

Polio control after certification: major issues outstanding

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Abstract Now that the global eradication of wild poliovirus is almost within sight, planning for the post-certification era is becoming a priority issue. It is agreed that a stockpile of appropriate polio vaccines will need to be established, and a surveillance and response capacity will need to be maintained, in order to protect the world against any possible future outbreaks attributable either to the persistence of wild poliovirus or vaccine-derived polioviruses (VDPVs) or to the unintentional or intentional release of poliovirus from a laboratory or vaccine store. Although it has been suggested that the stockpile should consist of monovalent oral poliovirus vaccine (mOPV), many questions remain concerning its nature, financing, management, and use — in particular, because of uncertainties over future national vaccination policies, and over the availability of different vaccines, after the certification of wild poliovirus eradication. There are further uncertainties concerning the possible role and efficacy of inactivated poliovirus vaccine (IPV) used either routinely or in outbreak control in low-hygiene settings, the potential for rapid geographical spread of polioviruses should an outbreak occur after certification, and the risks inherent in introducing additional oral polio vaccine (OPV) viruses into populations in which the vaccine coverage and prevalence of immunity have declined, and which may thus favour the spread of VDPVs. Given these important gaps in knowledge, no country should discontinue polio vaccination until a coordinated policy for the post-certification era has been developed and the recommended measures have been put in place.

Keywords Poliomyelitis/prevention and control; Poliovirus vaccine, Inactivated/supply and distribution; Immunization/trends; Poliovirus/isolation and purification/pathogenicity; Certification/standards; Carrier state; Disease outbreaks/prevention and control; Immunization programs/trends; Containment of biohazards/standards; Laboratory infection/prevention and control; Time factors; Health policy; World health (*source: MeSH, NLM*).

Mots clés Poliomyélite antérieure aiguë/prévention et contrôle; Vaccin antipoliomyélique inactivé/ressources et distribution; Immunisation/orientations; Poliovirus humain/isolement et purification/pathogénicité; Certification/normes; Porteur germes; Epidémie/prévention et contrôle; Programmes de vaccination/orientations; Maîtrise risque biologique/normes; Infection laboratoire/prévention et contrôle; Facteur temps; Politique sanitaire; Santé mondiale (*source: MeSH, INSERM*).

Palabras clave Poliomiélitis/prevención y control; Vacuna antipolio de virus inactivados/provisión y distribución; Inmunización/tendencias; Poliovirus/aislamiento y purificación/patogenicidad; Certificación/normas; Portador; Brotes de enfermedades/prevención y control; Programas de inmunización/tendencias; Contención de riesgos biológicos/normas; Infección de laboratorio/prevención y control; Factores de tiempo; Política de salud; Salud mundial (*fuentes: DeCS, BIREME*).

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Introduction

When the global eradication of wild poliovirus has been attained, a prerequisite for its certification is that plans — and materials — be in place to deal with any future polio outbreaks (1, 2). An initial report on “Stopping a polio outbreak in the post-eradication era” was presented in 1999 and published in 2001 (3). The present paper provides an update of that report, emphasizing recent developments, and calls attention to issues that require consideration for detailed policy formulation in the future.

Sources and risks of poliovirus outbreaks after certification

Polio outbreaks following certification might be caused by either wild or vaccine-derived poliovirus (VDPV), they could

originate from various sources, and they could occur anywhere. Several recent events have shown the variety of potential sources and attest to the reality of these risks.

Wild polioviruses in production facilities

Although it has been hoped that inactivated poliovirus vaccine (IPV) production will be possible from Sabin virus stocks, rather than from wild viruses, as is currently the case, it is still unclear whether this will be feasible (4). This implies that IPV production might remain dependent on wild-type viruses, despite the continued risk of escape as has been shown from IPV production facilities in the past (5). To reduce this risk, it is expected that after global certification all manufacturers of IPV will have implemented biosafety level (BSL)-3/polio containment requirements.

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Escape from laboratories

A major effort is now under way to make an inventory of wild polioviruses held in laboratories, and to ensure that these viruses are either destroyed or held in proper conditions (6). This is a difficult challenge. Several recent events illustrate the variety of the risks involved and the difficulty in preventing them entirely.

