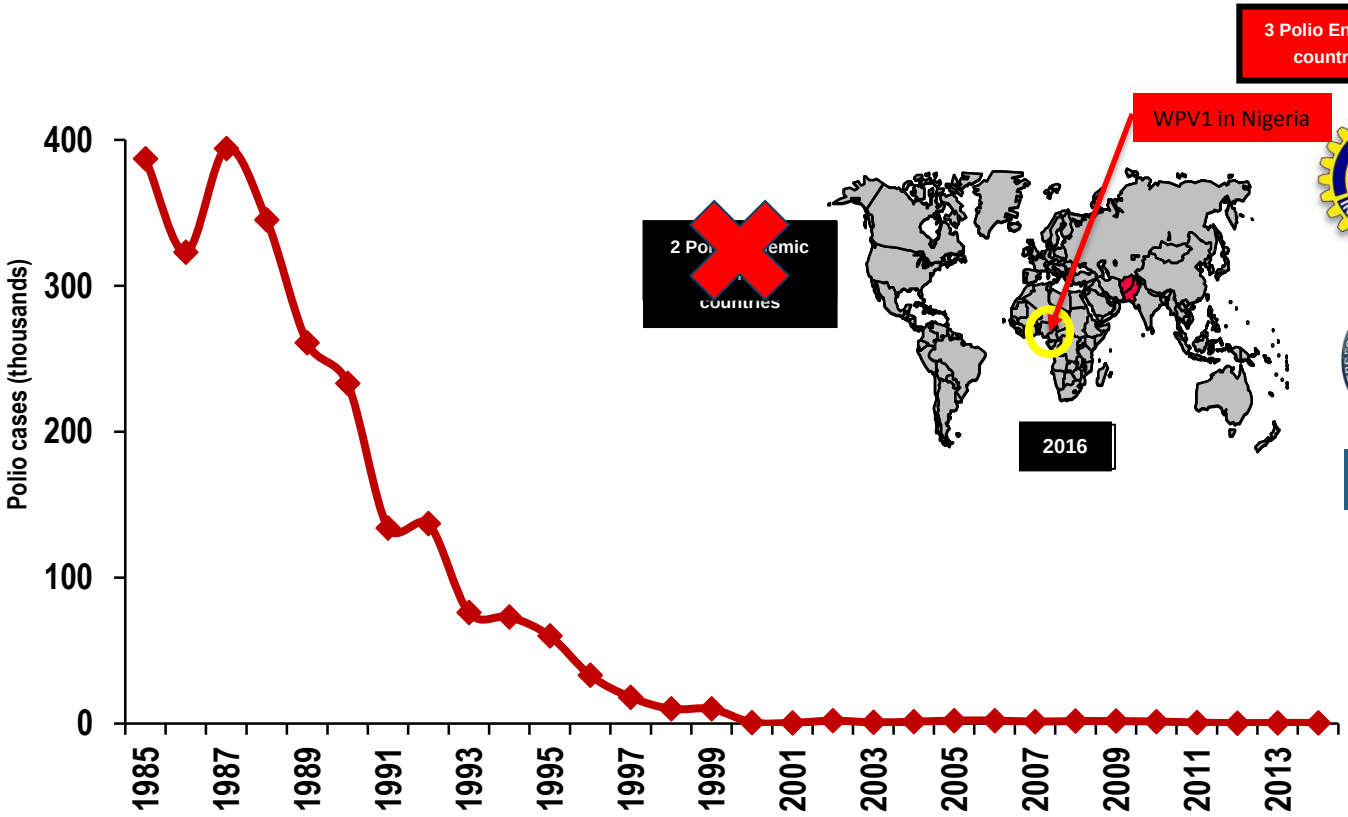
Polio vaccination programs – towards polio eradication

- 1974: World Health Organization starts the EPI program (Expanded Program on Immunization)
- Poliovaccine included in the program
- National immunization days (NIDs)
- Ambition to stop transmission via polio vaccination worldwide

  = go for eradication!

Only after eradication can polio vaccination be stopped!

