A developing country perspective on vaccine-associated paralytic poliomyelitis

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Abstract When the Expanded Programme on Immunization was established and oral poliovirus vaccine (OPV) was introduced for developing countries to use exclusively, national leaders of public health had no opportunity to make an informed choice between OPV and the inactivated poliovirus vaccine (IPV). Today, as progress is made towards the goal of global eradication of poliomyelitis attributable to wild polioviruses, all developing countries where OPV is used face the risk of vaccine-associated paralytic poliomyelitis (VAPP). Until recently, awareness of VAPP has been poor and quantitative risk analysis scanty but it is now well known that the continued use of OPV perpetuates the risk of VAPP. Discontinuation or declining immunization coverage of OPV will increase the risk of emergence of circulating vaccine-derived polioviruses (cVDPV) that re-acquire wild virus-like properties and may cause outbreaks of polio. To eliminate the risk of cVDPV, either very high immunization coverage must be maintained as long as OPV is in use, or IPV should replace OPV. Stopping OPV without first achieving high immunization coverage with IPV is unwise on account of the possibility of emergence of cVDPV. Increasing numbers of developed nations prefer IPV, and manufacturing capacities have not been scaled up, so its price remains prohibitively high and unaffordable by developing countries, where, in addition, large-scale field experience with IPV is lacking. Under these circumstances, a policy shift to increase the use of IPV in national immunization programmes in developing countries is a necessary first step; once IPV coverage reaches high levels (over 85%), the withdrawal of OPV may begin.

Keywords Poliovirus vaccine, Oral/adverse effects; Poliomyelitis/epidemiology/chemically induced; Poliovirus vaccine, Inactivated/therapeutic use/economics; Poliovirus/drug effects; Immunization programs; Developing countries (*source: MeSH, NLM*).

Mots clés Vaccin antipoliomyélitique Sabin/effets indésirables; Poliomyélite antérieure aiguë/épidémiologie/induite chimiquement; Vaccin antipoliomyélitique inactivé/usage thérapeutique/économie; Poliovirus humain/action des produits chimiques; Programmes de vaccination; Pays en développement (*source: MeSH, INSERM*).

Palabras clave Vacuna antipolio oral/efectos adversos; Poliomielitis/epidemiología/inducida químicamente; Vacuna antipolio de virus inactivados/uso terapéutico/economía; Poliovirus/efectos de drogas; Programas de inmunización; Países en desarrollo (*fuente: DeCS, BIREME*).

الكلمات المفتاحية: لقاح شلل الأطفال، اللقاح الفموي لشلل الأطفال، التأثيرات الضائرة للقاح الفموي لشلل الأطفال، شلل الأطفال، وبائيات شلل الأطفال، شلل الأطفال المحرض كيميائياً، لقاح شلل الأطفال المعطَّل، الاستعمال العلاجي للقاح شلل الأطفال المعطَّل، اقتصاديات شلل الأطفال المعطَّل، التأثيرات الدوائية لفيروس شلل الأطفال، برامج التمنيع، البلدان النامية (**المصدر:** رؤوس الموضوعات الطبية، **المكتب الإقليمي لشرق المتوسط**)

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Introduction

"From a humanitarian perspective, eradication provides the ultimate in health equity and social justice, bringing identical and universal benefits to every person globally" (*1*). This article examines how identical and universal these benefits have been. Industrialized countries used either the inactivated poliovirus vaccine (IPV) or the oral poliovirus vaccine (OPV), alone or in sequence, in routine immunization, and thereby rapidly controlled or even eliminated poliomyelitis caused by wild polioviruses (*2–4*).

WHO advocated OPV exclusively for developing countries both in the Expanded Programme on Immunization (EPI, established in 1974) and for polio eradication (from 1988) (*5*). The five promised advantages of OPV were low cost; ease of administration; high vaccine efficacy for low number of doses; mucosal immunity to stop virus transmission; and vaccine-related virus spread contributing to "contact immunization" (*1, 5–7*). Accumulated experience and evidence question the reality or impact of some of the putative advantages of OPV (*8–11*). Consequently, eradication has been an uphill task in developing countries, necessitating nearly 100% OPV coverage with 10–15 doses per preschool child, given in EPI activities and through supplementary immunization campaigns (*7*).

