

Round Table Discussion

Will the three steps for containment of polio-virus be enough to convince policy-makers?

Barry D. Schoub¹

Two obstacles — the laboratory containment of wild-type poliovirus and uncertainties about the threat posed by vaccine-derived poliovirus (VDPV) — still stand in the pathway towards the final eradication of poliovirus. Both issues have generated considerable controversy. Dowdle et al. have proposed a systematic and logical approach to the containment of wild-type poliovirus, which needs to be carefully considered (1).

Isolated incidents of poliovirus escape from laboratories and inactivated polio vaccine (IPV) production facilities have been well documented (2–4). The consequences of such accidents could be far greater in a post-immunization world and cannot be ignored. The “roadmap” outlined by Dowdle et al. spells out three essential steps for containment — minimize the sites keeping the virus, minimize any operations that could pose a risk of spread, and minimize the susceptibility of workers who are potentially exposed to the virus. Undoubtedly, if effectively implemented, this would greatly reduce the risk of accidental spread. But will it be enough to assure future policy-makers when the final decision comes to stop vaccination?

Much has been learnt from smallpox eradication and much wisdom can still be gleaned from that programme. However, laboratory containment was indeed simpler with smallpox and not entirely comparable to poliovirus. Biological materials contaminated with or containing wild-type poliovirus will be far more difficult to identify than in the case of smallpox, and live virus might well reside in specimens that are labelled and stored as something else (5). Unfortunately, there will be no short-cuts to the detailed laboratory documentation required for a comprehensive inventory of potential laboratory sources of virus — a task that will be particularly exacting with middle-income countries that have a combination of extensive laboratories, both inside and outside the virology field, and adequate freezer space, but perhaps inadequate record keeping.

The potential weak link in Dowdle et al.’s roadmap is its reliance for containment security on the commitment of a substantial number of laboratories that may wish to retain stocks and perhaps even work with live virus. The cessation of polio immunization must demand very special measures, even though absolute security and containment will never be achievable. First, the global regulation of laboratories needs to now be looked at with greater urgency, and poliovirus containment could well be the much-needed catalyst for this. This responsibility is probably best undertaken by WHO. Mechanisms will need to be implemented to enforce compliance, such as a requirement that reagent and material distribution be restricted to registered laboratories only. Second, eradicated infectious agents might well need a very special category of biohazard classification to justify the especially stringent laboratory regulations that were pioneered by smallpox eradication.

As was the case with smallpox, restricting the storage of virus stocks to very few laboratories should not be difficult to defend, given the global effort expended to eradicate the virus and the potential threats for the future. It should follow the smallpox example of having only two laboratories worldwide — or perhaps, at most, one laboratory per WHO region — registered to keep live poliovirus. Without this kind of reassurance it is difficult to see that national public health authorities would be willing to stop immunization. ■

Conflicts of interest: none declared.

1. Dowdle WR, Wolff C, Sanders R, Lambert S, Best M. Will containment of wild poliovirus in laboratories and inactivated poliovirus vaccine production sites be effective for global certification? *Bulletin of the World Health Organization*. 2003;81:59-62.
2. Pike RM. Laboratory-associated infections: summary and analysis of 3921 cases. *Health Laboratory Science* 1976;13:105-14.
3. World Health Organization. Wild poliovirus type 2-reference strains isolated in India. *Weekly Epidemiology Record* 2003;78:88.
4. Mulders MN, van Loon AM, van der Avoort HG, Reimerink JH, Ras A, Bestebroer TM, et al. Molecular characterization of a wild poliovirus type 3 epidemic in The Netherlands (1992 and 1993). *Journal of Clinical Microbiology* 1995;33:3252-6.
5. Davies M, Bruce C, Bewley K, Outlaw M, Mioulet V, Lloyd G, et al. Poliovirus type 1 in working stocks of typed human rhinovirus. *Lancet* 2003;361:1187-8.

