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toute une vie en bonne santé

Lessons learned from the safety evaluation of novel live attenuated serotype 2 oral poliovirus vaccines candidates under contained use *vs.* deliberate release regulatory framework

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Poliomyelitis (polio)

- A highly infectious viral disease mainly affecting young children
- Non-enveloped enteroviruses with single positive RNA genome (*Picornaviridae* family)
- 3 serotypes (1, 2 and 3)
- Transmission predominantly by faecal-oral route, in developed countries by respiratory route
- Virus multiplies in the intestine from where it can invade the CNS and cause paralysis
- Poliovirus infections mostly asymptomatic; <1% of all polio infections in children result in poliomyelitis
- Death-to-case ratio: 2-5% among children; 15-30% for adults

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Polio vaccines

Inactivated polio vaccine (IPV) - Salk strains

- Protection against poliovirus types 1, 2 and 3
- Administration by injection
- Prevents paralysis, but no prevention of infection of the gut
- No risk of vaccine associated poliomyelitis

Oral polio vaccines (OPV) - Sabin strains

- Monovalent oral polio vaccines (mOPV1, mOPV2 and mOPV3)
- Bivalent oral polio vaccine (bOPV) => protects against poliovirus types 1 and 3
- Trivalent oral polio vaccine (tOPV) => protects against poliovirus types 1, 2 and 3
- Oral administration; Very low cost
- Induce gut immunity => Limit replication and excretion (shedding in stool) => Provide potential barrier to spread from person to person
- Vaccine of choice for the global eradication programme
- Sabin strains can spread when OPV vaccine coverage is low => Genetic drift, loss of attenuation characteristics => Outbreaks of pathogenic **cVDPV** (circulating vaccine-derived poliovirus)

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Polio eradication

Global Poliomyelitis Eradication Initiative (GPEI - WHO)

- http://www.polioeradication.org
- Launched in 1988, start of intensive vaccination campaigns
- Poliomyelitis cases reduced by 99%
- **WPV2** declared eradicated in 2015; **WPV3** last reported in November 2012; Overall reduction in **WPV1** cases since 2013
- European region officially declared **polio-free** since 2002
- **Polio Endgame Strategy 2019-2023**
  => Interrupt transmission of all wild poliovirus (WPV)
  => Stop all circulating cVDPV and eliminate the risk of emergence of future VDPVs
  => Ensure potential sources of poliovirus are properly contained or removed (surveys and inventories, certification processes, guidance…)
- **GAPIII**: WHO global action plan to minimize poliovirus facility-associated risk after type-specific eradication of WPV and sequential cessation of oral polio vaccine use

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Polio eradication

Development of novel genetically stable OPV2 vaccine

- 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 (WHO Strategic Advisory Group of Experts): Withdrawal of OPV2 component of tOPV from routine use (2016)
- Using mOPV2 in outbreak situation of cVDPV2: fighting fire with fire
- Why not IPV? => Shortage of IPV vaccines; Does not provide mucosal immunity and does not prevent shedding of the virus

=> Development of two novel candidate serotype 2 poliovirus vaccines (CDC's polio laboratory, National Institute for Biological Standards and Control - UK, University of California - San Francisco)
=> Monovalent; Oral; Live attenuated; GMOs class of risk 1
=> Confer humoral and mucosal immunity provided by Sabin 2 vaccine, but with improved genetic stability

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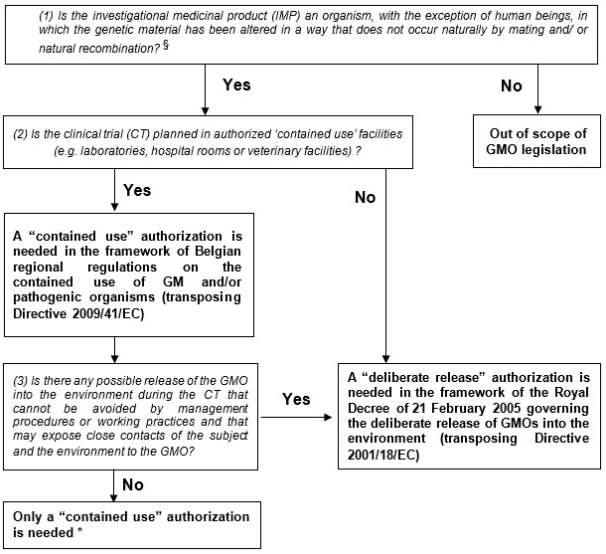
Clinical trials with GMOs in Belgium



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Clinical trials with nOPV2 vaccine candidates

2017 - Contained use - Why and how?

