

Framework for evaluating the risks of paralytic poliomyelitis after global interruption of wild poliovirus transmission

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Abstract With the interruption of wild poliovirus transmission globally, the need for new policies to deal with the post-certification era will rapidly arise. New policies will be required in four areas: detection and notification of circulating polioviruses; biocontainment of wild, vaccine-derived and attenuated strains of poliovirus; vaccine stockpiles and response mechanisms; and routine immunization against polioviruses. A common understanding of the potential risks of paralytic poliomyelitis in the post-certification period is essential to the development of these policies. Since 2000, there has been increasing international consensus that the risks of paralytic poliomyelitis in the post-certification era fall into two categories: those due to the continued use of the oral poliovirus vaccine (OPV) and those due to future improper handling of wild polioviruses. The specific risks within both categories have now been defined, and an understanding of the frequency and potential burden of disease associated with each is rapidly improving. This knowledge and clarity have provided a framework that is already proving valuable for identifying research priorities and discussing potential policy options with national authorities. However, this framework must be regarded as a dynamic tool, requiring regular updating as additional information on these risks becomes available through further scientific research, programmatic work, and policy decisions.

Keywords Poliomyelitis/prevention and control/chemically induced; Poliovirus vaccine, Oral/adverse effects; Poliovirus/growth and development; Containment of biohazards; Risk assessment/standards; Certification; Policy making (*source: MeSH, NLM*).

Mots clés Poliomyélite antérieure aiguë/prévention et contrôle/induite chimiquement; Vaccin antipoliomyélique Sabin/effets indésirables; Poliovirus humain/croissance et développement; Maîtrise risque biologique; Evaluation risque/normes; Certification; Choix d'une politique (*source: MeSH, INSERM*).

Palabras clave Poliomiélitis/prevención y control/inducida químicamente; Vacuna antipolio oral/efectos adversos; Poliovirus/crecimiento y desarrollo; Contención de riesgos biológicos; Medición de riesgo/normas; Certificación; Formulación de políticas (*fuentes: DeCS, BIREME*).

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Introduction

In 1988 the World Health Assembly, an annual meeting of the Ministers of Health of all Member States of WHO, approved a global effort to eradicate poliomyelitis (1). Subsequently, and as the result of the largest international public health initiative in history, by the end of 2002, 209 of the world's 216 countries, territories, and areas had interrupted the transmission of indigenous wild polioviruses (2). With poliomyelitis now on the verge of becoming the first disease to be eradicated in the 21st century, international attention is focusing increasingly on the development of policies for the post-certification era — the period that would begin immediately after the world is certified as free of wild poliovirus transmission (3).

Although experience from the campaign to eradicate smallpox has offered important insights into the range of issues that may arise in the development of such policies (4), by 2000 it was evident that these issues would be more complex in the case of polio for a

variety of reasons, including differences in the characteristics of the vaccines used and in the geopolitics of the era in which each eradication campaign was conducted (5). Consequently, in April 2002, WHO and a number of its partners in the Global Polio Eradication Initiative sought the views of a wide range of experts in public health and policy development (6). A recurring theme of that consultation was the need to consolidate into a single framework the available information on the risks of paralytic poliomyelitis in the post-certification era. This paper presents the major policy requirements for the post-certification era and the framework which has since been developed to facilitate a common understanding of the potential risks of polio in that period.

Policy requirements for the post-certification era

For the post-certification era, specific policies are required in four broad areas: first, detection and notification of circulating

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polioviruses; second, biocontainment of wild, vaccine-derived and attenuated strains of polioviruses; third, vaccine stockpiles and response mechanisms; and fourth, routine immunization against polioviruses (Table 1) (7). All of these policy areas are interrelated, highlighting the need for a common risk framework to underpin and guide decisions in each area.