Can effective containment of wild polio-viruses in laboratories and inactivated poliovirus vaccine production sites ever be achieved?

Anton M. Van Loon²

Permanent eradication of poliomyelitis requires the cessation of (wild) poliovirus circulation in the human population and effective containment of wild polioviruses in laboratories and inactivated poliovirus vaccine (IPV) production sites. Dowdle et al. (1) discuss the principles underlying effective containment and conclude that, although absolute containment can never be guaranteed, it is technically and operationally possible on a global scale. However, although it is now generally accepted that the strategy and tools for the interruption of wild poliovirus transmission will be effective, if applied correctly, the need for and feasibility of laboratory containment of wild polioviruses are still being debated (2–4).

Probably the greatest challenge for containment is the search for and destruction or adequate containment of all wild poliovirus infectious or potentially infectious materials. The *WHO global action plan for laboratory containment of wild poliovirus* (Global Action Plan) (5) provides a clear and logical framework and process for this formidable task and requires that a variety of laboratories — and not only the virological laboratories — search their freezers thoroughly for the presence of wild poliovirus (potentially) infectious materials. Recent studies have shown that collections of potentially infectious materials may indeed contain wild polioviruses, and stressed the need for such a search (6).

¹ Private Bag X4, Sandringham, Johannesburg 2192, South Africa (email: barrys@nicd.ac.za).

² Department of Virology G04.614, Eijkman Winkler Centre for Microbiology, Infectious Diseases and Inflammation, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX, Netherlands (email: a.m.vanloon@azu.nl).

The greatest risk will probably come from laboratories engaged in virological diagnosis or research. Searching their freezers is a formidable job, particularly when adequate archiving systems for freezers are lacking. Also, the mislabelling or contamination of stocks of rhinoviruses or enteroviruses with (wild) polioviruses (7, 8) will present considerable risks.

In recognition of these issues WHO has developed guidelines and a checklist for assessing the quality of the laboratory survey. These checks, however, cannot assess the thoroughness of the search carried out in laboratories, which is the weakest part of the laboratory survey and can hardly be remedied by independent onsite inspections. This is one of the reasons that Dowdle et al. conclude that “ultimately, the responsibility for effective containment of wild poliovirus materials rests on the individual laboratory”. This is not a very reassuring thought as complacency and accidents do happen, and even intentional release cannot be excluded. The recent cases of poliomyelitis due to a prototype type 2 poliovirus (9) emphasize this issue.

Because accidents do happen, the other principles mentioned by Dowdle et al. — minimal risks from handling wild poliovirus (potentially) infectious materials, and minimal risk of workers and the population subsequently being infected — are also important. The consequences of wild poliovirus transmission from the laboratory to the community will be minimal if laboratory workers and the general population are maximally protected against poliovirus infection by adequate vaccination. This, however, will be difficult to achieve because even oral poliovirus vaccine (OPV) does not fully protect against (re)infection and because some countries will probably stop polio vaccination once eradication has been certified.

Once wild poliovirus transmission has been stopped, effective containment will depend on biosafety level (BSL-3)/polio containment for storing and handling wild poliovirus stocks. BSL-3/polio facilities, procedures, and training will be needed for laboratories that wish to continue working with wild polioviruses. Again, recent events — the severe acute respiratory syndrome (SARS) coronavirus incident in Singapore (10) — underscore that laboratories have difficulty in taking their responsibility, and stress the need for a legal framework and onsite inspections.

IPV-producing facilities will probably handle the largest quantities of wild polioviruses. Nevertheless, I do not believe that they represent a true threat to effective containment. The few remaining facilities have agreed with WHO on the requirements for the safe production of IPV (11), and they will probably soon be able to switch to an OPV-based IPV. In addition, these facilities are located in countries that will probably continue high-quality routine polio vaccination (IPV) for many years after global certification.