- With the global withdrawal of OPV type-2 vaccines in May, 2016, and GAPIII containment requirements, the Belgian CA agreed for an initial study (First in-human testing - Phase 1) performed in **fully vaccinated adults residing in a contained environment**, to avoid potential environmental contamination
- Strong support from WHO; Funded by the Bill & Melinda Gates Foundation
- First new oral polio vaccines administered to humans since the 1960s
- ***Van Damme et al. (2019).*** *The Lancet 394(10193), p.148-158*
- **Fully contained, purpose-built facility** => **POLIOPOLIS** (temporary infrastructure for a period of 2 years, build on the Parking of the Antwerp University Hospital)
- Containment: **BSL-1** with sas
- **Tanks** at the contained unit for stool collection, dirty water collection (toilets, showers, wash basins, ..)
- **Waste water and stools decontaminated** (Chlorine Dioxide) before further processing in ordinary sewage
- Contained **unit decontamined** (Chlorine Dioxide) after use by the first cohort of volunteers and after completion of the second trial

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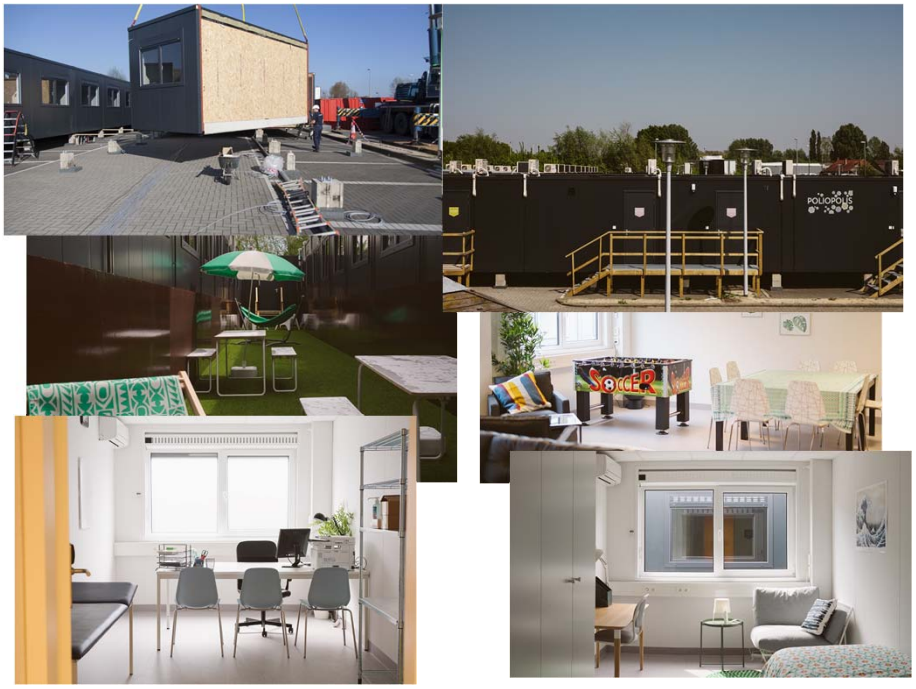

(https://www.uantwerpen.be/nl/onderzoeksgroep/cev/vaccinstudies/studies/uantwerpen-helpt-polio-wereld-uit/)

Clinical trials with nOPV2 vaccine candidates

2017 – Contained use - Inclusion criteria

- 2 x 15 adults (18-50 yr), **previously IPV-primed** (Dutch) => Low or no intestinal immunity; Replication of novel OPV2 vaccine would be challenged in OPV-primed subjects and have impact on shedding
- Willingness to adhere to all prohibitions and restrictions necessary for full containment for the study duration
- **No intended travel** to polio-endemic countries or the Netherlands (because of low vaccination coverage in the so-called "Bible belt")
- No professional food handling activity or household or professional contact with immunosuppressed individuals or people without a full poliovirus vaccination
- Participants in **quarantaine for 28 days**
- If shedding persisted after quarantaine, participants allowed to leave but requested to remain in Belgium (home or hotel) and to continue providing stool samples in an ambulatory manner by use of provided chemical toilets and mandatory containers for infectious waste disposal

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Clinical trial with nOPV2 vaccine candidates

