Round Table

Will containment of wild poliovirus in laboratories and inactivated poliovirus vaccine production sites be effective for global certification?

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Abstract The absolute laboratory containment of any virus cannot be guaranteed, but a wealth of experience indicates that effective containment of wild poliovirus materials for global certification is technically and operationally feasible. Effective containment is based on the principles of minimal wild poliovirus infectious and potentially infectious materials in laboratories; minimal risks of operations in laboratories and inactivated poliovirus vaccine production facilities; minimal susceptibility of workers to wild poliovirus infection and shedding; and minimal susceptibility of populations to wild poliovirus spread. Each principle alone is imperfect, but collectively they greatly minimize the risks of transmitting wild poliovirus from the laboratory to the community.

Keywords Poliovirus; Variola virus; Containment of biohazards/methods; Laboratories/standards; Laboratory infection/prevention and control; Poliovirus vaccine, Inactivated; Certification/standards (*source: MeSH, NLM*).

Mots clés Poliovirus humain; Virus variole; Maîtrise risque biologique/méthodes; Laboratoire/normes; Infection laboratoire/prévention et contrôle; Vaccin antipoliomyélitique inactivé; Certification/normes (*source: MeSH, INSERM*).

Palabras clave Poliovirus; Virus variola; Contención de riesgos biológicos/métodos; Laboratorios/normas; Infección de laboratorio/prevención y control; Vacuna antipolio de virus inactivados; Certificación/normas (*fuente: DeCS, BIREME*).

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Introduction

The Global Commission for the Certification of the Eradication of Poliomyelitis (GCC) will declare the world free of wild poliovirus transmission when no wild virus has been found for at least three consecutive years and all laboratories possessing wild poliovirus materials have adopted appropriate measures of laboratory containment (*1*). The strategy for achieving appropriate containment is described in *WHO's global action plan for laboratory containment of wild poliovirus* (Global Action Plan) (*2*), which is "a systematic plan of action to minimize the risk of reintroduction of wild polioviruses from the laboratory to the community". Effective containment for global certification is based on four principles (*3*): (1) minimal wild poliovirus infectious and potentially infectious materials in laboratories; (2) minimal risks of operations in laboratories and inactivated poliovirus vaccine (IPV) production facilities that might expose the workers or the community to wild poliovirus; (3) minimal susceptibility of workers to wild poliovirus infection and shedding; and (4) minimal susceptibility of community to wild poliovirus spread. This report describes the actions that address each of these principles and compares the containment of wild poliovirus with that of smallpox virus, which has been successfully in effect for more than 20 years (*4*).

Minimal wild poliovirus infectious and potential infectious materials in laboratories

The Global Action Plan requires each country to alert all biomedical laboratories to the impending eradication of polio, encourage laboratories to destroy all unneeded wild poliovirus infectious and potentially infectious materials, and establish a national inventory of laboratories retaining such materials (*5*). For purposes of containment, all polioviruses and laboratory derivatives of such viruses are considered wild except those strains approved by national control authorities for use as oral polio vaccines (OPV).

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Vaccine derived isolates genetically consistent with an extensive period of virus excretion or transmission in the community are also considered wild (*2*). The past ubiquitous nature of wild poliovirus and its use in many laboratories require that the global survey include several hundred times more than the 800 laboratories surveyed for the containment of smallpox virus.

The laboratory survey and inventory became an integral component of regional certification, first in the Western Pacific Region (certified in 2000) and then in the European Region (certified in 2002). At September 2003, 82/87 (94%) countries and territories in these two regions have completed national surveys of over 57 990 laboratories/institutions and submitted national inventories listing a combined total of over 450 laboratories retaining wild poliovirus materials. Even though containment was not a consideration at the time of certification in the Region of the Americas (1994), activities are now being conducted in all 48 countries/territories of the region, with the majority planning to submit a national inventory by the end of 2003.

