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Poliopolis - Pushing boundaries of scientific innovation for disease eradication

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Abstract

Global polio eradication appears to be within reach with endemic wild poliovirus circulation limited to only three countries in the world. To complete and sustain eradication of all types of polioviruses, cessation of oral polio vaccine (OPV) use is considered necessary to mitigate risks of vaccine-derived poliovirus circulation and generation of vaccine-associated paralytic poliomyelitis. As a first step in this direction, following the global withdrawal of type 2 Sabin poliovirus from routine immunisation in May 2016, the attenuated live form of this vaccine strain is restricted for use only in outbreak response. Its handling is guided by the strict containment (GAPIII) provisions and controlled by the World Health Organization.

Under such unprecedented changes in global immunisation policies, development and testing of novel type 2 poliovirus vaccines face unique challenges. We describe the creation of a novel purpose-built containment facility, Poliopolis, and its use to study the humoral immunogenicity, excretion dynamics and reversion characteristics of two novel serotype 2 OPV candidates in healthy adult volunteers, which may be a model for future endeavours in vaccine development for emergency use.

SUMMARY

The Poliopolis experience is the first of its kind, established in an unprecedented manner under the WHO containment recommendations (GAPIII) and with severe time constraints to implement an operationally challenging clinical trial with vaccine candidates that cannot yet be used under deliberate release conditions. The successful planning and implementation of this study should

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not only pave the way for rapid clinical development of the safer OPV formulations but should also provide a planning and contextual framework for future studies under containment to support global health initiatives such as those funded by CEPI in pandemic preparedness planning.

INTRODUCTION

Polio is very close to becoming the second vaccine-preventable disease ever to be eradicated. Three countries, Nigeria, Pakistan and Afghanistan remain endemic for transmission of one of the three wild polioviruses. In 2015 wild type 2 polio was certified eradicated with the last naturally-occurring case reported in 1999. Wild type 3 polio transmission has also likely been interrupted with no case or environmental isolation since 2012.[1,2] Although the Sabin live attenuated trivalent oral poliovirus vaccine (OPV) has played a major role in interrupting polio transmission globally, in rare circumstances it can revert to neurovirulence resulting in vaccine-associated paralytic poliomyelitis (VAPP) in vaccinees or their close contacts.[3] In settings of low population immunity due to poor immunisation coverage, excreted OPV strains can also acquire neurovirulence and transmissibility, leading to circulating vaccine-derived polioviruses (cVDPV). The risk of cVDPV spread in polio-free countries has been illustrated in the past two decades, with outbreaks reported from the Caribbean, Asia and Africa and most recently, in situations of social breakdown such as Ukraine, Syria and Iraq, and Nigeria and Somalia.[2,4–12] A particular concern is the transmission of polioviruses including cVDPV from such regions into neighbouring countries and beyond.[13,14]

The need for novel polio vaccines

Polio eradication will not be complete unless the risks of spread and transmission from all types of polioviruses, including VDPV, are adequately mitigated. The endgame of polio eradication, therefore, has complex vaccine choices. Trivalent inactivated polio vaccine (IPV) induces excellent humoral immunogenicity and thereby prevents paralysis, but its impact on intestinal immunity – and as such on transmission – is limited compared with OPV.[15–17] Therefore, in settings of poor sanitation and hygiene where the faecal-oral route of transmission predominates, OPV is a more effective vaccine to interrupt person-to-person transmission, and thus has typically been the vaccine-of-choice for outbreak response.

However, the risks of VAPP and VDPV from OPV, although rare, are an important consideration in the context of achieving and sustaining complete eradication of polio. With the global cessation of all Sabin type 2 vaccine use, intestinal immunity to type 2 is also on the decline. Under these circumstances, in the event of a vaccine-derived type 2 polio outbreak, the use of the current stockpiled monovalent OPV2 is the only option for outbreak control but brings with it its own risk of generating new type 2 cVDPVs. To minimise this risk and to ensure completeness of eradication, a scientific consortium supported by the Bill & Melinda Gates Foundation in coordination with vaccine developers and global agencies (WHO, PATH) has developed novel OPV vaccine strains proven in pre-clinical models to be less transmissible and genetically more stable than the Sabin OPV, and so less likely to revert to neurovirulent strains that are shed in vaccinees' stools.