The incidence of vaccine-associated paralytic poliomyelitis (VAPP) was considered low enough to qualify OPV as "one of the safest vaccines in current use" by WHO (*12, 13*). In the pre-EPI era, 600 000–800 000 cases of polio occurred annually, the vast majority in developing countries. Many experts accepted VAPP as a price for the greater benefit of controlling wild poliovirus

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using OPV. The countries themselves, however, had no opportunity to make an informed choice between vaccines. While progress is made towards eradication, VAPP is now becoming more frequent than polio attributable to wild poliovirus infection (*14–16*). How many VAPP cases, if any, are acceptable in developing countries? Will continued occurrence of VAPP jeopardize the very success of eradication? Will options to eliminate VAPP be affordable? These are essential questions to be solved from a developing country perspective.

The risk and burden of VAPP in developing countries

Clinically, VAPP is indistinguishable from polio caused by wild poliovirus, with an identical incubation period, range of severity and case-fatality rate (*12–21*). In surveillance for eradication, poliovirus isolates from children with acute flaccid paralysis (AFP) are characterized as wild or vaccine-derived by reliable laboratory techniques. Identification of wild virus confirms "polio" but all other cases including VAPP are classified as "non-polio" (*14, 15*). Finding vaccine-derived virus in cases of AFP does not prove VAPP, as it may be a mere passenger infection. Applying specific diagnostic criteria, there were 139 cases of VAPP in Latin America in 1989–91 and 181 cases in India in 1999 (*14, 15*). Assuming an annual average of 45 cases in Latin America, the total in Latin America and India is 226 cases a year. Thus the annual global burden of 120 cases of VAPP expected by the WHO Technical Consultative Group (TCG) for Poliomyelitis Eradication is a gross underestimate (*17*). A realistic estimate could be as high as 400–800 (*16*).

WHO determined the annual incidence of VAPP in European countries to be 0.4–3.0 per million vaccinated children and documented intercountry variations in its frequency (*12,13*). Disease surveillance to detect VAPP was recommended in countries using OPV, but was not included in the EPI (*12, 13*). Thus the risk of VAPP remained unnoticed in developing countries. Geographical variation in the risk of VAPP has been confirmed in all subsequent studies (*2–4, 14–16, 18, 19*). Prior to the introduction of immunization, polio incidence showed considerable geographical variation, and its determining factors may also apply to VAPP (*16*). In India, the annual incidence of polio in the 1970s and 1980s was 20–40 per 100 000 population (or 2 cases per 1000 children under five years of age), one of the highest in the world (*22–25*). The incidence of VAPP in India, based on 181 cases in 125 million under-5-year-old children in one year, of 1.45 per million children per year, or seven cases per million birth cohorts, is also one of the highest in the world (*16, 17*). Developing countries with high incidence of polio should have been warned about VAPP, but its incidence was not prospectively assessed. Today, available data are inadequate to project a realistic incidence of VAPP in developing countries.

Norway introduced IPV in 1956 and shifted to OPV in 1967. During 1967–78 the frequency of vaccine-recipient VAPP was one per 400 000 vaccinated children and that of contact VAPP one per 100 000 vaccinated children, as a consequence of which Norway reverted to IPV in 1979 (*3*). In the USA, annual risk of VAPP was one case per 750 000 vaccinated children for an average of eight cases per year, for which reason OPV was abandoned in favour of IPV (*18, 20, 21*). In Latin America the risk was one case per 1.1–1.2 million first doses distributed, but risk for subsequent doses was "substantially higher than in the USA" (*14*). It is clear that VAPP occurs only if vaccine-related polioviruses infect children. There are geographical variations in the frequency of infection following the first or subsequent doses (*8–11*). The infection rate following one dose in a temperate region is achieved with three doses in India (*8–11*). To match the rate for three doses in the USA, 10 doses are required in India (*9*). Because of gross differences in the number of doses given in different settings, "doses of vaccine distributed" is not a suitable denominator for intercountry comparison of the risk of VAPP (*16*).