- Type 2 poliovirus was thought to have been removed from human populations in 1999. However, in late 2002 and early 2003, seven cases attributable to MEF-1, a strain of poliovirus type 2 used in many laboratories, were detected in India (7). The source of this virus is still unclear.
- Wild poliovirus has been found in laboratory samples not related to or labelled as polio — for example, in stool specimens collected from children with diarrhoea (8) and from rhinovirus reference materials (9, 10).
- The recent *de novo* synthesis of a poliovirus in a laboratory (11), and the deliberate release of anthrax as a terrorist weapon in late 2001, have heightened general fears of the possible deliberate release of polio, despite the fact that it is acknowledged to be a poor bioterrorist weapon (3).

Vaccine-derived polioviruses

VDPVs could pose a problem after certification, because of the continued use of oral poliovirus vaccine (OPV) in some countries, because of the continued circulation of virus after cessation of vaccination, or because of its reintroduction from stored vaccine or from laboratories.

The possibility that Sabin vaccine strains might prove sufficiently transmissible to persist in populations with low vaccine coverage, and that they might revert genetically towards wild-type transmissibility and virulence, was merely an hypothesis until 1999 (12), but it has been shown to be a reality in at least four outbreaks (13–16). It is clear that persistent transmission of VDPVs can and does occur, that these viruses undergo constant genetic change during circulation (presumably towards wild-type transmissibility), and that they are particularly likely to appear under circumstances in which hygiene standards are poor and vaccine coverage is low (17). The full temporal, population, and geographical extent of VDPV transmission in the four recognized episodes has yet to be defined, and this is an important issue for study. These “outbreaks” of VDPVs were controlled by massive application of OPV in supplementary immunization activities.

Shifting vaccination policy

A crucial factor influencing predictions of outbreak risks in the post-certification era, and plans for outbreak control, is the pattern of vaccine policies, and levels of coverage, that will be in place at certification and thereafter. Views on this issue have changed appreciably in recent years.

It is likely that most countries will continue with routine polio vaccination at least until certification and that the majority of countries will continue to use OPV. It is also likely that an increasing number of high-income and perhaps some middle-income countries will have shifted to using IPV, or IPV–OPV combinations, by that time. Such shifts are being driven largely by concerns to avoid the risk (albeit very low, approximately two to four cases per million birth cohort per year (18)) of vaccine-associated paralytic poliomyelitis (VAPP). In addition, it now appears that several high-income countries will continue to use IPV vaccines routinely after certification of the end of wild poliovirus transmission.

It is far less clear what the rest of the world (the middle-income and low-income countries) will do after certification. In theory, each will have the choice of continuing with OPV, shifting to IPV, or discontinuing polio vaccination altogether. As long as OPV continues to be used, anywhere in the world, there will be a continued risk of the introduction of virulent VDPVs into other populations.

Shifting views on IPV

Although the global eradication initiative emphasized OPV as its major weapon against wild poliovirus, there is increasing appreciation that IPV has an important place in current and future polio control.

The role of IPV in developing country settings — immunogenicity

It is clear from the experience of those Western countries that have used IPV for decades that IPV is able to deter wild poliovirus and OPV circulation in settings with high standards of hygiene, but there is no evidence for such deterrence in crowded conditions with poor standards of hygiene. Recent studies of IPV in the Gambia, Oman, and Thailand found that seroconversion was inversely related to levels of maternally derived antibody, and that an early vaccination schedule (i.e. doses at 6, 10, 14 weeks) may lead to suboptimal seroconversion. Protection against infection or transmissibility was not assessed in these trials (19). The issue is complicated further by the fact that the levels of IPV vaccination (in terms of coverage and numbers of doses, which would be required to prevent virus circulation) will be contingent on previous vaccination history in the population and on any waning of immunity that may occur in the absence of circulating wild poliovirus or VDPV. The accumulation of evidence on this subject poses a major research challenge, and is of high priority.

