Research

Theme Papers

Search for poliovirus carriers among people with primary immune deficiency diseases in the United States, Mexico, Brazil, and the United Kingdom

Neal A. Halsey,[1,2] Jorge Pinto,[3] Francisco Espinosa-Rosales,[4] María A. Faure-Fontenla,[5] Edson da Silva,[8] Aamir J. Khan,[1] A.D.B. Webster,[6] Philip Minor,[7] Glynis Dunn,[7] Edwin Asturias,[1] Hamidah Hussain,[1] Mark A. Pallansch,[9] Olen M. Kew,[9] Jerry Winkelstein,[2] Roland Sutter,[9] & the Polio Project Team*

Objective To estimate the rate of long-term poliovirus excretors in people known to have B-cell immune deficiency disorders.
Methods An active search for chronic excretors was conducted among 306 persons known to have immunoglobulin G (IgG) deficiency in the United States, Mexico, Brazil, and the United Kingdom, and 40 people with IgA deficiency in the United States. Written informed consent or assent was obtained from the participants or their legal guardians, and the studies were formally approved. Stool samples were collected from participants and cultured for polioviruses. Calculation of the confidence interval for the proportion of participants with persistent poliovirus excretion was based on the binomial distribution.
Findings No individuals with long-term excretion of polioviruses were identified. Most participants had received oral poliovirus vaccine (OPV) and almost all had been exposed to household contacts who had received OPV. Polioviruses of recent vaccine origin were transiently found in four individuals in Mexico and Brazil, where OPV is recommended for all children.
Conclusion Although chronic poliovirus excretion can occur in immunodeficient persons, it appears to be rare.

Keywords Poliovirus/isolation and purification; Carrier state; Poliomyelitis/chemically induced/transmission; Poliovirus vaccine, Oral/ adverse effects; IgA deficiency; IgG deficiency; Common variable immunodeficiency; Agammaglobulinemia; United States; Mexico; Brazil; United Kingdom (*source: MeSH, NLM*).

Mots clés Poliovirus humain/isolement et purification; Porteur germes; Poliomyélite antérieure aiguë/induite chimiquement/transmission; Vaccin antipoliomyélitique Sabin/effets indésirables; IGA, Déficit; IgG, Déficit; Immunodéficit commun variable; Agammaglobulinémie; Brésil; Etats-Unis; Mexique; Royaume-Uni (*source: MeSH, INSERM*).

Palabras clave Poliovirus/ aislamiento y purificación; Portador; Poliomielitis/inducida químicamente/transmisión; Vacuna antipolio oral/efectos adversos; Deficiencia de IgA; Deficiencia de IgG; Inmunodeficiencia variable común; Agammaglobulinemia; Estados Unidos; México; Brasil; Reino Unido (*fuente: DeCS, BIREME*).

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[1] Institute for Vaccine Safety, Department of International Health, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21205, USA (email: tproveau@jhsph.edu). Correspondence should be sent to Dr Halsey at this address.
[2] Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
[3] Department of Pediatrics, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil.
[4] Immunology Department, Instituto Nacional de Pediatría, Mexico City, Mexico.
[5] Immunology and Rheumatology Laboratory, Hospital Infantil de México Federico Gomez, Mexico City, Mexico.
[6] Department of Immunology, University College Medical School, London, England.
[7] National Institute for Biological Standards and Control, Hertfordshire, England.
[8] Oswaldo Cruz Foundation, Rio de Janeiro, Brazil.
[9] Centers for Disease Control and Prevention, Atlanta, GA, USA.

* **Polio Project Team**
Brazil: Claudete Araujo (Universidade Federal de Minas Gerais), Marluce Vilela (Universidade de Campinas-UNICAMP), Cristina Jacob and Antonio Pastorino (Instituto da Criança-Universidade de São Paulo), Anete Grumach and Dewton Vasconcelos (Universidade de São Paulo-São Paulo), Beatriz Carvalho (Universidade Federal de São Paulo-UNIFESP), Virgínia Ferriani (Universidade de São Paulo-Ribeirão Preto), Nelson Rosario (Universidade Federal do Paraná), Aluce Ouricuri (Hospital dos Servidores do Estado do Rio de Janeiro), and Norma Rubini (Universidade Estadual do Rio de Janeiro).
United States: Roger H. Kobayashi (UCLA School of Medicine), Craig M. Moffat (Salt Lake Clinic), Mark A. Posner (Allergy/Asthma Specialists PC), Robert Albert Dracker (North Syracuse, NY), Alexander R. Lawton (Vanderbilt University School of Medicine), A. Timothy Linehan (Burns Clinic, Petoskey, MI), and William R. Lumry (Dallas, TX).