2017 – Contained use - Outcome

- Both vaccine candidates are safe and immunogenic in adults
- Evidence of increased genetic stability of the viral genome (deep sequencing), with a lower risk of reversion to neurovirulence relative to Sabin OPV2
- No nasopharyngeal shedding was observed (but low number of participants to draw clear conclusions)

2017 – Contained use - Challenges

- Keep the volunteers happy and busy
- Delay of 4-5 days before stool samples results are obtained (from CDC)
- **Shedding in stool !!!**

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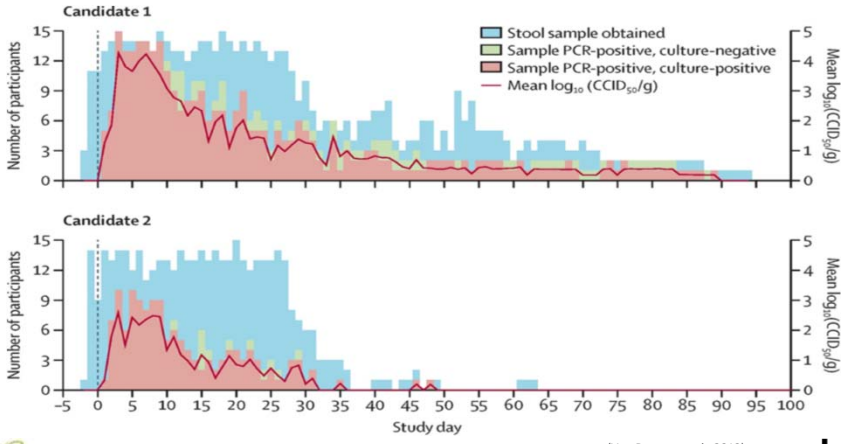
Clinical trial with nOPV2 vaccine candidates

2017 - Contained use - Shedding



(Van Damme et al., 2019)

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Clinical trial with nOPV2 vaccine candidates

2017 – Contained use - Challenges – Shedding !!!

- **Longer than the containment period** in 47% of participants receiving vaccine candidate 1 and 27% participants receiving candidate 2
- **Last day of shedding** = day 89 in a participant receiving candidate 1 and day 48 in a participant receiving candidate 2
- **Resumed in 20% of participants** for a further 3-6 days
- A few non-shedders went back to NL but showed again shedding after a few days
- A few participants were allowed to go back home in the NL while shedding was still occuring
  => Avoid the tensions associated with duration of study, uncertainty about how long-term measures are really needed, pressure from home or employer, the fact that non-shedders who have left for NL are shedding back and still stay in NL
  => Volunteers can always decide to leave with or without informing the sponsor (risk of "loosing" them)
- Home address in Belgium gives no guarantee => Some participants travelled to the NL to visit family
- Delay to get PCR results from CDC also a difficulty

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Clinical trial with nOPV2 vaccine candidates

2018 – Deliberate release - Why and how?

- May 2018 : Request for performing a larger study => No physical containment measures but extensive plan for monitoring of stool samples and follow-up
- Partly based on the experienced learned from the CT under contained use (not all results available)
- June 2018 - CAG (WHO Containment Advisory Group) => *Sufficient information has been provided to conclude that both nOPV2 candidate vaccines could be considered for use, according to the specific terms of usage already provided, outside the containment requirements of GAPIII (for clinical trials, stockpile, outbreak response, production, quality control testing)*
- Big expectations of WHO towards nOPV2. R&D on nOPV2 is a top priority
  (WHO planning to file it on the Emergency Use Listing, and deploy the use of it by end 2020 for outbreak immunization. WHO trying to find producers willing to finish and fill nOPV2)
- Polio eradication is difficult (impossible?) to achieve (even more obvious today)
  => more mOPV2 than expected could be needed
  => nOPV2 strains = Safer alternative to mOPV2 vaccine for outbreak response

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Clinical trial with nOPV2 vaccine candidates

2018 – Deliberate release - Why and how?