Detection and notification

For the purposes of polio eradication, surveillance for wild poliovirus in endemic or recently endemic areas has relied on the identification, notification, and investigation of all cases of acute flaccid paralysis (AFP) in children aged less than 15 years (8). This syndromic reporting of AFP has served the dual purpose of increasing the sensitivity of clinical reporting systems to detect wild poliovirus circulation while providing a key indicator against which the performance of national and subnational surveillance systems could be evaluated. (Even in the absence of wild poliovirus, surveillance systems should be able to detect at least 1 case of AFP per 100 000 children aged less than 15 years, where AFP is caused by something other than polio (8)). Although there are international reporting standards for AFP, countries are under no obligation to meet them, except for the purpose of obtaining polio-free certification. In the post-certification era, some system of clinical and virological surveillance will need to continue indefinitely, perhaps within the context of WHO's International Health Regulations (9), to ensure very rapid reporting and response to any circulating poliovirus.

Containment of poliovirus stocks

Substantial work has been done to ensure the identification and safe handling of wild poliovirus stocks in polio-free areas. Major developments in this area of work, usually referred to as poliovirus containment, include the publication of the *WHO global action plan for the laboratory containment of wild polioviruses* in 1999 following wide public consultation (10). That same year, the World Health Assembly in a formal resolution called on all Member States to begin implementing and reporting on the steps outlined in that document (11). By the end of 2002, 149 countries had established a plan of action and initiated a survey of laboratories containing wild poliovirus stocks or potentially infectious materials; 79 of these countries had reported completion of the inventory (C. Wolff, personal communication, 2003).

This progress, particularly in several large industrialized countries, shows that wild poliovirus containment is operationally feasible. In the post-certification era, containment issues will become more complex, requiring consensus on the appropriate level of containment for vaccine (e.g. Sabin) strains of poliovirus, as well as wild poliovirus stocks. The recent documentation of polio outbreaks caused by circulating vaccine-derived polioviruses (cVDPVs) reinforced the relevance of this small, but real, risk in the development of post-certification policies (12–15). The level of containment required for vaccine-derived poliovirus (VDPV) strains in the post-certification era will depend on the risk they pose for polio outbreaks and whether population immunity to poliovirus will be maintained through the continued use of polio vaccines.

Routine polio immunization policy

Although eradication has been defined as the elimination of a “specific agent as a result of deliberate efforts [such that] intervention measures are no longer needed” (16), the emergence of cVDPVs, combined with heightened concerns about poliovirus as a potential tool for bioterrorists, has revitalized the debate among public health experts as to whether a world without polio vaccination would ever be feasible (3, 17, 18). In fact, the recent increase in the perceived security risk of a deliberate release of an eradicated agent in a non-immune population has even stimulated discussions on redefining the term “eradication” as not requiring the cessation of the control measures (19). In 1998, before the first episode of cVDPV had been documented, a WHO-convened meeting of experts concluded that “... routine immunization with oral poliovirus vaccine (OPV) *should* stop and immunization with inactivated poliovirus vaccine (IPV) can stop ...” once certain criteria had been satisfied. These three criteria were: termination of wild poliovirus transmission; containment of laboratory stocks of polioviruses; and the demonstration that vaccine-derived viruses did not circulate for a prolonged period after OPV vaccination ceased (20). Despite this conclusion, the occurrence of further cVDPV episodes, as well as concerns about bioterrorism, has reinforced the need for a risk framework that contains both qualitative information on the nature of each risk and quantitative data on the magnitude of these risks.

Polio vaccine stockpiles

In 2001, the technical oversight body for the global polio eradication initiative (GPEI) added a fourth criteria to those that would need to be met before the cessation of polio immunization could be considered: “... the establishment of global vaccine stockpiles, and the production capacity for OPV, in case wild polioviruses are detected in the post-immunization era” (21). This area of work involves a plethora of issues, ranging from what the most appropriate vaccines (IPV, OPV) and formulations (monovalent, trivalent) are to issues of governance and the size of the stockpiles over time, relative to population immunity profiles (22).

The interrelatedness of the four major policy areas described above highlights the need for a common understanding of the risks of paralytic poliomyelitis in the post-certification era. The following section outlines the framework that was developed during 2000–02, which is being used increasingly as the basis for discussing post-certification policy options with decision-makers, particularly in countries that use OPV.