Containment of wild poliovirus (infectious) materials becomes a crucial issue once wild poliovirus transmission has been stopped. The consequences of reintroduction of wild poliovirus into the community will remain limited in regions with sustained high polio vaccination coverage but would be disastrous in other countries. As with the eradication initiative itself, the strategies for containment are sound and should be effective. However, the quality of their implementation will determine their true effectiveness. ■

Conflicts of interest: none declared.

1. Dowdle WR, Wolff C, Sanders R, Lambert S, Best M. Will containment of wild poliovirus in laboratories and inactivated poliovirus vaccine production sites be effective for global certification? *Bulletin of the World Health Organization* 2003;81:59-62.
2. Dove AW, Racionello VR. The polio eradication effort: should vaccine eradication be next? *Science* 1997;277:779-80.
3. Racionello VR. It is too early to stop polio vaccination. *Bulletin of the World Health Organization* 2000;78:359-60.
4. Henderson DA, Inglesby Jr TV, O’Toole T. Countering the post-eradication threat of smallpox and polio. *Clinical Infectious Diseases* 2002;34:79-83.
5. World Health Organization. *WHO global action plan for laboratory containment of wild polioviruses*, 2nd ed. Geneva: World Health Organization; 2003.
6. World Health Organization. Wild poliovirus found in stored potential infectious materials. *Polio Lab Network* 2002;8:1-2.
7. Davies M, Bruce C, Bewley K, Outlaw M, Mioulet V, Lloyd G, Clegg C. Poliovirus type 1 in working stocks of typed human rhinoviruses. *Lancet* 2003;361:1187-8.
8. Savolainen C, Hovi T. Caveat: poliovirus may be hiding under other labels. *Lancet* 2003;361:1145-6.
9. World Health Organization. Poliovirus type 2 (MEF-1) found in northern India. *Polio Lab Network* 2003;9:1-2.
10. Biosafety and SARS incident in Singapore September 2003. *Report of the review panel on new SARS case and biosafety*. Singapore: Ministry of Health; 2003. Available from: URL: <http://www.moh.gov.sg/sars>
11. World Health Organization. *Guidelines for the safe production and quality control of IPV manufactured from wild polioviruses*. Geneva: World Health Organization; 2003.

Containment of wild poliovirus in the laboratory is a realistic goal

Jagadish M. Deshpande¹

Efficient surveillance systems (acute flaccid paralysis (AFP), enterovirus and/or environmental) will be required for many years to ensure the complete eradication of wild poliovirus, the absence of vaccine-derived poliovirus (VDPV), and early warning should resurgence occur. The eradication of polio will not be complete until the risk of reintroduction of wild poliovirus from laboratory stocks is also eliminated.

To minimize the risk of wild poliovirus being introduced into the community, the *WHO action plan for the laboratory containment of wild poliovirus* (Global Action Plan) has been prepared (1). Containment activities are at advanced stages in regions that have been certified polio-free, and they have begun in all other regions. Concern has, however, been expressed about the wild virus containment and post-eradication vaccination policies (2-4).

As discussed by Dowdle et al. (4), the containment plan focuses attention on wild poliovirus and potential infectious material. Oral polio vaccine (OPV)-derived polioviruses have also been included because their neurovirulence and transmissibility resembles those of the wild poliovirus. VDPV isolates show extensive periods of virus transmission in the community and their virion protein (VP)1 region usually shows 85–99% nucleotide sequence homology with OPV strains. There is evidence that vaccine-derived viruses may evolve into transmissible pathogens, even in adequately immunized populations (5). Sabin-like isolates that differ from the attenuated vaccine virus

¹ Enterovirus Research Centre, Haffkine Institute Compound, A. Donde Marg, Parel, Mumbai 400012, India (email: erc@bom3.vsnl.net.in).

in their VP1 region by 0.1–0.6% are not uncommon. The vaccine virus can undergo mutations during the initial passages through the human intestine, but it is unclear which mutations predispose the virus to become VDPV. The widely available poliovirus differentiation methods might not be sensitive enough to pick up early stage VDPV and the molecular basis of poliovirus transmissibility is not yet fully understood. Therefore, it will be prudent to include all poliovirus isolates (wild, VDPV, and Sabin-like) for containment. Laboratories possessing any poliovirus stocks should be listed in the national inventories.