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Introduction

Susceptible individuals usually excrete polioviruses for 2–6 weeks, and occasionally for up to 137 days after they have been immunized with oral poliovirus vaccine (OPV) (*1–5*). The shed viruses frequently show increased neurovirulence and are often transmitted to close contacts. Patients with B-cell immune deficiency disorders are at increased risk of complications associated with enterovirus infections, including chronic meningoencephalitis, long-term intestinal excretion of the viruses, and vaccine-associated paralytic poliomyelitis (VAPP) (*6*). Nineteen individuals with excretion of vaccine-derived polioviruses for six or more months have been reported in the literature or to WHO (*7–9*) (D. Wood, personal communication, 2003). All but three of these individuals are known to have stopped excreting polioviruses or died. Some became paralysed several years after acquiring the intestinal infection (*7*, *10*). Viruses isolated in the stool of vaccinated individuals typically revert to increased neurovirulence, and long-term excretors shed viruses that are often as neurovirulent as wild-type viruses (*7*, *11–13*). Persistent intestinal poliovirus excretors could theoretically reintroduce polioviruses into general circulation if routine immunization of children was stopped after the eradication of wild-type viruses (*10–14*). We studied people known to have B-cell immune deficiency disorders in four countries in order to estimate the rate of long-term poliovirus excretors in this at-risk population.

Methods

Study population

United States

Families registered with the Immune Deficiency Foundation (www.primaryimmune.org) were sent a letter inviting people 3–35 years of age with common variable immune deficiency (CVID), X-linked agammaglobulinaemia (XLA) or selective immunoglobulin A (IgA) deficiency to participate in the study. Participants who returned a postcard were mailed a consent form, a brief questionnaire, a request for laboratory results validating the diagnosis, and instructions for collecting and shipping a stool specimen. Subsequently, selected immunologists were asked to enroll patients with CVID or XLA who were two or more years of age.

Mexico

Eligible people were recruited from the immunology clinics at the Hospital Infantil de Mexico "Dr Federico Gomez" and Instituto Nacional de Pediatria.

Brazil

Participants were recruited from nine referral centres for the treatment of primary immunodeficiencies, and virus cultures were performed at the Enterovirus Laboratory (WHO Regional Reference Laboratory at Instituto Oswaldo Cruz, Rio de Janeiro). The diagnostic criteria for CVID, XLA, and selective IgA deficiency were based on the International Consensus Guidelines for Diagnosis of Primary Immunodeficiencies (*15*).

United Kingdom

Participants with primary immunodeficiency were recruited from patients attending an immunology clinic at the Royal Free Hospital in London.

Consent and Institutional Review Board approvals

Written informed consent was obtained from participants or their legal guardians and assent was obtained from children aged five years or more. These studies were approved by the Joint Committee on Clinical Investigation (JCCI) at the Johns Hopkins University School of Medicine or the Committee on Human Research (CHR) at the Johns Hopkins Bloomberg School of Hygiene and Public Health. The study of people in the United States was approved by the Centers for Disease Control and Prevention (CDC; Atlanta, GA) Institutional Review Board, the study in Mexico by Instituto Nacional de Pediatria, and the study in Brazil by the Federal University of Minas Gerais and other participating institutions.

Specimen collection and processing

WHO-recommended kits were used for collection of 5–10 g of stool. *Protocult* (©1990 ABC Medical Enterprises, Rochester, MN) receptacle collection devices were shipped to individuals in the United States. Specimens were then shipped by overnight delivery to New York, Wisconsin, Texas, or California state health department laboratories in the United States or transported in refrigerator packs by participants to the immunologists and then to laboratories in Mexico City (Instituto Nacional Diagnostica y Referencia Epidemiologio) and Brazil. In the United Kingdom, stool samples were sent by post to the National Institute for Biological Standards and Control. Specimens not processed immediately were frozen at –70° C until cultured for polioviruses in accordance with WHO guidelines on L20B and either HEp-2 or RD cell lines (*16*). In the United Kingdom samples were cultured on L20B, RD, and HEp-2 cells. Cell cultures testing positive for polioviruses were further characterized by partial genomic sequencing at either the CDC or at the Oswaldo Cruz Foundation (Rio de Janeiro, Brazil) (*17*). The results of the cultures were submitted to the family and/or treating physician as per the family's request. Individuals with positive cultures for poliovirus had an additional specimen collected approximately three months later, which was tested using the same procedure. Polymerase chain reaction for poliovirus was also performed on stool samples in the United Kingdom.