Laboratory containment activities have also begun in WHO regions not yet certified polio free. At September 2003, all 28 non-endemic countries of the South East Asia and Eastern Mediterranean Regions have started the activities and 14 (50%) have already submitted a national inventory. Additionally, six pilot countries in the African Region began implementation this year with plans in place for using their experiences to assist the remaining non-endemic countries to start in early 2004.

When one year has elapsed without isolation of wild polioviruses anywhere in the world, WHO will notify nations that biosafety level (BSL)-3/polio containment is required for all wild poliovirus stocks. Laboratories that do not intend to meet the increased biosafety requirements will have one year following this notification to evaluate their stocks, destroy unneeded wild poliovirus infectious and potentially infectious materials, or transfer such materials to a qualified laboratory. Unlike smallpox virus containment with only two authorized laboratories (United States and the Russian Federation), laboratories may retain wild poliovirus materials if they are listed on a national inventory and meet the proscribed biosafety conditions. The large number of laboratories on the global inventory is expected to decrease greatly as countries and institutions consider the financial costs of containment and critically evaluate the responsibilities inherent in retaining a virus that is no longer transmitted in nature. Many laboratories have already documented and reported the destruction of all wild poliovirus materials. Numerous other countries, institutions, and laboratories have indicated their intention to destroy such materials at the appropriate time when asked to do so.

Minimal risk of operations in laboratories and IPV production facilities that might expose workers or the community to wild poliovirus

Laboratories

From 1941 to 1976, 12 cases of laboratory-associated poliomyelitis were reported, each representing an opportunity for transmission of the virus to the community (*6*). Since that time, highly effective biosafety standards for laboratory facilities, equipment, and practices have been developed to protect the community from the release of infectious materials into the environment and the laboratory worker from infections through needle sticks, spills, splashes or sprays, sharp objects, mouth pipetting, or centrifuging. However, not all laboratories of the world are equipped to meet those standards, and not all countries currently require them for poliovirus. A limited outbreak of seven poliomyelitis cases in late 2002 and early 2003 in India was associated with a common wild poliovirus type 2 laboratory reference strain that also served as the type 2 component of IPV (*7*). The source and mechanism of virus transmission in this incident remain unclear, but this outbreak illustrates the crucial need for adequate biosafety precautions in the laboratory, even before poliovirus transmission has been stopped.

In theory, wild poliovirus can be transmitted from the laboratory to the community through contaminated clothing, improperly inactivated waste and disposal streams, or an unrecognized infection of a laboratory worker or contact. The highest risks remain those laboratory operations involving poliovirus replication. The lowest risks are non-replicative, biosafety-appropriate operations performed with potentially infectious clinical and environmental materials. The biosafety requirements of the Global Action Plan reflect these different risks.

At the moment, the Global Action Plan recommends biosafety level-2 (*8*) for all work with wild polioviruses, with additional requirements for restricting laboratory access, and maintenance of accurate records of wild poliovirus materials (BSL-2/polio). Universal adoption and practice of these basic operating standards should provide a high degree of protection against inadvertent transmission of polioviruses and other infectious agents.

When two years have elapsed without isolation of wild polioviruses anywhere in the world, high-containment (BSL-3/polio) requirements will go into effect for all laboratories working with wild poliovirus infectious materials. Laboratories performing non-replicative procedures with potentially wild poliovirus materials may continue to work under BSL-2/polio conditions, which include the use of standard class II biosafety cabinets (*2*).

IPV production sites

The large volumes and high concentrations of wild poliovirus involved in preparing inactivated poliovirus vaccine make IPV production sites a particular containment concern. For example, in 1994 a wild poliovirus reference strain was recovered from an 18-month-old child whose father had been exposed to a spill in an IPV production facility (*9*). Inadvertent spillages might never be totally eliminated. However, the current strict rules of good manufacturing practices combined with oversight by national and international authorities make it highly likely that IPV production facilities will continue to operate under carefully controlled and monitored conditions.

To complement currently existing safeguards, WHO has issued guidelines for the safe production and quality control of IPV manufactured from wild polioviruses (*10*) that additionally require the introduction of comprehensive biosafety measures equivalent to large-scale BSL-3/polio containment in all facets of live production and testing. All IPV manufacturers have agreed to implement the outlined BSL-3/polio conditions at the time of global certification. Several vaccine manufacturers are also investigating the use of attenuated OPV strains for production of IPV to additionally reduce biosafety concerns.