Progress towards Wild Poliovirus Eradication: 1988 - 2017



The Global Polio Eradication Initiative (GPEI)

- 2013: GPEI launched the Polio Eradication and Endgame Strategic Plan with the objective to end all polio disease globally
- Wild-type poliovirus 2 eradicated, but type 2 Sabin virus causative agent of cVDPV (circulating vaccine-derived poliovirus) outbreaks and ~ 30% of VAPP (vaccine-associated paralytic polio)
  - SAGE: withdrawal of OPV2 component of tOPV from routine use
  - reduced risk of VAPP and introduction of new type 2 VDPVs, but events or outbreaks may continue for a while

Post swith cVDPV2 outbreaks reported from all sources (AFP, Contacts, ENV, others)

Six cVDPV2 outbreaks reported after the switch, from 4 countries

Analysis of sequencing data by using assumption of 1%nt change/year at a uniform rate, it seems that all outbreaks except Maniema (DRC) possibly may have seeded before the switch

Number of outbreaks reported in first 12 months after switch are within the expected range as projected before the switch

Slide courtesy: WHO/GPEI; SAGE WG 2017 presentations

- Using mOPV2 in outbreak situation of VDPV2: fighting fire with fire
- Why not IPV?
  - Shortage of IPV vaccines
  - immunogenicity not sufficient

Development of novel OPV2 vaccine with an improved benefit/risk profile

Development of genetically stable OPV2 vaccine

- Criteria
  - confer humoral and mucosal immunity provided by Sabin 2 vaccine, but with better genetic stability

- Development of two novel candidate serotype 2 poliovirus vaccines
  - monovalent
  - oral
  - live attenuated
  - genetically engineered !!!

→ Genetically modified organisms!

Requirements to test nOPV2 vaccines

- To be tested in a way that **no** body fluids or stools of vaccinees enters the environment!

- To be tested in fully **contained** situation!

- Preferably in IPV-primed volunteers
  - Low or no intestinal immunity
  - Replication of novel OPV2 vaccine would be challenged in OPV-primed subjects and have impact on shedding

Study Design

- Single center
- First in human (Phase 1)
- Blinded
- 30 adults (18-50 yr), previously IPV-primed
- In quarantaine – 28 days (shedding)

- **To avoid risk of transmission/contamination** between subjects receiving different candidate vaccines:
  - the study will be conducted with each candidate vaccine **sequentially**.
  - The **first 15 subjects** will all be enrolled in the same Group and receive the same nOPV2 candidate and
  - the **next 15 subjects** will be enrolled in the second Group and receive the corresponding nOPV2 candidate.
- Enrollment of Group 2 to start after departure of Group 1 and full decontamination of the facility

With the support of the Bill&Melinda Gates Foundation

Contained facility

Needed steps and procedures

- In parallel **with NRA and EC submission**
- As it is a temporary infrastructure for the period of 2 years, **planning permission received from the municipality** to build the contained unit on the Parking of the Antwerp University Hospital:

Needed steps and procedures: Biosafety permission

- **Biosafety permission** – now called environmental permission to be received from the local municipality
- This dossier needs to be submitted at the moment of the study start, because of contained conditions, but we understood that the Regional Authorities would like to review the dossier before submission (WIV)
  - prepared by medical team and by both **bio-safety coordinators** of the hospital and the University.

Needed steps and procedures

- Plans and facility need approval by the **fire brigade** and **local police department** (‘terrorist target’)
- Location **close to the roads**: easy for waste managment
- **Tanks foreseen** at the contained unit for stool collection, dirty water collection (toilets, showers, wash basins, ..)
  - **Waste water and stools will be de-contaminated** (by using Chlorine Dioxide) before further processing in ordinary sewage
- Contained **unit will be de-contamined** after use by the first cohort of volunteers by application of Chlorine Dioxide
- Location **close to hospital in case of emergency** in the quarantine unit – training of personnel/SOP/special emergency vehicle ready for use (decontamination of vehicle lasts 3 to 4 hours)

April 3rd 2017

Start vaccination of cohort 1: May 22nd 2017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POLIOPOLIS

Biosafety permission

- Description of the activity, incl safety measures taken
- Description biological material, incl biosafety level
- Health and environmental risk analysis
  - Risk analysis activity
  - Description facility
  - Safety measures incl. personal safety measures
  - Gowning procedures
  - Waste management and decontamination procedures
- Accident prevention and contingency plans
- SOPs