- Phase 2, placebo-controlled, multicenter study
- Same GMOs as for phase 1 study
- 332 healthy volunteers, aged 15 to 50 years, of which 200 have been vaccinated with OPV and 132 with IPV
- Same exclusion criteria as for phase 1 study (no intended travel to polio-endemic countries or the Netherlands; no professional food handling activity or household or professional contact with immunosuppressed individuals or people without a full poliovirus vaccination…)
  + Code of conduct
- No quarantaine; Volunteers can leave the clinical setting after administration
- A participant will be considered to have completed the study if he/she has completed all study related procedures 42 days after the last study vaccination and shedding is PCR negative on three consecutive stool samples
- October 2018: The trial is authorized by the Belgian CA

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Clinical trial with nOPV2 vaccine candidates

2018 – Deliberate release – Risk assessment

- Belgium is considered as the potential deliberate release area
- Increased genetic and phenotypic stability of the nOPV2 candidate vaccines compared to Sabin OPV2 strain (deep sequencing results on shed virus samples)
- Volunteers will shed the GMOs (via feces) for several weeks.
  But no health effects anticipated for unintentionally exposed individuals
- Consequences of an unintentional transmission of a genetic variant of a nOPV2 candidate vaccine to an individual is likely be less hazardous than an unintentional transmission of genetic variants of the recipient Sabin OPV2 strain
- No evidence for circulation of type C enteroviruses in the Belgian population that could recombine with candidate nOPV2 vaccines in humans if co-infection occurs
- On the basis of the characteristics of the nOPV2 candidates and the proposed conditions of release (including proposed inclusion/exclusion criteria and instructions for study subjects), **risks, if any, are considered negligible**

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Clinical trial with nOPV2 vaccine candidates

2018 – Deliberate release – Risk management

- A RT-rtPCR method to detect and differentiate between Sabin2 and the two nOPV2 candidate vaccines is available
- Recommendation from CAG (2018)
  => Countries performing trials with nOPV2 should consider the implementation of environmental monitoring for polioviruses to monitor duration and amount of shedding around the trial sites, around trial subjects continuing to shed virus after the end of the trial period and monitoring of their close and family contacts. These should take into consideration the poliovirus reproductive rate [which depends on factors such as population density, sanitation and hygiene conditions (population, environment, sewage systems and treatment)] and relevant factors (e.g., study population, number of subjects, etc)
  => No action in Belgium

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Clinical trial with nOPV2 vaccine candidates

2018 – Deliberate release – Concerns

- During evaluation, **concerns from CA's of other Member States**…
  - NL and DE => Using the EU system of exchange of information established under Article 11 of Directive 2001/18/EC (based on the SNIF)
  - NL => Same comments in the frame of the public consultation foreseen in the Belgian legislation
- Need to address more in depth the likelihood that the GM vaccine virus would spread to susceptible populations in other countries and the possible associated (delayed) effects
- How measures and/or exclusion criteria will be implemented or endorsed in view of minimizing the transboundary movement of volunteers and of the nOPV2 candidate vaccines?

Specific measures addressing these concerns:
=> **Residence in Belgium** (incl. for Dutch people)
=> **No travel** to the Netherlands in particular in the "Bible belt" zone, until 3 months after 1st dose administration
=> **No contact** with family members living in areas with low vaccination coverage

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Clinical trial with nOPV2 vaccine candidates

2018 – Deliberate release – Concerns – General considerations

- ERA can be extrapolated to receiving environments in neighbouring countries. No explicit distinction between vulnerable groups in Belgium or other neighbouring countries
- As with any other clinical trial with ambulatory volunteers, a transboundary movement of the product tested (in this case the GMO) cannot be excluded => in terms of risk for the environment or human health, the proposed measures are proportionate and adequate in the context of the intended trial
- Potential consequences of releasing nOPV vaccine candidates or their genetic variants will at worst be comparable to the consequences associated to the historical use of Sabin OPV2 in routine vaccine campaigns in European countries (until 2001 in Belgium) and a Phase 4 study with OPV-vaccinated adults conducted in Belgium late 2015 (EudraCT 2015-003325-33)
- No report of adverse consequences for the environment or human population at large associated to the use of Sabin OPV2 and its transmission in Belgium or its neighbouring countries over the last decades

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Clinical trial with nOPV2 vaccine candidates

Lessons learned

- Risk Management more challenging than Risk Assessment
- Full physical containment impossible to achieve and to warrant in cases where shedding is anticipated or known to occur
- Long-period quarantaine raises ethical questions
  + Participants may leave a clinical trial at anytime
- DR regulatory framework is the only one allowing an in-depth assessment of the risk for the environment and the general population (not CU framework)
- Participants may potentially travel across EU => How to manage information to/from other MS ?
  - Is SNIF sufficient under DR ?
  - What about Member States using the CU framework only ?
  - What about post-release information ?

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