Minimal susceptibility of workers to wild poliovirus infection and shedding

Fully immunized laboratory workers are a crucial element in effective containment. OPV and IPV stimulate comparable levels of serum immunoglobulin G (IgG) antibodies, effectively preventing viraemia and infection of the nervous system (*11*, *12*). Protection provided by either vaccine may persist for life. OPV

immunization more closely mimics the action of natural infection, offering the advantage of more broadly stimulating nasal and duodenal secretory immunoglobulin A (IgA) antibodies, which are considered to be the first line of defence against virus infection. A high percentage of people immunized with either vaccine and then challenged with OPV show protection against infection of the oropharynx (*13*, *14*). Intestinal infections occur with immunization of either vaccine, but fewer infections occur among OPV vaccinees.

The differences between IPV and OPV in preventing infection of the laboratory worker are more qualitative than absolute (*11*). Unlike vaccinia (*12*, *15*), neither of the two polio vaccines provides uniform protection against infection or reinfection. However, if an infection occurs in an immunized laboratory worker, any reduction in quantity and time of virus shedding may reduce the chance of infecting others.

Minimal susceptibility of community to wild poliovirus spread

When smallpox eradication was certified, many countries had already discontinued routine vaccination, mandating the need for high-security laboratory containment (*4*). When wild poliovirus eradication is certified, universal immunization recommendations will remain in force, greatly reducing the risk of wild poliovirus spread and providing additional opportunities to review inventories, poliovirus programmatic needs, and laboratory containment practices. Enforcement of the first three principles of effective containment will increase greatly in importance if present high immunization coverage rates begin to decline over time or if countries cease polio immunizations.

Issues

One year before global certification, each country must submit to the Regional Certification Commission (RCC) the final national inventory of institutions/laboratories retaining wild poliovirus materials and full documentation of wild poliovirus containment. When satisfied that documentation is complete, the RCC will certify to the GCC that laboratory containment in the region has been achieved. The quality of that documentation represents the combined qualities of the national laboratory survey, the national inventory of laboratories, and the biosafety facilities and practices of such laboratories and IPV production sites.

Pilot studies of the WHO assessment guidelines (*16*) in the European and Western Pacific Regions have shown that the quality and completeness of national laboratory surveys and laboratory inventories can be readily assessed. More difficult to assess is the quality and completeness of the signed laboratory form reporting the presence or absence of wild poliovirus materials. Opportunities for independent validation of laboratory freezer contents will vary according to national laws and regulations. In many countries, legal evidence of non-compliance is required before laboratory holdings may be inspected. However, even where permissible, onsite inspection is unlikely to detect intentionally or unintentionally mislabelled materials or stocks of other viruses contaminated with wild poliovirus (*17*, *18*). Similarly, oversight by national authorities or international authorities can ensure that appropriate certification level biosafety facilities and practices are in place in all laboratories on the global inventory, but they cannot ensure the day-to-day quality of laboratory operations. Ultimately, the responsibility for effective global containment of wild poliovirus materials rests on the individual laboratory. Therefore, it is crucial that each nation ensure that all laboratories on its national inventory have biosafety-appropriate facilities, high standards of laboratory practice, qualified supervision, trained staff, and institutional leadership committed to containment.

The BSL-3/polio high containment required for certification of eradication is anticipated to remain in effect until international decisions are made on global immunization policies in a polio-free world. At that time, post global certification containment requirements will be based on the effectiveness of existing containment practices, the number and location of countries anticipated to modify or stop immunization, and an evaluation of the need for more stringent containment measures, consistent with the increased consequences of virus transmission to the community.