The role of IPV in developing country settings — availability and coverage

Fundamental to assessing the role of IPV in the future are issues concerning the availability of IPV within combination vaccines that might be used in developing countries. There is a trend towards the use of such vaccines in the wealthier nations, but these vaccines remain prohibitively expensive for poorer nations today, unless provided through external assistance. The potential availability of IPV was recently assessed, and it was concluded that, given adequate lead time (5–7 years), sufficient quantities of IPV could be produced to cover the needs of all the world's children (20). However, routine coverage levels are currently too low in many countries to allow a confident shift to IPV vaccines. On the more positive side, there are major efforts to raise routine vaccination coverage levels throughout the world, and the Global Alliance for Vaccines and Immunization (GAVI) has set a goal of 90% coverage for each country by the year 2010 (21). It is in the interest of the Global Polio Eradication Initiative (GPEI) to be in the forefront of the effort to achieve high routine coverage in all countries.

Shifting views on the polio vaccine stockpile

There has been general agreement for some years that vaccination cannot be stopped, and recommendations for stopping vaccination cannot be made, without first establishing a stockpile of vaccine for emergency use should it be needed (1, 2).

This stockpile would be required to control any outbreaks that might occur, in order to prevent the re-establishment of virulent polioviruses. It is now appreciated that a stockpile would be appropriate after certification, even if nations continue to vaccinate.

A stockpile of at least 500 million doses of monovalent OPV (mOPV) of each of the three poliovirus types was first proposed in 2001 (3). Oral vaccines have for several decades been considered the vaccines of choice for outbreak control because of their ease of administration, their relatively rapid induction of immunity and their superiority over IPV in inducing mucosal immunity. The mOPV was recommended as it would allow rapid type-specific response, and avoid seeding additional virus types into the population.

The numbers of doses that would be appropriate for a global stockpile have recently been revised, taking into account experience with the circulating VDPV (cVDPV) episodes to date (numbers of doses employed in campaign responses to these outbreaks) and including a factor to compensate for a decline in the proportion immune over time after certification and cessation of massive polio vaccination initiatives. This approach has led to predictions of increasing stockpile demand over time in the future, rising to 850 million doses of each mOPV type by 5 years after certification (H. Everts, WHO unpublished analysis, 2003).

This stockpile would be for global use, and “owned” and controlled by WHO. It has been recommended that at least two manufacturers should continuously produce the vaccines, so that the world production capacity would be maintained (3). There are important outstanding issues concerning the size, vaccine type, location, and management of the polio vaccine stockpile. Although monovalent vaccine is, in principle, simple to manufacture (monovalent stocks are produced en route to standard trivalent vaccines), no monovalent vaccines are currently licenced, and thus these products raise major regulatory issues that have yet to be resolved.

Post-certification outbreak control

A variety of post-certification outbreak scenarios might arise, depending on the following factors:

- the immunity profile of the affected population and surrounding areas and nations, and of the world. This is itself a function of current and past vaccination policies — for example, age-specific coverage over the time since certification and of any waning of immunity that might occur;
- the type of virus involved — that is, single or multiple types, wild, vaccine-derived, or “reverted” vaccine-derived virus (whose phenotype may resemble wild virus);
- the interval between “introduction” of virus and outbreak recognition;
- the geographical extent of transmission by the time of ascertainment and thereafter;
- the nature of the populations concerned (in particular, hygiene status, public health infrastructure, socioeconomic level, and population density and movement).

The issue of ascertainment is crucial in that only a very small minority of infections will be evident clinically: perhaps 1 in 200 wild virus infections, 1–2 per million Sabin vaccine virus infections, and some intermediate proportion of VDPV infections will cause paralytic disease which might be suspected as attributable to polio. The likelihood that any individual case will be suspected as polio will be a function of the index of suspicion of the health care personnel involved — a suspicion

that is certain to wane in the years after certification. There will be delays before virological confirmation of any case, allowing further time for virus to spread. Table 1 shows the delays from the detection of cases of imported wild poliovirus, or the first case of cVDPV, to the initiation of mass vaccination campaigns. Even in recent years, with polio control a very high priority, it has been difficult to detect, confirm, and institute control measures in less than 2 months. Therefore, by the time an index case has been confirmed, it is likely that many thousands of individuals will have been infected over a large geographical area (3). Poor hygiene, crowding, low prevalence of immunity, and population mobility will all favour rapid spread. These concerns indicate that high priority should be given to maintaining surveillance and diagnostic capability on a global basis, including continued support for the laboratory network facilities required to identify and to type polioviruses.