Importantly, systematic implementation of the containment action plan will enable the regulating authorities, especially in developing countries, to review and enforce appropriate biosafety practices in biomedical research, teaching, and service laboratories. Yet, the quality and completeness of the search for material containing wild poliovirus within each laboratory and its reporting, on which the success of the action plan rests, is largely voluntary. This may jeopardize the entire exercise. To that end, government agencies (National Task Force) may make on-site inspection of laboratories an integral part of their national action plan.

The chances of accidental release of wild poliovirus will be high when the virus stocks are handled excessively, particularly as freezers are searched and decontamination of unwanted wild poliovirus stocks and infectious material is carried out. These activities need to be performed under the advice, guidance, and supervision of trained virologists. Advantage should be taken of the current peak level OPV immunization activities to start containment activities in as-yet polio-endemic countries so that if an untoward incident occurs the virus can be prevented from circulating. We now know that the MEF-1 virus detected in seven cases of AFP in India in late 2002 and early 2003 did not spread widely because of the ongoing national immunization days that increased population immunity (6).

Once the containment plan has been carried out, the transmission of wild poliovirus from the laboratory to the community might occur through inappropriate handling or unrecognized infection of a laboratory worker. Encouragingly, there are no reports of escaped wild poliovirus from polio network laboratories, even though they have handled and maintained wild poliovirus infectious clinical specimens and virus isolates in large numbers. Moreover, although the source of the MEF-1 virus has not yet been identified, none of the polio network laboratories was implicated. Thus, the experience within the global polio lab network gives much assurance that biosafety level (BSL)-2/polio practices provided sufficient safeguard against the inadvertent introduction of poliovirus to communities.

Polioviruses that hide under mislabelled stocks or as contaminant in other enterovirus stocks or reagents (7–9) pose a high risk of wild virus being introduced to the communities. Testing a collection of enteroviruses for the presence of wild poliovirus is a formidable task that no laboratory would want to undertake. It may be worthwhile encouraging laboratories to destroy unneeded enteroviruses isolated in poliovirus-permissive cells. Otherwise, all such isolates should be treated as potential wild poliovirus infectious materials if they were collected during the polio-endemic period.

Although the perceived risk of intentional release of wild poliovirus to communities is extremely important from the point of view of post-eradication vaccination policy, intentional release may be treated as a special case not linked to the certification of

polio eradication. The possibility of biological weapons being used by terrorist groups has increased greatly over the past few years, and it is likely that certain groups of people or countries would keep wild poliovirus stocks for biological warfare. If maintained at freezing temperatures poliovirus remains viable for many years. It is very easy to produce unlimited quantities of high titre poliovirus stocks from small amounts of preserved material. Even if all wild poliovirus stocks are eventually destroyed, it would still be possible to synthesize infectious poliovirus in a sophisticated molecular biology laboratory (10). It is thus understood that the risk of resurgence of polio in the future cannot be completely eliminated. Post-polio eradication vaccination policy will be driven by the risk assessment from time to time. Although the inadvertent release of wild poliovirus from the laboratory may be almost completely eliminated, intentional introduction of the virus can only be fought. ■

Conflicts of interest: none declared.