Over the past few years, two novel oral polio vaccine type 2 (nOPV2) candidates based on attenuated serotype 2 polioviruses derived from a modified Sabin 2 infectious cDNA clone have been designed, engineered, produced and tested in a series of preclinical studies.[18,19] The intent is to stockpile such vaccines for emergency use if and when needed for outbreak response.[20,21]

Given the current unique situation of global certification of wild type 2 poliovirus eradication, the subsequent global cessation of all elective use of OPV containing type 2 from May 2016, and the recommendations of the WHO Global Action Plan to minimise poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use (GAPIII),[22] studies with new live polio vaccines require containment measures.[23] In the current context of multiple and increasing type-2 cVDPV outbreaks taking place in different parts of the world, this paper summarises the implementation of a unique project that allowed the first-in-human phase 1 clinical study (reported in the accompanying paper[24]) with two attenuated nOPV2 candidates to evaluate these novel vaccines in healthy adult volunteers under an unprecedented setting of containment, extensive monitoring and time pressure.[24]

The rationale for containment

The objectives of this first-in-human phase 1, blinded, single-centre trial were the assessment of the safety and the immunogenicity of the two nOPV2 candidates in healthy adult volunteers. This also included extensive assessment of viral shedding in stool samples and testing of shed virus for genetic stability and neurovirulence following oral receipt of one of the two nOPV2 candidates. In addition to containment recommendations (GAPIII), which currently apply to all type 2 polioviruses, the novelty of the genetically modified nOPV2 viruses necessitated performing the study in a fully contained environment with maximal effort to avoid any accidental release into the environment by ensuring that all biological samples that could potentially contain vaccine virus were captured and contained for subsequent decontamination.

Previous quarantine and human challenge studies reported isolation of clinical trial volunteers for 9 to 14 days.[25–27] In view of the nature of orally administered polioviruses and available shedding data a longer quarantine period of 28 days was recommended for the study on nOPV2 candidates. Shedding data reported in a study in Panama of previously IPV-vaccinated children challenged with licensed OPV2 vaccine indicates that one week after challenge 78.3% experience shedding with a median faecal titre of 4.45 log $CCID_{50}$ (50% of the cell culture infectious dose), which dropped to 46% and 2.75 log $CCID_{50}$, respectively after 3 weeks.[16] Across studies, 63–100% of IPV-vaccinated children demonstrate faecal excretion at 7–10 days.[17,28,29] One recent study in 144 IPV-primed adults challenged with OPV1, showed that 98% were infected, at a peak stool titre of $10^{6.0}$ $CCID_{50}$/gram and shed the challenge virus for a mean of 13 days.[26] Thus, a novel purpose-built facility was created for sufficient numbers of study volunteers to be accommodated in isolation from the external environment for a period of 28 days, a unique situation for a vaccine trial.

Planning

The Centre for the Evaluation of Vaccination (University of Antwerp, Belgium) was contacted by the Bill & Melinda Gates Foundation in December 2016 with a request to perform a phase 1 study with the novel OPV2 candidates. To ensure the vaccine strains did not get into the environment through excretion of virus in stools from the vaccinated volunteers and potential manual transmission, the capture of all excreted fluids from the vaccinated volunteers and standard collection and disposal of clothing and all other materials handled by them, e.g. towels, disposable eating utensils, uneaten food, and all waste would have to be strictly enforced. As standard phase 1 facilities are not designed to meet these specific requirements and after having screened alternative containment facilities like isolated holiday accommodations, unoccupied buildings (like un-used or empty closed centres for asylum seekers), together with the specificity of the study and the biosafety requirements, it was decided that the only option was to construct a new purpose-built quarantine facility. A geographical requirement was that the facility had to be located close to a hospital in case of any medical emergency, and in view of the participation of the personnel of the Centre for the Evaluation of Vaccination, the Antwerp University Hospital was readily identified as the site-of-choice. Acknowledging that the facility would not be a permanent structure, the original intention being for a duration of two years, it was agreed that the University of Antwerp would construct a temporary self-contained unit. The transitory nature of the facility immediately suggested building it using purpose-built modular “containers”.