Table 1. Important areas in which new policies will be required for poliomyelitis in the “post-certification” era

Policy areas	Example issue(s)
Detection and notification	<ul style="list-style-type: none"> • Future role of acute flaccid paralysis surveillance strategy • Role of International Health Regulations
Biocontainment	<ul style="list-style-type: none"> • Requirements for vaccine strains • Verification of containment
Vaccine stockpiles	<ul style="list-style-type: none"> • Type of vaccine(s) and formulations • Location and governance of stockpiles
Routine immunization	<ul style="list-style-type: none"> • Type of vaccine used, if any • Risk of vaccine-derived polioviruses during cessation of oral poliovirus vaccine

Risks of poliomyelitis in the post-certification era

The risks of paralytic poliomyelitis occurring in the post-certification era fall into two major categories: risks related to the continued use of the OPV and risks associated with the unsafe handling of wild polioviruses. Both categories have three main risks, all of which are being increasingly understood and most of which are now quantifiable. Table 2 summarizes the frequency and annual burden of disease associated with each of these risks in the pre-certification era. Both of these risks, however, will change substantially in the post-certification era, depending on future policy decisions.

Risks due to continued use of OPV

The three risks that arise from the continued use of OPV are: vaccine-associated paralytic poliomyelitis (VAPP); cVDPVs; and immunodeficient long-term excretors of vaccine-derived polioviruses (iVDPVs). VAPP is caused by a VDPV that has regained neurovirulence during replication in the gut of a vaccinee. Although over 30% of OPV vaccinees will excrete VDPVs that show enhanced neurovirulence (23), VAPP occurs at a rate of approximately 1 case per 750 000 to 1 million children receiving their first dose of OPV (24, 25). The rate is stable in all areas where OPV is used, with nearly the same number of cases associated with subsequent doses and among close contacts of vaccinees. On the basis of the vaccine used in routine childhood immunization programmes around the world in 2002 (OPV vs IPV), it was estimated that between 250 and 500 cases of VAPP are occurring annually (26). Data from polio-free areas that have continued to use OPV suggest that the risk of VAPP remains stable as long as OPV is used for primary immunization against polio.

Although the risks, frequency, and burden of cVDPVs have only recently been described, they are being increasingly understood. The risk of such episodes had been postulated for some time (27) before the first outbreak of poliomyelitis due to a cVDPV was observed in 2000 when 22 children were paralysed over a 12-month period on the Caribbean island of Hispaniola by a type 1 cVDPV (12). A second such outbreak, also due to a type 1 poliovirus, occurred in the Philippines over a 4-month period in 2001, paralysing three children (13). In 2002, a third cVDPV outbreak was documented in Madagascar, with four children paralysed by a type 2 VDPV over a 1-month period (14).

In all three outbreaks, cVDPV transmission was rapidly interrupted following mass immunization with OPV. Retrospective analyses of viruses from Egypt suggest that a type 2 VDPV also circulated in that country, paralysing at least 32 children between 1988 (year of first paralysed case) and 1993 (15). At the molecular level, all of these cVDPVs had undergone recombination with species C non-polio enteroviruses in the non-capsid region. At a population level, all cVDPVs appear to have arisen in a setting of continued OPV use in a polio-free population with low or relatively low routine immunization coverage. Although cVDPV episodes are currently rarer than VAPP cases, the future burden of cVDPV disease is conditional on national/international polio immunization policies and coverage. In the post-certification era the burden of disease due to cVDPVs could be substantially greater than that due to VAPP if OPV use continues and low immunization coverage is widespread.