If there are one or more cases of poliomyelitis attributable to wild poliovirus or VDPV after certification, management decisions will need to be swift, and it should be assumed that the population involved is far larger than that demonstrably affected at the time. Efforts may be made to restrict travel beyond the actually or potentially affected area, although this would in fact be difficult to enforce (22). The traditional control measures of isolation, contact tracing and follow-up, quarantine, and travel restrictions, so successful in controlling severe acute respiratory syndrome (SARS) (23), would be inappropriate for polio because most infections remain subclinical.

Responsibility for managing the outbreak will rest with national authorities, assisted by experienced groups, who preserve the wisdom of recent years of the polio eradication initiative, perhaps coordinated by the Global Alert and Response Unit of WHO (24). The preservation of this expertise, and the insurance of adequate continued surveillance and response capability, will be important elements of this planning.

According to current thinking, control of any outbreak will depend on mOPV vaccine. However, such an approach raises major problems in itself, being tantamount to “fighting fire with fire”, as the use of such vaccines would introduce additional live viruses into the population, which may themselves be transmitted and be subject to selective pressures to revert towards wild-type transmissibility and virulence. If the population involved is “closed”, it should be possible to raise coverage to extremely high levels and thereby to drive out whatever wild poliovirus or VDPV was responsible for the outbreak, as has been demonstrated repeatedly in the global programme in recent years. The issue of removing the introduced mOPV and any derived VDPVs will arise, but we will at least have the experience of the final stages of the global programme on which to base policy (e.g. reliance on OPV campaigns or introduction of IPV).

Most populations, however, are not discrete or “closed”, and a major problem with outbreaks in the post-certification era will be that of geographical extent; this differentiates them from outbreaks over recent years during the GPEI. The very high polio vaccine coverage in virtually all populations of the world, during the past decade, has restricted the spread of the last remaining wild viruses and the known VDPVs.

Geographical spread will be a major problem for the management of any outbreak in an unvaccinated or undervaccinated population. At present we lack a credible outbreak control approach that does not carry an appreciable risk of reintroducing OPV viruses and vaccination into much — if not all — of the world, or at least to all countries which have not switched to routine IPV with high coverage.

Table 1. Paralysis onset, date of reporting, and institution of mass vaccination campaigns following imported cases of wild poliovirus or AFP^a cases with cVDPV^b, 1999–2003

Country	Year	Serotype	Date of paralysis onset	Date reported	Date of mass vaccination campaign	Interval from paralysis to mass vaccination
Imported						
China	1999	Wild PV1 ^c	11 Oct 99	15 Dec 99	21 Jan 00	102 days
Syrian Arab Republic	1999	Wild PV1	26 Nov 99	29 Nov 99	4 Mar 00	98 days ^d
Myanmar	2000	Wild PV1	17 Jan 00	17 Jan 00	21 Feb 00	35 days ^d
Cape Verde	2000	Wild PV1	16 Aug 00	16 Aug 00	16 Oct 00	61 days
Islamic Republic of Iran	2000	Wild PV1	4 Sep 00	23 Sep 00	29 Dec 00	116 days
Nepal	2000	Wild PV1	14 Nov 00	14 Nov 00	9 Dec 00	25 days ^d
Bulgaria	2001	Wild PV1	24 Mar 01	24 Mar 01	28 May 01	65 days
Georgia	2001	Wild PV1	2 Sep 01	3 Oct 01	25 Feb 01	~6 months
Algeria	2001	Wild PV1	13 Oct 01	April 02	29 Jun 02	~6 months
Zambia	2001	Wild PV1	11 Dec 01	19 Dec 01	11 Mar 02	82 days
Burkina Faso	2002	Wild PV1	17 Sep 02	19 Sep 02	5 Oct 02	16 days ^d
Ghana	2003	Wild PV1	2 Feb 03	6 Feb 03	6 Jun 03	124 days
Lebanon	2003	Wild PV1	23 Jan 03	23 Jan 03	5 Jun 03	133 days
AFP						
Dominican Republic	2000	cVDPV1	12 Jul 00	24 Jul 00	Dec 00	~5 months
Haiti	2000	cVDPV1	30 Aug 00	30 Aug 00	Feb 01	~6 months
Philippines	2001	cVDPV1	15 Mar 01	27 Mar 01	2–8 Feb 02	~11 months
Madagascar	2002	cVDPV2	20 Mar 02	28 Mar 02	25 Sep 02	189 days