As soon as conceptual plans for the construction were available the interactions with technical support services, biosafety experts and the local municipality were initiated. Other expert groups and authorities including the local police and fire brigade became involved later in the planning. In the subsequent five months the environmental and building applications were submitted and approved, approvals from the Ethics Committee and Belgian Regulatory authorities were obtained, and an intervention dossier for the fire brigade was finalised. One of the key challenges was to find technical and balanced solutions to the diverse and sometimes conflicting concerns of these groups, e.g. easy access for the fire brigade while the police wanted limited access to ensure external safety and easy control of the area (particularly with the externally located effluent containment tanks). Further considerations were the requirements for the “contained use” of genetically modified organisms[30] and the stringent restrictions for OPV2, when developing entry and exit procedures, emergency plans, and waste and effluent treatment processes. The close collaboration that developed between the clinical trial team, the facility manager and the respective university and hospital (bio)safety officers to find workable technical solutions and procedures also formed the basis for submitting the necessary applications and obtaining the approvals from the competent authorities (including the specific regional biosafety notification for a contained use of a GMO, reference SBB 219 2017/0209K).

Building the infrastructure, “Poliopolis”

Due to the proactive planning and early off-site manufacture of the pre-fabricated modules by the company who designed them, the facility, now named Poliopolis, was constructed over the course of three days in April 2017 and finalised within one month. This was

exactly five months after the decision was taken to set up this study, during which period all necessary local and national building and scientific approvals were obtained. The final construction was a one storey building composed of 66 specially designed and constructed linked modules that housed all facilities in a contained environment (Figure 1). Facilities included private, individual bedrooms for a maximum of 17 volunteers, a common kitchen and dining room, a recreation room with TV and library, a fitness room with gymnasium equipment, shower rooms and toilets (including separate toilets for study staff), and a laboratory facility for on-site testing and sample preparation. There were also offices for the clinical staff and the study psychologist to examine and interview participants and collect samples. In addition there was a room for decontamination of materials, and four separate entrances and exits (Figure 2) – namely, an entrance for staff where they put on protective clothing (overall, overshoes and gloves) and a separate exit for removal of said clothing - the two rooms being connected by pass-through lockers where their outdoor clothing and personal belongings, laptops or cell phones were stored during their visit to the facility. The staff exit room also had a shower facility. In case clinical staff had been contaminated, e.g. disruption of the overshoes, they had to take a shower of at least five minutes and redress with clean clothes that were kept available in that room. When the volunteers left the facility after 28 days, a similar procedure was followed for decontamination.

There was a separate entrance for receipt of goods (food, laboratory supplies, etc.) and an exit for the materials and goods leaving the facility after external decontamination (e.g. waste materials for incineration, stool and other samples from the participants). These were the only means of entry into the facility, although fire exits that could only be unlocked from the inside were also present. All entrances and exits were linked with alarm systems to ensure no unauthorized access in or out of the facility once the trial was underway. These entrances and exits worked as “air-locks”, when the outside door was opened with a magnetic key, the inner door could not be opened until the outside door was closed again. This prevented anyone from entering or exiting the facility without being identified or dressed as required.

The kitchen was equipped with one-way glass windows allowing volunteers to look outside but preventing the public from seeing into the facility. Individual bedrooms and clinical offices had windows onto a central atrium which was open to the sky. This area was set up with garden furniture to allow participants to be outside, together with a barbecue facility for social events during the trial. Power and water were supplied directly from the hospital building, while the capture and containment of all waste meant that no sewage services were necessary.

All study personnel involved in direct interaction with the volunteers had to avoid contamination or accidental release of study vaccines or samples into the environment through use of body coverings (gowning), but not masks or eye protection. Since the risk of spread of vaccine virus through aerosols or droplets in the study population was considered negligible, air filtration of the facility and masking of the study personnel were not considered necessary, although masking and eye protection were recommended during medical visits when oro-pharyngeal swabs were taken.

The importance of wearing a gown was implicit to avoid any potential release of vaccine virus particles into the external environment on clothing of personnel leaving the contained facility, so training of personnel was critical to success. Hence, competency of gowning/de-gowning procedures was clearly documented, and periodic gowning certification conducted to confirm personnel maintained consistent practices. As with study personnel, all people who entered the facility were administered an IPV booster dose at least 14 days before study start and were trained in the gowning/de-gowning procedure by a qualified person.

A dedicated emergency team and vehicle was on constant stand-by although never used to provide transport between the facility and the emergency room of the university hospital in the case of any medical emergency. As decontamination of the vehicle following transport of a vaccinated volunteer would take 3–4 hours, this precluded use of a standard emergency vehicle.