The third risk of paralytic polio due to the continued use of OPV is the potential for iVDPVs to re-seed the general population. Such long-term carriers (i.e. >1 year) are extremely rare, however, with only 19 identified in the 40 years of widespread use of the oral polio vaccine (7). Of these, only two are known to be alive and still excreting a VDPV, and no secondary transmission has been documented. Thus, the risk of an iVDPV reintroducing poliovirus into the general population is very low and is expected to decrease with time. In addition, there have been no secondary cases due to these iVDPVs, there has been no known episode of secondary spread, and the excreted viruses have not undergone recombination with species C non-polio enteroviruses. All of these iVDPV episodes have been documented in high-income or high-/middle-income countries in individuals with severe congenital immunodeficiency syndromes who required regular immunoglobulin therapy to survive. As such individuals in a low income country would not be expected to survive for a long period once they were symptomatic, and with high-income countries increasingly switching to IPV for routine immunization, the incidence of iVDPV is expected to decrease. Given the high levels of sanitation in high-income and high-/middle-income countries, combined with the fact that most of these countries will maintain high population immunity with IPV for the foreseeable future, it is unlikely that viruses from iVDPVs would spread in the future (3).

Table 2. Risks of paralytic poliomyelitis in the immediate^a post-certification era

Risk Factor	Potential risks	Frequency in the pre-certification era	Annual burden of disease in pre-certification era	Probable evolution of risk
Continued use of OPV ^b	VAPP ^b	1:2.4 million doses of OPV ^c	250–500 cases	Stable
	cVDPV ^d	3 episodes in 1999–2002	~10 cases	Conditional
	iVDPV ^e	19 known cases since 1963	<1 case	Decrease
Improper handling of wild polioviruses	Release from an IPV ^f site	1 episode (no cases)	Negligible	Decrease
	Release from a laboratory stock	1 incident under investigation	NA ^g	Decrease
	Intentional release	No episodes	0	Conditional

^a See text for a discussion of how these risks could change over time, and the potential consequences.

^b VAPP = vaccine-associated paralytic poliomyelitis.

^c OPV = oral poliovirus vaccine.

^d cVDPV = circulating vaccine-derived poliovirus.

^e iVDPV = immunodeficient long-term excretors of VDPVs.

^f IPV = inactivated poliovirus vaccine.

^g NA = information not yet available.

Risks due to the handling of wild polioviruses

The three risks of paralytic polio due to the handling of wild poliovirus in the post-certification era are: inadvertent release of virus from an (IPV) production site; inadvertent release from a laboratory; and intentional release. The rarity or lack of such events in recent years makes it particularly difficult to quantify the risks, frequency, and burden of each of these in the post-certification era.

Only one episode of wild poliovirus release from an IPV manufacturing site has been shown to date. The episode occurred in 1992, when a reference strain of wild type 1 poliovirus, which is used in the production of IPV was isolated from a young child being investigated for diarrhoea (11, 28). The subsequent epidemiological investigation found that the child's father was employed in an IPV production site where he worked with wild polioviruses. No cases of paralysis occurred. In a separate incident, a reference strain of type 3 wild poliovirus, which is also used in the production of IPV, was isolated from a child in a country where IPV is produced (11, 28). The subsequent investigation did not, however, establish a link between an IPV production facility and the isolate. The risk of an inadvertent release of a wild poliovirus from an IPV production facility is decreasing due to the implementation of standard, industry-wide biocontainment standards (i.e. BSL-3/polio) (29). Furthermore, the likelihood of such a release re-establishing transmission is low because of the high routine IPV immunization coverage and sanitation levels in those countries in which it is produced (3). The future risk of an inadvertent release from such a site, however, is conditional on whether new sites are established for wild poliovirus IPV production in countries that do not have high routine immunization coverage and/or the capacity to closely regulate compliance with biocontainment standards.

Although the inadvertent release of wild poliovirus from a laboratory has caused cases of paralytic poliomyelitis in the pre-vaccine era (30), there is no evidence that this resulted in the widespread transmission of a laboratory strain. In the polio vaccine era, there have been no documented episodes of inadvertent releases from a laboratory that have caused outbreaks. However, in 2002–03 a laboratory strain of type 2 wild poliovirus was isolated from a total of seven children with clinical polio in India (31). Preliminary molecular analysis of these strains from the children suggests that the cases were the result of multiple point introductions rather than the sustained circulation of this virus. This reinforces the need to introduce containment activities in the limited number of countries that remain polio-endemic. Progress in the implementation of containment of wild poliovirus stocks, particularly in the 87 countries of the polio-free WHO regions of the Western Pacific and Europe, suggests that the risk of inadvertent release of wild polioviruses from laboratory stocks is decreasing (32).