Outbreaks of VAPP, a warning signal

The attenuation of polioviruses has resulted in drastic reduction in infectiousness and transmissibility (*9, 26*). The median monkey oral infectious dose of Sabin virus (type 1) is 4 $\log_{10}$ higher than that of wild virus (Mahoney strain) (*9, 26*). When $10^{6.5}$ median cell culture infectious doses of Sabin virus (type 3), ten times higher than in OPV, were given to antibody-negative children in India, only 76% became infected (*27*). Vaccine-related polioviruses do not establish sustained circulation in the community, in contrast to wild polioviruses. Neurovirulence may re-establish by genetic reversion (*28, 29*). If both neurovirulence and transmissibility are regained, the resultant circulating vaccine-derived poliovirus (cVDPV) becomes wild-like (*30*). A cVDPV type 2 circulated for 10 years (1983–93) in Egypt, causing 32 cases of polio (*31*). A cVDPV type 1 circulated silently in the Dominican Republic and Haiti from 1998 and caused an outbreak of polio (21 confirmed and 15 probable cases) from July 2000 to July 2001, until interrupted by outbreak response vaccination (*30*). Since then, cVDPV has been detected in small clusters in Madagascar, the Philippines and Romania (*32* and D. Wood, personal communication, 2003).

In Haiti, the national immunization days were discontinued and immunization coverage declined after polio eradication was certified in the Americas in 1991. The resultant population mix of non-immune children and recently immunized vaccine virus-shedding children offered the milieu for a revertant virus to spread silently and cause outbreaks, as seen in Egypt and Haiti (*30, 31*). If immunization coverage remains high, as in the Philippines and Romania, such revertants do not spread widely. Thus, both continuing OPV and its gradual or abrupt discontinuation may carry the risk of emergence of cVDPV. Any developing country wanting to discontinue OPV to avoid VAPP risks the emergence of cVDPV, unless children are adequately protected with IPV.

Even if cVDPVs emerge only rarely and in a distant community, they are a threat everywhere as they could circulate widely and be imported elsewhere. Therefore, rich countries using IPV are unlikely to discontinue it until OPV has been discontinued everywhere. This upsets the economic attraction of eradication — the saving from discontinuing immunization (*33*). As the elimination of wild viruses was accomplished in most developing countries using OPV, the few remaining countries also must follow suit to achieve success without losing time to execute a change in policy. Therefore it is necessary to consider only the issue of eliminating the risk of VAPP using IPV where wild viruses have been eliminated. Once VAPP is also globally "eradicated", discontinuing polio immunization will become feasible. Thus, the availability and affordability of IPV and its suitability in EPI in developing countries are the critical aspects of the solution to the problems of sporadic VAPP and emergence of cVDPV. Discontinuing OPV in developing countries is in the best public health and economic interests of industrialized countries too.

IPV and the final phase of polio eradication

Well-off countries are replacing OPV with IPV to eliminate VAPP. Currently, 22 countries are using IPV exclusively and eight more have a sequential schedule of IPV and OPV (D. Wood, personal communication 2003). This situation has begun to evolve as rich–poor disparity. Global public health leaders are divided on the acceptability of VAPP in developing countries. Some perceive the double standard, as developing countries will be exposed to a risk that the industrialized nations will avoid (*34*). The philosophical attraction of disease eradication is that it will achieve equity in health benefit globally (*1*). Equity demands that no child will develop polio attributable to wild poliovirus or vaccine-related virus. The hope expressed "that politicians in developing countries and zealous ethicists in the developed world … will not demand, in the name of equity in health, a total switch to IPV" (*35*) deserves rejection. The opportunity to advance a developing country perspective, even if only in a journal article, is comforting. The immediate responsibilities of WHO and its partner agencies in polio eradication are to assess the economic repercussions of eliminating the risk of sporadic and outbreak VAPP, to alert developing countries and donors to the risk, and to design ways of minimizing and sharing the costs.

At present, very few manufacturers produce IPV and the production capacity is only 100 million doses (*35*). This is insufficient for meeting the increasing demand even from industrialized countries. Since demand outstrips supply, the price remains high. The volume of manufacture affects the cost of a vaccine. The current low volume of IPV manufacture was determined by low demand in previous years, which in turn was determined by the exclusive OPV policy in developing countries. A change in policy and an assured future market volume will encourage established manufacturers to augment, and new companies to invest in, IPV production. Such market forces are bound to lead to a reduction in the price of IPV. If IPV is combined with the diphtheria–tetanus–pertussis vaccine (DTP), one separate shelf item and additional health worker–child contacts and injections can be avoided, reducing the overall cost of polio immunization. Today, OPV is given both according to routine schedules as well as in annual pulse campaigns, increasing the cost of vaccine administration. Even after the certification of eradication of wild polioviruses, the continued use of OPV for an interim period for interrupting transmission of any lurking virus anywhere — or its importation to new territories — will have to be through pulsing, for the routine method was inadequate to halt transmission in the past. In Haiti the pulse campaigns were discontinued, paving the way for emergence of the outbreak of polio caused by vaccine-derived wild-like poliovirus (*30*). The large expenses for pulse campaigns will also be saved with the use of IPV under EPI.