External decontamination

A special decontamination team was established and trained for a rapid, effective decontamination response according to a dedicated standard operating procedure (SOP) describing an emergency response plan, including an incident command system for emergency responses.

As noted, all waste water was collected for subsequent decontamination, which included not only water from toilets, but also from showers, wash basins in bathrooms and kitchens, and clothes-washing facilities. Two double-walled 20,000 L capacity tanks were set up the outside of the facility (see Figure 3) for collection and storage of waste water, for subsequent collection and decontamination by a specialized company.

A two-pronged approach was chosen to ensure adequate disinfection of the collected waste water, initially using chlorine dioxide treatment followed by a pH increase through addition of sodium hydroxide prior to discharge in a municipal waste water treatment plant. Chlorine dioxide was selected as disinfectant based on several scientific studies showing high efficacy of the active substance in killing poliovirus in waste water.[31–33] One of these studies indicated that approximately 5 $\log_{10}$ killing (i.e. > 99.999% reduction) was reached with a dose of 5 mg/L.[33] To ensure equivalent or more disinfection efficacy, a dose of 90 mg/L was used for decontamination of the waste water.

For decontamination of the facility, chlorine dioxide gas was used. In addition to its high efficacy in killing poliovirus, chlorine dioxide gas has the added benefit of being smaller than all microorganisms, with a molecular size of 0·124 nm (1·24 × 107 mm), so no organism can be concealed from the gas. Chlorine dioxide gas can be accurately measured in real time from multiple points within the area being decontaminated, guaranteeing that the correct dosage needed for an effective decontamination is being met before the decontamination is deemed complete and aeration is started. The chlorine dioxide product used was Diox Forte 0·75%, which contains 7·5 g/L chlorine dioxide and is registered as a sterilant capable of eliminating all viruses, bacteria, fungi, and spores. This product, amongst others, is approved for water disinfection in Belgium. Increasing the pH added another disinfection step to prevent contamination by contact with the waste water outside

the contained facility. The WHO report on the thermostability of vaccines reports a strong decrease in the stability of OPV as the pH increases above 8.[34]

Discharge of the decontaminated waste water into a municipal waste water treatment plant introduced another geographic requirement for the facility – to be located near a road that allowed easy access to the containment tanks designed to capture all the waste water for transport to a specialized decontamination facility.

In addition to decontamination of the waste water, tailored procedures needed to be established for the decontamination of the entire facility upon departure of all volunteers, intermittent decontamination of waste containers and decontamination of the belongings of the volunteers upon departure in a dedicated room within the facility. Decontamination with chlorine dioxide was again chosen for its characteristics as described above, but also as it leaves no post-decontamination residue, so all equipment (including sensitive electronics) could be left inside the facility during a decontamination cycle without risk of corrosion or other damage.

Quality control and assessment

Operating within a contained environment necessitates preparations to prevent circumstances that might result in occupational injury, ill health, or adverse environmental impact. In order to anticipate and prevent such circumstances, a structured approach was needed to identify hazards or forms of public health concern. Extensive health and environmental risk assessments were performed before the start of the study to determine the appropriate protective measures needed. Based on this assessment, SOPs were written including information about the hazards identified and how these can be mitigated. Personal safety measures, gowning procedures, waste management and decontamination procedures, accident prevention and contingency plans were among the most important potential hazards identified. In addition, a comprehensive communication plan was drafted with the support of the communication team of the University of Antwerp. Clearly, dealing with any incidents of potential virus escape via accidental release or need for emergency medical care of a vaccinated volunteer were among the most important risks to address and necessitated an emergency preparedness plan.

A specific concern of a clinical trial in a quarantine situation is that one must be prepared to adjust and adapt in case a volunteer has to leave a clinical trial at any point of time. The critical requirement in this context was the agreement to abide by a specially prepared SOP for anyone who left early so that they can be monitored with stool collection and testing until negative for viral shedding. In this case arrangements were made for any potential early leavers to be accommodated in a local hotel in Antwerp where they would be provided with a chemical toilet to contain all stools and additional tailored guidance on hygienic measures, travel and contact restrictions. They were expected to continue to report to the study team with submission of stool samples on a daily basis.