The final risk for the reintroduction of wild poliovirus into the human population is through intentional release. To date, there have been no known or suspected episodes of intentional release of wild poliovirus. Although the future risk of such an event is largely conditional on national and international decisions on routine polio immunization policy in the post-certification era, this risk is not expected to be significant. There are several reasons for this. First, standard assessments of potential biological agents suggest that poliovirus would not be a candidate organism for biowarfare and would be an unlikely agent for

bioterrorism (3, 33). In addition to the morbidity and mortality rates associated with poliovirus infection being very low compared with other potential agents, the fragility of the virus would make it difficult to disperse in a manner necessary to re-establish transmission (34). Second, most of the industrialized countries that might be considered probable targets for bioterrorists have already signalled their intention to continue using IPV to maintain population immunity in the post-certification era. Finally, although the potential for intentional reintroduction of polio into the human community cannot be eliminated entirely, it can be substantially reduced through effective containment.

Changing risks, and consequences, over time

Although it is now relatively straightforward to identify, rank, and quantify the risks of paralytic poliomyelitis in the immediate post-certification era, it is essential to recognize that these risks, and their potential consequences, will change substantially over time. This variability is the result of several factors, including future containment, surveillance, and immunization policy decisions at the international level; the degree to which such policies are implemented at national and subnational levels; and the development of additional tools for mitigating each risk. For example, within a few years of stopping routine immunization with OPV, the risks due to the continued handling of wild polioviruses would probably be much greater than those due to OPV. However, the production of IPV from Sabin or other attenuated poliovirus strains would substantially reduce the risks associated with future IPV manufacture. The development of an antiviral agent effective against polioviruses could eliminate the risk posed by iVDPVs, while expanding the arsenal for responding to a circulating poliovirus in the post-certification era. Most importantly, the potential burden of disease due to the reintroduction of any circulating poliovirus will increase over time in the post-certification era as the gap in population immunity to polioviruses increases. These examples amply demonstrate the need to regard this risk framework as a dynamic tool, the future use of which will depend on the regularity and completeness with which it is updated.

From risk framework to post-certification policies

Among the particularly valuable outcomes of the 2002 Global Health Forum on post-certification policy development was the guidance on moving from a risk framework to international health policy. The meeting highlighted three particular issues that would be important in this regard: first, ensuring that the best possible scientific evidence was available to inform the risk framework, as well as the options for managing those risks; second, undertaking broad international discussion on the nature of the risks and the options for their management; and third, using multiple forums, including the World Health Assembly, to inform decision-makers on the evolution of policy options, publicly discuss and debate those options, and establish international consensus on each of the four policy areas described above (Table 1).

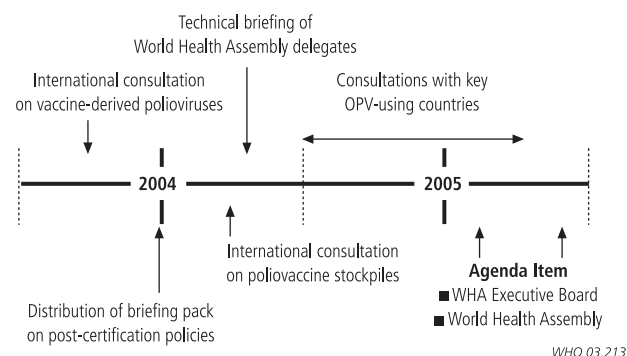
The risk framework described here has already proven useful for defining knowledge gaps and guiding the scientific and operational research required to address those gaps. Foremost among the gaps being addressed are those on the magnitude, frequency, and risk factors for cVDPV, the risk of a cVDPV arising from an iVDPV, and the frequency of wild poliovirus in laboratory stocks of "potentially infectious materials". On the risk management

side, the framework has prompted a more aggressive programme of work on the size and governance of vaccine stockpiles and the vaccine of choice. New work has been instituted to understand the timelines for, and implications of, restarting OPV production should it be needed in a post-OPV immunization era.