1. World Health Organization. *WHO global action plan for laboratory containment of wild polioviruses*, 2nd ed. Geneva: World Health Organization; 2003. WHO document WHO/V&B/03.11. Available from: URL: <http://www.who.int/vaccine.documents/>
2. Wood DJ, Sutter RW, Dowdle WR. Stopping poliovirus vaccination after eradication: issues and challenges. *Bulletin of the World Health Organization* 2000;78:347-57.
3. Dowdle WR, Gary HE, Sanders R, van Loon AM. Can post-eradication laboratory containment of wild poliovirus be achieved? *Bulletin of the World Health Organization* 2002;80:311-6.
4. Dowdle WR, Wolf C, Sanders R, Lambert S, Best M. Will containment of wild poliovirus in laboratories and inactivated poliovirus vaccine production sites be effective for global certification? *Bulletin of the World Health Organization* 2004;82:59-62
5. Cherkasova EA, Korotkova EA, Yakovenko ML, Ivanova OE, Eremeeva TP, Chumakov KM, et al. Long-term circulation of vaccine derived poliovirus that causes paralytic disease. *Journal of Virology* 2002;76:6791-9.
6. World Health Organization. Wild poliovirus type 2-reference strain isolated in India. *Weekly Epidemiological Record* 2003;78:88.
7. Savolainen C, Hovi T. Caveat: poliovirus may be hiding under other labels. *Lancet* 2003;361:1145-6.
8. Davies M, Bruce C, Bewley K, Outlaw M, Mioulet V, Llyod G, et al. Poliovirus type 1 in working stocks of typed human rhinoviruses. *Lancet* 2003;361:1187-8.
9. World Health Organization. Contaminants show up in the least expected places ... *Polio Lab Network Quarterly Update* 2003;9:3.
10. Cello J, Paul AV, Wimmer E. Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science* 2002; 297:1016-8.

Poliovirus vaccine strains will continue to circulate long after wild strains have been eradicated

Hermann G. Schatzmayr¹

Before discussing the eradication of the poliovirus, we must first evaluate the differences between the poliovirus and smallpox strains, and between the eradication programmes of each virus. Smallpox virus strains in all but two of the diagnosis laboratories have been destroyed; however, live poliovirus vaccine strains will

¹ Oswaldo Cruz Foundation, Av. Brasil 4365, Manguinhos, Rio de Janeiro, RJ 21045 900, Brazil (email: hermann@ioc.fiocruz.br).

continue to circulate in many countries as oral vaccine strains or recombinants of them, long after wild strains have been eradicated.

Smallpox is a single virus that has two varieties, *variola major* (vera) and *variola minor* (alastrim), which differ in virulence. The genomes of these strains are very stable, and no recombinations with other poxviruses were known to occur during the smallpox eradication programme. Poliomyelitis is caused by an RNA virus with three serotypes and vaccine and wild strains, which have been circulating in many countries for decades. The virus can undergo recombination after replication in the human gut, and this has a tendency to increase the virulence of the vaccine strains.

Because most developing countries will probably continue to use the oral poliovirus vaccine (OPV) as the price of the inactivated product is so high, poliovirus will continue to circulate and infect vaccinees and contacts with vaccine-derived or partially modified polio strains. This situation is very different from what happened after smallpox eradication, when the vaccine was no longer used.

It seems likely, therefore, that we will be unable to avoid the poliovirus circulating in the coming years. The reference

wild strains should be maintained only in vaccine production facilities and in the WHO-certified laboratories that are responsible for the genomic differentiation of polio strains. No more than ten of these laboratories in total should be distributed throughout all the WHO regions. The role of the reference laboratories for the molecular evaluation of new isolated strains will be essential for following the genome characteristics of the circulating strains and the OPV-associated cases that will undoubtedly arise.

The issue of poliomyelitis and poliovirus eradication will not be complete unless inactivated poliovirus vaccine is offered at an affordable price to all countries. We consider that this important matter should be pursued by WHO and related organizations in the public and private sectors involved in disease prevention and vaccine production. Achieving this goal would eliminate any risk of poliovirus infection, either under natural conditions or in those caused by laboratory-derived strains. ■

Conflicts of interest: none declared.