The final question is about the suitability of IPV in the EPI system for assured interruption of unrecognized surviving, imported or introduced wild poliovirus or cVDPV anywhere. Experience with IPV in developing countries is meager on account of the policy to use exclusively OPV. There are several sources of information that IPV will be suitable, but they are not elaborated here (*9–11, 36, 37*). More details may be found in two recent publications (*10, 11*). However, the schedule of injections in EPI — at 6, 10 and 14 weeks — is not ideal in order to get the best antibody response in infants (*36–38*). In countries where the frequency of antibody response to OPV is excellent, this schedule may not match it (*36–38*). In contrast, where the frequency of response to OPV is low, which is the case in most developing countries, the IPV responses will be superior (*12*). Any deficiency in antibody response can be more than overcome with one booster injection of DTP-combined IPV in the second year of life (*39, 40*). Thus, the level of immune protection achieved at present by the fifth year of life with OPV (given in the EPI schedule plus annual 2-dose pulses until 5 years of age) can be matched with that achieved in the second year of life using IPV. Such an approach can be expected to offer better herd protective effect than that obtained with multiple doses of OPV (*9, 10*). From both the humanitarian and scientific viewpoints any polio paralysis should be prevented, not merely that caused by wild viruses. Therefore, polio eradication must be perceived as truly the zero incidence of poliovirus infection, both wild and vaccine-derived, in developed and developing countries (*41*). ■

Conflicts of interest: none declared.

Résumé

Poliomyélite paralytique postvaccinale : le point de vue des pays en développement

Lorsque le Programme élargi de Vaccination a été créé et qu'on a introduit le vaccin antipoliomyélitique oral (VPO), exclusivement utilisé par les pays en développement, les responsables nationaux de la santé publique n'ont pas eu l'occasion d'effectuer un choix éclairé entre le VPO et le vaccin antipoliomyélitique inactivé (VPI). Aujourd'hui, au fur et à mesure des progrès réalisés vers l'objectif de l'éradication mondiale de la poliomyélite due aux poliovirus sauvages, l'ensemble des pays en développement dans lesquels le VPO est employé sont confrontés au risque de poliomyélite paralytique postvaccinale (PPPV). Il y a peu encore, la PPPV était mal connue et l'analyse quantitative de ce risque limitée, mais on sait bien aujourd'hui que l'utilisation continue du VPO fait perdurer le risque de PPPV. L'interruption ou la diminution de la couverture vaccinale par le VPO augmentera le risque d'émergence de poliovirus circulants dérivés d'une souche vaccinale (PcDSV) qui reprennent des propriétés de type « virus sauvage » et risquent de provoquer des flambées de poliomyélite. Pour éliminer le risque de PcDSV, il faut maintenir une couverture vaccinale très élevée aussi longtemps que le VPO est utilisé, ou remplacer ce dernier par le VPI. Interrompre la vaccination par le VPO sans d'abord parvenir à une couverture vaccinale élevée par le VPI serait imprudent compte tenu de la possibilité que les PcDSV apparaissent. Un nombre croissant de pays industrialisés préfèrent le VPI et, comme les moyens de production n'ont pas encore été augmentés proportionnellement, son prix reste prohibitif et hors de portée des pays en développement pour lesquels, en outre, une expérience de terrain à grande échelle de l'utilisation du VPI manque. Dans ces conditions, une réorientation des politiques vaccinales visant à accroître l'utilisation du VPI dans les programmes de vaccination nationaux des pays en développement est une première étape nécessaire ; une fois que la couverture du VPI sera importante (supérieure à 85 %), le retrait du VPO pourra être amorcé.