Although it is increasingly evident that VDPVs pose a real threat to the global goal of eliminating paralytic poliomyelitis due to circulating polioviruses, there are substantial challenges to translating this scientific fact into an international consensus, developing appropriate national policies, and then implementing those policies globally. For example, eliminating the risk of VDPVs would require that all countries stop using OPV for routine immunization. Not only would such cessation need to be relatively synchronized, it would also need to take place while surveillance sensitivity and population immunity against polio were as high as possible — probably very soon after global certification of eradication. Because many countries might prefer to replace OPV with IPV rather than stop polio immunization altogether, additional planning would be needed to ensure the availability of this vaccine in sufficient quantity and in the appropriate vaccine combinations. In the longer term, global surveillance capacity would need to be substantially enhanced to ensure that any circulating wild poliovirus was rapidly detected, reported, and responded to as an international public health emergency.

As the seven remaining polio-endemic countries accelerate their eradication efforts, it is increasingly important that international dialogue on post-certification policy be intensified. To facilitate these discussions, WHO and its polio-eradication partners are consolidating the available scientific data and policy options in advance of a planned technical briefing of delegates to the World Health Assembly in 2004. Depending on the outcome of this technical briefing, further progress towards the interruption of wild poliovirus transmission globally, and the generation of additional scientific data, it is anticipated that international deliberations on each of the four major areas of post-certification policy will accelerate in 2005 (Fig. 1). Central to the success of these deliberations will be ongoing discussions

Fig. 1. Timeline of major events in the development of post-certification policies for poliomyelitis (May 2003–May 2005)



with OPV-using countries, particularly those with large populations and national OPV production capacity, to better understand and respond to their concerns for the post-certification era.

Conclusions

With the interruption of wild poliovirus transmission globally, there will rapidly arise the need for new policies to deal with the post-certification era. Since 2000, there has been increasing international consensus that the risks of paralytic poliomyelitis in the post-certification era fall into two categories: risks due to the continued use of OPV and risks due to the future improper handling of wild polioviruses. This framework is proving to be particularly valuable in identifying research priorities and discussing potential policy options with national decision-makers, especially in OPV-using countries. However, this framework must be regarded as a dynamic tool, requiring regular updating as additional information on these risks becomes available through further scientific research, programmatic work, and policy decisions. ■

Conflicts of interest: none declared.

Résumé

Cadre d'évaluation des risques de poliomyélite paralytique après l'interruption mondiale de la transmission du poliovirus sauvage

Avec l'interruption mondiale de la transmission du poliovirus sauvage, de nouvelles politiques applicables après la certification deviendront rapidement nécessaires dans quatre domaines : détection et notification des poliovirus en circulation ; confinement des souches sauvages, vaccinales et atténuées ; réserves de vaccins et dispositions prises pour les ripostes ; vaccination systématique. Il est essentiel d'avoir une perception commune des risques potentiels de poliomyélite paralytique après la certification pour pouvoir élaborer ces politiques. Depuis 2000, il s'est dégagé de plus en plus clairement un consensus international sur la division de ces risques en deux catégories : ceux dus à la poursuite de la vaccination par le vaccin

antipoliomyélique buccal (VPO) et ceux dus à des futures manipulations hasardeuses des poliovirus sauvages. Dans les deux cas, ces risques sont désormais bien définis et l'on connaît de mieux en mieux la fréquence et la charge de morbidité potentielle qui peuvent s'y associer. Cette meilleure connaissance a permis de définir un cadre qui s'avère déjà utile pour déterminer les priorités en matière de recherche et étudier les différentes options politiques avec les autorités nationales. Ce cadre doit néanmoins être considéré comme un outil dynamique qui devra être régulièrement actualisé en fonction de l'évolution de la recherche scientifique, du travail programmatique et des décisions de politique pour intégrer les nouvelles données obtenues.