^a AFP = acute flaccid paralysis.

^b cVDPV = circulating vaccine-derived poliovirus.

^c PV1 = poliovirus type 1.

^d Mass campaign already planned before virus was detected

Cautionary perspective

The GPEI was predicated on an assumption that all vaccination could stop, once wild poliovirus circulation had ceased. This expectation was, in turn, based on an assumption that the transmissibility of OPV viruses was limited, and that these viruses would not persist long after the cessation of OPV vaccination. There was little formal discussion of this assumption in the early years of the initiative, and these views have had to be revised in recent years, as a result of analyses of transmissibility data, and observations of extensive transmission and genetic “reversion” of VDPVs. It now appears plausible that OPV-derived viruses will not disappear from the world on cessation of OPV vaccination in poor hygiene settings. Whether they might so disappear if such populations were to shift to IPV has not been demonstrated, but is a possibility that needs to be explored.

There has also been little consideration of the extent to which mucosal immunity to polioviruses may wane with time, after cessation of vaccination. Waning protection has been a notable issue for other vaccine-preventable diseases (e.g. varicella-zoster and pertussis) and might also prove important for polio (25).

Consideration of these risks, and of the difficulties of combating an outbreak of either wild virus or VDPV in a population that has discontinued vaccination, raises questions as to the wisdom of stopping polio vaccination in any large population. It is our view that decisions to cease polio vaccination altogether should not now be made, by any country, until evidence is available that this would not entail exposing the population to a serious risk of VDPV which

would revert within months to wild-type transmissibility and virulence.

At least as long as some countries of the world continue to use OPV vaccines, there will be a continued risk of VDPV introduction in areas with relatively low vaccine coverage or in populations objecting to vaccination. The appearance of clusters of cases attributable to such viruses will require intervention similar to what has been mounted against the recent outbreaks in Hispaniola, Madagascar, and the Philippines, (13–15).

Even if the entire world were to shift to IPV, there would still be a need for contingency planning on how to respond to an outbreak of wild virus or VDPV, e.g. in a population whose IPV coverage was low. Whether such a response should best be based on increasing IPV coverage, or on OPV campaigns, is not clear. This prospect adds to the urgency of gathering information on the extent to which IPV is able to deter wild or VDPV transmission in conditions of poor hygiene.

Finally, there must be recognition of the financial implications of whatever stockpile and emergency response plans are deemed appropriate on epidemiological grounds. The costs of the several options have yet to be estimated, but assurance of political and financial support for preparedness and for implementation of polio outbreak control in the post-certification era are major component challenges of the polio endgame.

Summary and conclusions

Planning for polio outbreak control in the post-certification era is difficult for many reasons. These include, in particular, the absence of experience of discontinuing OPV in poor-hygiene environments, the absence of information on the ability of IPV

to deter transmission of different types of poliovirus in populations living under conditions of high population density and poor sanitation, and the absence of reliable predictions of the vaccines and vaccination policies likely to be used in different countries of the world in the future. The issue of vaccine availability will be crucial, and it is important that this be determined more by public health needs than by the economics of the vaccine manufacturing industry.

Given the observed ability of VDPVs to persist and to revert towards the transmissibility and virulence characteristics of wild-type polioviruses; the absence of convincing evidence that such viruses will disappear in developing country settings after cessation of OPV vaccination, even if IPV vaccines are introduced and delivered at high coverage; and the difficulty of

rapidly ascertaining and containing an outbreak of wild virus or VDPV in the post-certification era, it is not yet evident that it will be safe for any nation to cease polio vaccination altogether, even after certification of the eradication of wild-type virus.