Resumen

Poliomielitis paralítica asociada a la vacuna: perspectiva de los países en desarrollo

Cuando se estableció el Programa Ampliado de Inmunización y se introdujo en los países en desarrollo el uso exclusivo de la vacuna antipoliomielítica oral (OPV), los dirigentes de la salud pública de los países no tuvieron la oportunidad de hacer una elección con conocimiento de causa entre la OPV y la vacuna antipoliomielítica inactivada (IPV). Hoy, a medida que se avanza hacia la meta de la erradicación mundial de la poliomielitis atribuible a poliovirus salvajes, todos los países en desarrollo en los que se usa la OPV se enfrentan al riesgo de poliomielitis paralítica asociada a la vacuna (PPAV). Hasta fechas recientes había poca conciencia de la PPAV y se habían realizado escasos estudios cuantitativos del riesgo, pero ahora se sabe perfectamente que el uso continuado de la OPV perpetúa el riesgo de PPAV. La disminución de la cobertura con la OPV o la interrupción de su administración aumentará el riesgo de que aparezcan poliovirus circulantes derivados de la vacuna que recobren propiedades similares a las del virus salvaje y ocasionen brotes de poliomielitis. Para eliminar el riesgo de que aparezcan estos virus habrá que mantener una cobertura muy elevada mientras se siga utilizando la OPV o habrá que sustituirla por la IPV. Sin embargo, debido a la posible aparición de poliovirus circulantes derivados de la vacuna, sería imprudente detener la vacunación con la OPV antes de haber alcanzado una alta cobertura con la IPV. El número de países industrializados que prefieren la IPV está en aumento, pero la capacidad de fabricación no se ha ampliado, por lo que su precio sigue siendo prohibitivo e inasequible para los países en desarrollo, en los cuales, además, no hay experiencia de campo a gran escala con la IPV. En estas circunstancias, el primer paso debería ser un cambio de política para aumentar el uso de la IPV en los programas nacionales de inmunización de los países en desarrollo; una vez que la cobertura de la IPV sea elevada (superior al 85%), se podrá empezar a retirar la OPV.

ملخص

السياسات في حيِّز التطبيق
شلل الأطفال الشللي المصاحب للقاح
وجهة نظر أحد البلدان النامية حول شلل الأطفال الشللي المصاحب للقاح

الملخص: عندما أسس البرنامج الموسَّع للتمنيع وأدخل اللقاح الفموي لشلل الأطفال في البلدان النامية على نطاق واسع، لم يكن لدى القادة الوطنيين للصحة العمومية فرصة للاطِّلاع على الاختيار بين اللقاح الفموي واللقاح المعطَّل لشلل الأطفال. واليوم، ومع إحراز تقدُّم نحو تحقيق هدف استئصال شلل الأطفال الذي تسبِّبه فيروسات شلل الأطفال البريّة من العالم، فإن جميع البلدان النامية التي يستعمل فيها اللقاح الفموي لشلل الأطفال تواجه خطر شلل الأطفال الشللي المصاحب للقاح، ولايزال الوعي حول شلل الأطفال الشللي المصاحب للقاح قليلاً، ولايزال تحليل احتمالات الخطر قليلاً، إلا أن من المعروف اليوم بوضوح أن تواصل استعمال اللقاح الفموي لشلل الأطفال سيزيد من احتمال خطر الإصابة بشلل الأطفال الشللي المصاحب للقاح، إن إيقاف أو إنقاص معدلات التغطية باللقاح الفموي لشلل الأطفال سيزيد من احتمال خطر بزوغ وسراية فيروسات شلل الأطفال المنبثقة عن اللقاحات، والتي تكتسب خصائص مشابهة للفيروسات البرية لشلل الأطفال، وقد تسبب فاشيات من شلل الأطفال. ومن هنا إذا أريد القضاء على احتمال خطر سراية فيروسات شلل الأطفال المنبثقة عن اللقاح، فإما أن يحافظ على معدلات عالية جداً للتغطية طيلة استعمال اللقاح الفموي لشلل الأطفال، أو يستعاض عن اللقاح الفموي لشلل الأطفال باللقاح الذي يعطى حقناً. وليس من الحكمة إيقاف اللقاح الفموي لشلل الأطفال قبل إحراز معدلات عالية للتغطية باللقاح الذي يعطى حقناً، إذ يكون ذلك على حساب احتمالات بزوغ فيروسات شلل الأطفال المنبثقة عن اللقاح. إن الأعداد المتزايدة من البلدان الصناعية تفضل استعمال اللقاح الذي يعطى حقناً لشلل الأطفال، كما أن عدم تزايد قدرات التصنيع يجعل أسعارها مرتفعة يصعب على البلدان النامية تحملها، وهناك نقص في الخبرة الميدانية حول استعمال اللقاح الذي يعطى حقناً لشلل الأطفال على نطاق واسع؛ وكل هذه الظروف أدت إلى تحول في السياسات إلى ضرورة ازدياد في استخدام اللقاح الذي يعطى حقناً لشلل الأطفال في البرامج الوطنية للتمنيع في البلدان النامية لتكون الخطوة الأولى والضرورية، وحالما يصل معدل التغطية باللقاح الذي يعطى حقناً لشلل الأطفال إلى مستويات مرتفعة (تزيد عن ٨٥٪) يمكن البدء بسحب تدريجي للقاح الفموي لشلل الأطفال.