Resumen

Marco para evaluar el riesgo de poliomielitis paralítica después de la interrupción mundial de la transmisión del poliovirus salvaje

Tras la interrupción de la transmisión del poliovirus salvaje a nivel mundial, se planteará rápidamente la necesidad de formular nuevas políticas para la era poscertificación. Así, se requerirán nuevas políticas en cuatro áreas: detección y notificación de los poliovirus circulantes; biocontención de las cepas salvajes, vacunales y atenuadas del poliovirus; reservas de vacuna y mecanismos de respuesta; e inmunización sistemática contra los poliovirus. Para formular esas políticas es fundamental comprender bien los riesgos potenciales de poliomielitis paralítica en la era poscertificación. Desde el año 2000, se observa un creciente consenso internacional en torno a la idea de que los riesgos de poliomielitis paralítica en la era poscertificación se resumen en dos: los debidos a la continuación de la administración de la vacuna antipoliomielítica oral (OPV), y los debidos a un

manejo inadecuado de los poliovirus salvajes en el futuro. Se han definido ya riesgos específicos dentro de esas dos categorías, y se está profundizando rápidamente en el conocimiento de la frecuencia y la carga potencial de morbilidad asociadas a cada una de ellas. Esa mayor amplitud y claridad de los conocimientos ha permitido configurar un marco que está ya demostrando su utilidad para determinar las prioridades de investigación y debatir las posibles opciones de política con las autoridades nacionales. Sin embargo, hay que ver en dicho marco un instrumento dinámico, que deberá actualizarse de forma periódica a medida que las nuevas investigaciones científicas, actividades programáticas y decisiones de política aporten más información sobre esos riesgos.

References

- World Health Assembly. *Global eradication of poliomyelitis by the year 2000*. Geneva: World Health Organization; 1988 (resolution 41.28).
- World Health Organization. Progress towards global eradication of poliomyelitis, 2002. *Weekly Epidemiological Record* 2003;78:138-44.
- Global Technical Consultative Group to the World Health Organization on the global eradication of poliomyelitis. 'Endgame' issues for the Global Polio Eradication Initiative. *Clinical Infectious Diseases* 2002;34:72-7.
- Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva: World Health Organization; 1988.
- Dowdle WR, De Gourville E, Kew OM, Pallansch MA, Wood DJ. Polio eradication: the OPV paradox. *Reviews in Medical Virology* 2003;13:277-91.
- Andrus JK, Ashley D, Dowdle WR, Feinglass LES, John TJ, Kitua AY, et al. Polio immunization policy in the post-certification era. Criteria for policy development. In: *Institute for Global Health & Taskforce for Child Survival and Development. Global health forum III. Post-certification polio immunization policy*. San Francisco (CA): Institute for Global Health; 2002.
- Report of the eighth meeting of the Technical Consultative Group (TCG) on the global eradication of poliomyelitis, Geneva, 24–25 April 2003*. Geneva: World Health Organization; 2003.
- Expanded Programme on Immunization. Acute flaccid paralysis surveillance: the surveillance strategy for poliomyelitis eradication. *Weekly Epidemiological Record* 1998;73:113-4.
- Hardiman M. The revised International Health Regulations: a framework for global health security. *International Journal of Antimicrobial Agents* 2003;21:207-11.
- WHO global action plan for laboratory containment of wild polioviruses. Geneva: World Health Organization; 1999. WHO document WHO/V&B/99.32.
- World Health Assembly. *Poliomyelitis eradication*. Geneva: World Health Organization; 1999 (resolution 52.22).
- Kew O, Morris-Glasgow V, Landaverde M, Burns C, Shaw J, Garib Z, et al. Outbreak of poliomyelitis in Hispaniola associated with circulating type 1 vaccine-derived poliovirus. *Science* 2002;296:356-9.
- Expanded Programme on Immunization. Acute flaccid paralysis associated with circulating vaccine-derived poliovirus, Philippines 2001. *Weekly Epidemiological Record* 2001;76:319-20.
- Expanded Programme on Immunization. Paralytic poliomyelitis in Madagascar, 2002. *Weekly Epidemiological Record* 2002;77:241-2.
- Centers for Disease Control and Prevention. Circulation of a type 2 vaccine-derived poliovirus — Egypt, 1982–1993. *Morbidity and Mortality Weekly Report* 2001;50:41-2, 51.
- Dowdle WR. The principles of disease elimination and eradication. In: *Global disease elimination and eradication as public health strategies. Proceeding of a conference held in Atlanta, Georgia, USA, 23–25 February 1998*. *Bulletin of the World Health Organization* 1998;76 Suppl 2:22-5.
- Henderson DA. Countering the post-eradication threat of smallpox and polio. *Clinical Infectious Diseases* 2002;34:79-83.
- Nathanson N, Fine P. Poliomyelitis eradication — a dangerous endgame. *Science* 2002;296:269-70.
- Dowdle WR. Perspectives for elimination: Eradication of diseases with vaccines. *Proceedings of the Pan American Health Organization conference on vaccines, prevention and public health: a vision for the future*. Washington (DC), Pan American Health Organization (forthcoming).
- Report of the meeting on the scientific basis for stopping polio immunization, Geneva, 23–25 March 1998*. Geneva: World Health Organization; 1998. WHO document WHO/EPI/GEN/98.12.
- Report of the seventh meeting of the Technical Consultative Group (TCG) on the global eradication of poliomyelitis, Geneva, 2002*. Geneva: World Health Organization; 2002.
- Fine PEM, Sutter RW, Orenstein WA. Stopping a polio outbreak in the post-eradication era. In: Brown F, editor. *Progress in polio eradication: vaccine strategies for the end game*. *Developmental biology*, vol. 105. Basel: Karger; 2001. p. 129-47.
- Minor PD, Dunn G. The effect of sequences in the 5' non-coding region on the replication of polioviruses in the human gut. *The Journal of General Virology* 1988;69:1091-6.
- Strebel PM, Sutter RW, Cochi SL, Biellik RJ, Brink EW, Kew OM, et al. Epidemiology of poliomyelitis in the United States: One decade after the last reported case of indigenous wild virus-associated disease. *Clinical Infectious Diseases* 1992;14:568-79.