Conclusions

The absolute laboratory containment of wild poliovirus, or any virus, cannot be guaranteed, but a wealth of experience indicates that effective containment is technically and operationally feasible on a global scale. The goal for global certification is the implementation of an effective containment system based on the principles of minimal wild poliovirus materials in laboratory facilities, minimal risk of operations in laboratories and IPV production sites, minimal worker susceptibility to infection and shedding, and minimal community susceptibility to poliovirus infection and spread. Each principle alone is imperfect, but collectively they will greatly minimize the risks of transmitting wild poliovirus from the laboratory to the community. ■

Conflicts of interest: none declared.

Résumé

Efficacité du confinement des poliovirus sauvages en laboratoire et de la limitation des sites de production du VPI pour la certification mondiale

S'il est impossible de garantir dans l'absolu le confinement d'un virus en laboratoire, un grand nombre d'expériences montrent à ce jour que, dans le cadre de la certification mondiale, le confinement efficace des matières renfermant des poliovirus sauvages est réalisable sur le plan technique et opérationnel. Il faut pour cela appliquer les principes suivants : conserver des quantités minimales de matériel infectieux ou potentiellement infectieux en laboratoire ; réduire au minimum les risques opérationnels dans les laboratoires et les sites de fabrication du vaccin antipoliomyélitique inactivé ; pour les employés de ces structures, présenter une sensibilité minimale à l'infection par le poliovirus sauvage et un risque minimal d'excrétion de celui-ci ; ramener au niveau minimal la sensibilité des populations à la propagation du virus sauvage. Chaque principe ne suffit pas à lui seul mais, appliqués conjointement, ils permettent une diminution importante du risque de transmission du poliovirus sauvage dans les communautés à partir des laboratoires.

Resumen

Contención del poliovirus salvaje en los laboratorios y en los centros de producción de vacuna antipoliomielítica inactivada: ¿una opción útil para la certificación mundial?

La contención absoluta de cualquier virus en el laboratorio no es algo que pueda garantizarse, pero la abundante experiencia adquirida indica que la contención del material de poliovirus salvaje con miras a la la certificación mundial sí es una alternativa técnica y operativamente viable. La eficacia de la contención se basa en los principios de reducción al mínimo del material de poliovirus salvaje infeccioso y potencialmente infeccioso; de los riesgos de las operaciones realizadas en los laboratorios y en los centros de producción de vacuna antipoliomielítica inactivada; de la vulnerabilidad de los trabajadores a la infección por poliovirus salvaje y a su eliminación; y de la vulnerabilidad de las poblaciones al poliovirus salvaje. Cada uno de esos principios es insuficiente por sí solo, pero aplicados conjuntamente reducen enormemente el riesgo de transmisión del poliovirus salvaje de los laboratorios a la comunidad.

ملخص

احتواء فيروسات شلل الأطفال والاستئصال العالمي

هل سيكون احتواء فيروسات شلل الأطفال في المختبرات ومواقع إنتاج اللقاح الذي يعطى حقناً ضد شلل الأطفال فعَّالاً في الاستئصال العالمي لشلل الأطفال؟

الملخص: لا يمكن ضمان الاحتواء المطلق في المختبرات لأي فيروس، إلا أن الخبرة المكتسبة أوضحت أن الاحتواء الفعَّال للمواد المتعلقة بالفيروسات البرية لشلل الأطفال من أجل الاستئصال العالمي لشلل الأطفال ممكن من الوجهتَيْن التقنية والميدانية. ويرتكز الاحتواء الفعَّال على المبادئ التالية: الحد الأدنى من العدوى بالفيروسات البرية لشلل الأطفال، ومن المواد التي يحتمل أن تحمل العدوى به في المختبرات، الحد الأدنى من احتمالات الخطر أثناء القيام بتشغيل المختبرات ومرافق إنتاج اللقاح المعطل لشلل الأطفال، الحد الأدنى من استعداد السكان لانتشار الفيروسات البرية لشلل الأطفال بينهم. ويعتبر كل مبدأ إذا إخذ لوحده غير كاف، ولابد من اجتماع المبادئ معاً لإنقاص احتمالات خطر سراية الفيروساتً البرية لشلل الأطفال من المختبرات إلى المجتمع لتصل إلى حدودها الدنيا.

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