Waste water treatment

Chemical inactivation 1:ClO2

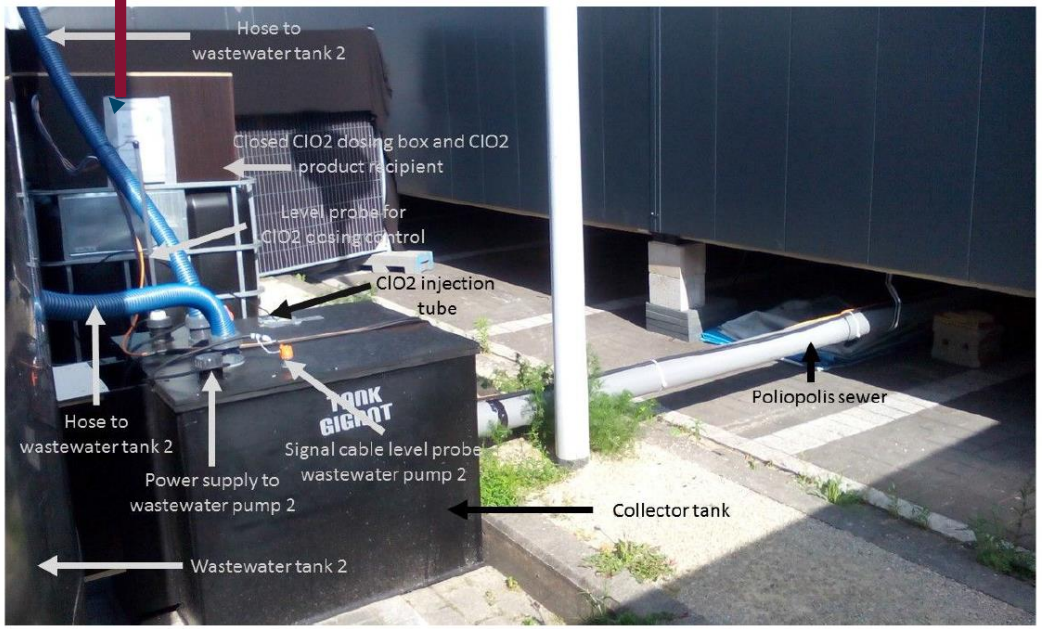
- Continuous ClO2 administration via dosing pump
- Log5 killing of poliovirus obtained with 5 mg/L ClO2: we used 90 mg/L
  - CLO2 smaller than all microorganisms with mol size of 0.124 nm
  - No post-decon residues (equipment can be left inside facility)
  - Accurate measurement in real time from multiple points

Chemical inactivation 2: NaOH

- After chemical inactivation 1 and prior to discharge of waste water, addition of NaOH to increase pH
  - Inactivation of potential residual vaccine virus

Set-up for waste water treatment – daily visual control and permanent monitoring

Fig. 1: Iwaki dosing pump and digital timer, situated in a locked box on the liquid chlorine dioxide product recipient.



Decontamination of the “contained” facility


Sealing van alle openingen


Sealing van alle openingen, incl. plaat waarlangs gas wordt toegediend in de contained unit


Alle gasleidingen gebruikt voor decon volledige unit

Plaatsing van bio-indicatoren


Plaatsing ventilatoren en luchtbevochtigers


Plaatsing ventilatoren en luchtbevochtigers


Plaatsing leidingen voor gastoevoer in alle ruimtes in de contained unit

Preparing the facility for “optimal” decontamination

Openzetten van alle kasten, schuiven, koelkasten, freezers, … om goede toegang van ClO2 gas te verzekeren

Verzamelen alle absorberend materiaal (linnen, matrassen (van elkaar gescheiden via lattoflex voor maximale toegang ClO2) en RMA vaten in fitness en leefruimte

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Starting the decontamination procedure


Flessen voor ClO2 toevoer (3 set-ups gebruikt

ClO2 over koolfilter voor aanbreng in de contained unit


Continue monitoring ClO2 concentratie in contained unit

Similar to all other decontamination methods, CD gas decontamination is a multi-step process. The 5 steps of the CD gas process are:

1. Precondition: Raising of relative humidity (RH) levels between 60-75%.
2. Condition: Hold time once relative humidity set point has been reached.
3. Charge: Generation and delivery of chlorine dioxide gas.
4. Exposure: Hold time once gas concentration set point has been reached. The exposure step is controlled through an “area under the curve” accrual of gas concentration until a target dosage has been met.
5. Aeration: Removal of chlorine dioxide gas.

Some challenges

- Conduct a phase 1 vaccine trial in the best conditions according to GCP-ICH & quarantaine conditions

- Keep the volunteers happy and busy
  - Daily medical visits
  - Medical & lab permanence / back up 7/24 - week/ WE
  - Twice a week psychological consultation
  - Permanent presence of a coordinator
    - Coordination of the social activities (BBQ, beer tasting, fitness,…)
    - Intervention when needed (attitude, verbal agression, …)
    - Contact between all teams
    - Organizing the work inside (cleaning, washing, cooking, …)

- FAMHP inspection during study
  - Safety measures (gowning,…)
  - IPV vaccination

“Support” team

- Technical department
- Pharmacist
- Lab team
- Monitoring (distance monitoring of scanned docs)
- Event manager
  - Food delivery every 2 or 3 days
  - Mistery calls/skype sessions
  - BBQ activity
  - Beer tasting
  - Poker evening
  - …
- Decontamination team

Thank you!!!

Any questions?????

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