Lessons learned

Planning and building a phase 1 quarantine infrastructure like Poliopolis is a very challenging activity, considering the timing, global urgency for early data generation, and

specifications of containment. The whole concept allows collection of high-quality data and samples on a daily basis but requires total dedication and commitment for the duration of the study, from the study team as well as the volunteers. The study ran from May 22 to August 22, 2017, partly coinciding with the summer holiday period, creating an additional challenge to guarantee the permanent availability of nurses, coordinators and doctors by switching and shifting weekends and holidays. Volunteers went through a two-stage screening process, with medical and psychological assessments. The psychologists selected participants who would be able to cope with the constraints on an individual level, as well as to ensure each group of 15 volunteers, who did not know each other in advance, could function as a group.

An inspection by the Regulatory Authorities in week 3 after the start of the phase 1 study confirmed the high quality of the planning, preparedness, building facility and SOPs. The accompanying paper describes how the study was successfully completed by all enrolled individuals, with no drop-outs, no issues with contamination, and no evidence of any leaks of the candidate viruses.

This detailed description of the novel purpose-built contained facility illustrates the major effort by all concerned in planning and rapid implementation that were needed to achieve success in the phase 1 novel polio vaccine study, allowing the analysis of the immunogenicity, safety, and shedding. The clinical trial conducted in the facility described here was the first major step in the development of new oral polio vaccines in more than five decades. The steps followed in envisioning, planning and implementing the operational aspects of this study might be a model for future quarantine and human challenge vaccine experiments, and an important example for other projects performed as part of emergency vaccine development programs. New and evolving global initiatives such as the Coalition for Epidemic Preparedness Innovations (CEPI) recognise the urgency to respond to pandemic threats with rapid implementation of vaccine trials under containment.[35]

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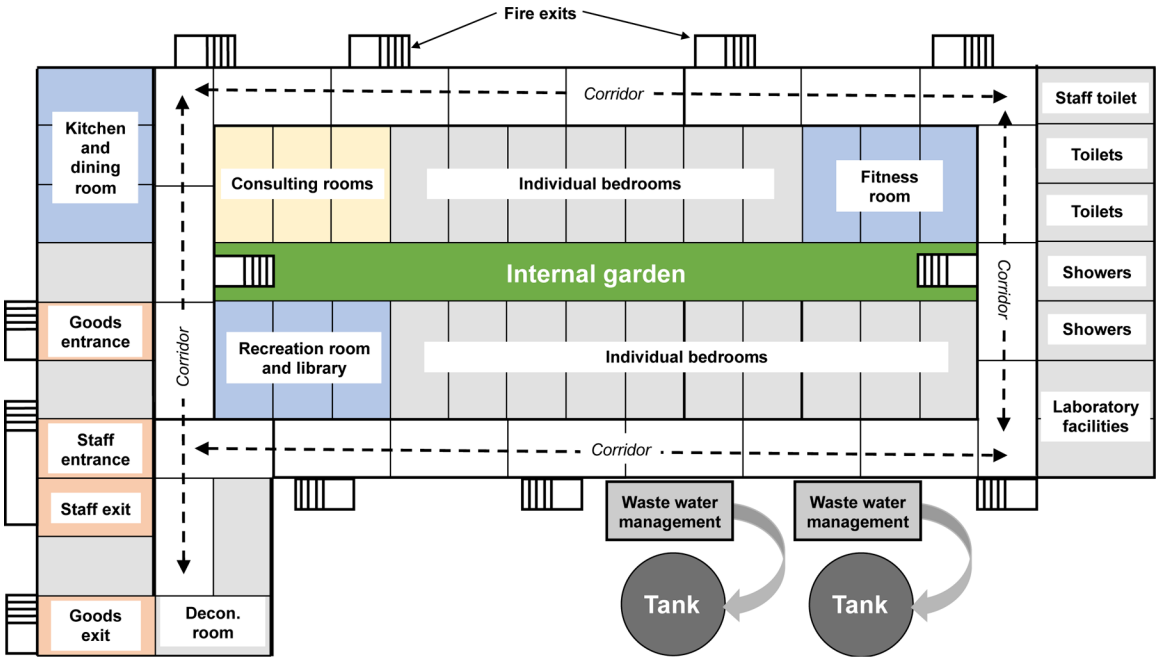

Figure 1.
Diagrammatic representation of the modular design of the Poliopolis facility.

Figure 2.
External appearance of Poliopolis showing the personnel entrance (left hand door) and exit (middle door) and the goods entrance and exit.

Figure 3.
External appearance of Poliopolis showing the two external waste water tanks.