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Commentary

A developing country perspective on vaccine-associated paralytic poliomyelitis

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I started to read the abstract to Jacob John's review on vaccine-associated paralytic polio (VAPP) in full agreement with his observation that wherever oral poliovirus vaccine (OPV) is used, there are risks of VAPP to vaccinees and their contacts. Indeed, where polio immunization programmes are poorly implemented, there are risks of circulating vaccine-derived polioviruses (cVDPV). However, by the time I reached the end of the abstract, I found myself seriously disagreeing with much of what Jacob John had to say, and even more so by the end of the article.

Jacob John raises the spectre of cVDPV to give credibility to the potential seriousness of revertent vaccine strains. We have known for many years that VAPP is a rare but measurable consequence of the use of OPV, and until relatively recently there had been no concern that outbreaks of polio followed VAPP cases. The greatest risks of cVDPV are when immunization coverage is low, but VAPP is more likely to occur the higher the coverage in any population.

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I was seriously worried when I read the proposition that developing countries should shift to inactivated polio vaccine (IPV), and that once IPV coverage reached high levels, the withdrawal of OPV could begin. Did this mean that developing countries should introduce IPV as well as using OPV and discontinue the latter only when the IPV coverage was high? How would that impact on the costs of polio eradication? How would high IPV coverage be achieved? What does this say about inequalities when some children who will receive OPV are denied the benefits given to others, who receive IPV, within the same country? And how could a mixed programme be implemented in a developing country?

Many of Jacob John's arguments are based on the belief that many more doses of OPV are needed per child to protect against polio in developing countries than would be needed if IPV were used in the routine programme, and he advocates a switch to IPV to prevent the high cost of supplementary campaigns with OPV. This argument could be justified only if there was convincing evidence that IPV is as effective as or more effective than OPV in interrupting polio transmission in a developing country setting. Also, routine coverage would need to be sufficient to prevent the accumulation of enough children who are susceptible to polio and who might, therefore, sustain the transmission of wild polioviruses should they occur — or even cVDPV should there be any OPV being used in the population. Given that the countries currently posing the final barriers to polio eradication are those with the lowest immunization coverage through routine services, this seems to be a high-risk approach. He suggests that primary immunization with diphtheria–tetanus–pertussis (DTP)-IPV plus a dose of DTP-IPV in the second year would be as effective as — and safer than — primary OPV immunization followed by annual doses in campaigns, until a child reached 5 years of age. Although this may be valid for individual protection, it brings high risks on a population basis, most especially in countries where routine primary coverage is low and routine fourth doses do not even exist.

It is true that many countries are switching to IPV, and it is also true that VAPP is as much a tragedy for the individual as the natural disease itself. Jacob John fails to identify how routine coverage can be brought up to levels at which IPV can be substituted for OPV, or even convinces that it needs to be used universally once polio transmission has been interrupted. In Cuba, where there is no routine provision of OPV outside of annual campaigns, cVDPV has not been documented in the face of excellent surveillance.

Finally, I was concerned by the statement that "developing countries … should have been warned about VAPP". Polio eradication represents a phenomenal global partnership in health, between countries and international organizations. Nevertheless, there are responsibilities on all of the partners to be properly informed, especially those who accept responsibilities on behalf of their populations. ■

Conflicts of interest: none declared.