25. Andrus JK, Strebel PM, de Quadros CA, Olive JM. Risk of vaccine-associated paralytic poliomyelitis in Latin America, 1989–91. *Bulletin of the World Health Organization* 1995;73:33-40.
26. *Report of the interim meeting of the Technical Consultation Group (TCG) on the global eradication of poliomyelitis, Geneva, 13–14 Nov 2002*. Geneva: World Health Organization; 2003. WHO document WHO/EPI/GEN/02.
27. Fine PEM, Carneiro IAM. Transmissibility and persistence of oral polio vaccine viruses: Implications for the global poliomyelitis eradication initiative. *American Journal of Epidemiology* 1999;150:1001-21.
28. Mulders MN, Reimerink JHJ, Koopmans MPG, van Loon AM, van der Avoort HGAM. Genetic analysis of wild type poliovirus importation into The Netherlands (1979–1995). *Journal of Infectious Diseases* 1997;176:617-24.
29. *Guidelines for the safe production and quality control of IPV manufactured from wild polioviruses*. Geneva: World Health Organization (WHO Technical Report Series) (forthcoming).
30. Dowdle WR, Birmingham ME. The biologic principles of poliovirus eradication. *The Journal of Infectious Diseases* 1997;175 Suppl 1:S286-92.
31. World Health Organization. Wild poliovirus type II — reference strains isolated in India. *Weekly Epidemiological Record* 2003;78:88.
32. World Health Organization. Global progress towards laboratory containment of wild poliovirus, July 2001–August 2002. *Weekly Epidemiological Record* 2002;77:375-79.
33. Rotz LD, Khan AS, Lillibridge SR, Ostroff SM, Hughes JM. Public health assessment of potential biological terrorism agents. *Emerging Infectious Diseases* 2002;8:225-30.
34. Vaccines and Biologicals. *New polio vaccines for the post-eradication era, Geneva, 19–20 January 2000*. Geneva: World Health Organization; 2000. WHO document WHO/V&B/00.20.