Even if all countries do continue with routine polio vaccination in the post-certification era, there will still be a need for outbreak response capability in the event of the (re)appearance of wild-type virus or cVDPV, to ensure that the achievement of the global programme in ridding the world of virulent polioviruses is maintained. Detailed planning for such a response, and assurance of political and economic support for its implementation, are high priorities for the global programme. ■

Conflicts of interest: none declared.

Résumé

Lutte contre la poliomyélite après la certification : principales questions en suspens

Avec l'éradication mondiale du poliovirus sauvage pratiquement à portée de la main, planifier la période qui va suivre la certification devient une priorité. On s'accorde à reconnaître qu'il faudra constituer des réserves suffisantes de vaccins et maintenir des moyens de surveillance et de riposte pour protéger le monde contre de futures flambées dues soit à la persistance de virus sauvages ou de virus dérivés de souches vaccinales, soit à la libération accidentelle ou délibérée de poliovirus à partir d'un laboratoire ou un entrepôt de vaccins. Bien que l'on ait proposé de constituer des réserves de vaccin antipoliomyélique buccal monovalent (VPOm), de nombreuses questions restent en suspens sur la nature, le financement, la gestion et l'utilisation de ce vaccin, notamment en raison des incertitudes concernant les futures politiques de vaccination nationales et de la disponibilité

de différents vaccins après la certification de l'éradication du virus sauvage. D'autres points d'interrogation demeurent : rôle éventuel et efficacité du vaccin antipoliomyélique inactivé utilisé soit systématiquement, soit pour lutter contre les flambées dans un environnement où l'hygiène est insuffisante ; risque de propagation géographique rapide des poliovirus en cas de flambée après la certification ; risques liés à l'introduction de nouveaux virus venant du VPO dans des populations où la couverture vaccinale et la prévalence de l'immunité ont baissé, ce qui pourrait alors favoriser la propagation des virus dérivés de souches vaccinales. Compte tenu de tous ces points d'interrogation, aucun pays ne devrait interrompre la vaccination antipoliomyélique avant d'avoir établi une politique coordonnée post-certification et appliqué toutes les recommandations.

Resumen

Control de la poliomiélitis tras la certificación: principales cuestiones pendientes

Ante la aparente inminencia de la erradicación mundial del poliovirus salvaje, la planificación de la era poscertificación está convirtiéndose en una cuestión prioritaria. Es algo admitido que habrá que acumular vacuna antipoliomiélica y que será necesario mantener la capacidad de vigilancia y respuesta, a fin de proteger al mundo contra cualquier brote que pudiera declararse en el futuro como consecuencia ya sea de la persistencia de poliovirus salvajes o de origen vacunal, ya de la liberación, intencional o no, del poliovirus de un laboratorio o de depósitos de la vacuna. Aunque se ha señalado que las reservas deberían ser de la vacuna antipoliomiélica oral monovalente (mOPV), subsisten muchos interrogantes en lo que atañe a su naturaleza, financiamiento, manejo y uso, sobre todo por la incertidumbre existente respecto a las futuras políticas nacionales de vacunación y la disponibilidad

de las diferentes vacunas una vez certificada la erradicación del virus salvaje. Hay además otras incertidumbres relacionadas con lo siguiente: la posible función y eficacia de la vacuna inactivada usada ya sea sistemáticamente o contra brotes en entornos insalubres, el riesgo de propagación geográfica rápida de los poliovirus en caso de declararse un brote después de la certificación, y los riesgos inherentes a la introducción de virus OPV adicionales en poblaciones cuya cobertura de vacunación y prevalencia de inmunidad hayan disminuido, lo que favorecería la propagación del virus vacunal. Habida cuenta de esas importantes lagunas en nuestros conocimientos, ningún país debería interrumpir la vacunación antipoliomiélica mientras no se haya formulado una política coordinada para la era poscertificación y no se hayan puesto en práctica las medidas recomendadas.

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