Calculation of the confidence interval for the proportion of participants with persistent poliovirus excretion was based on the binomial distribution (Stata Corporation, Stata Statistical Software: Release 7.0; College Station, TX, 2001).

Results

Baseline characteristics of the study population recruited from different centres are shown in Table 1. Participants with IgG deficiency ranged from 1.5 to 71 years of age, but the median ranges were from 11.8 to 18.1 years. There was a slight predominance of males with CVID and a striking predominance of males with agammaglobulinaemia. Four females had one of the different forms of autosomal recessive congenital agammaglobulinaemia.

In the United States, 212/529 potentially eligible members of the Immune Deficiency Foundation returned a postcard and were mailed consent forms and instructions, and 88 submitted specimens to laboratories. An additional 37 patients were contacted directly by their immunologists. In Mexico, Brazil, and the United Kingdom, participants were enrolled by their immunologist or primary care provider. Participants were recruited as they presented for routine care. Immunologists estimated that 75–100% of eligible persons participated at different centres.

Table 1. **Baseline characteristics of the study population recruited from different centres**

	Agammaglobulinaemia	CVID[a]	Hypogammaglobulinaemia	IgA[b]	Total
United States					
No. of participants	20	65	0	40	**125**
Gender (M/F)[c]	19/1	31/34	NA[d]	20/20	
Median age at enrollment (years)	11.81 (5 –38)[e]	18.08 (5–71)[e]	NA[d]	26.69 (5–89)[e]	
Mexico					
No. of participants	20	5	8[f]	0	**33**
Gender (M/F)[c]	18/2	4/1	5/3	NA[d]	
Median age at enrollment (years)	7.2 (1.5–19)[e]	6.9 (5.5–8.27)[e]	6.76 (1–16.7)[e]	NA[d]	
Brazil					
No. of participants	25	70	0	0	**95**
Gender (M/F)[c]	24/1	42/28	NA[d]	NA[d]	
Median age at enrollment (years)	13.21 (2.4–31)[e]	15.29 (1.5–45.6)[e]	NA[d]	NA[d]	
United Kingdom					
No. of participants[g]	18	75	1[f]	0	**94**
Gender (M/F)[c]	18/0	39/36	1/0	NA[d]	
Total	**83**	**215**	**9**	**40**	**347**

[a] CVID = common variable immune deficiency.
[b] IgA = immunoglobulin A.
[c] M/F = male/female.
[d] NA = not applicable.
[e] Figures in parentheses are ranges.
[f] Two individuals had hyper IgM syndrome with severe hypogammaglobinaemia.
[g] Age range: 5–75 years.

Table 2. **Virus isolations from people with IgG[a] deficiency disorders, by country**

	Vaccine-like polioviruses	Adenoviruses	Non-polio enteroviruses	No viruses	Total studied
United States	0	3	0	81	84[b]
Mexico	1	0	4	28	33
Brazil	3	0	15	77	95
United Kingdom	0	0	0	94	94
Total	**4**	**3**	**19**	**280**	**306**

[a] IgG = immunoglobulin G.
[b] Stool culture from one participant with common variable immune deficiency was lost.

One stool specimen was obtained from all participants in the United States, Mexico, and Brazil unless the first culture tested positive for a poliovirus. In the United Kingdom, 74 patients provided two separate stool samples on different days, and 20 provided one sample.

In the United States, at least 91/125 (73%) participants had received one or more doses of OPV and 63 (50%) were known to have received three doses. In the United States, one or more family members had received oral polio vaccine after the diagnosis of immune deficiency disorder in 36 (29%) participant families. All participants in Mexico and Brazil had received OPV. In the United Kingdom, 24/94 (26%) patients provided data showing that they had been given OPV in childhood; information was inadequate for the remaining participants.

In the United States, all participants with XLA were receiving intravenous immune globulin (IVIG), and most participants with CVID were receiving replacement IVIG. In Mexico and Brazil, all participants with XLA or CVID were receiving IVIG replacement therapy. In the United Kingdom, all participants were receiving IVIG.

Culture results

United States

One specimen from a participant with CVID was lost. No polioviruses were isolated from the other participants in the United States (Table 2). Adenoviruses were isolated from two participants with CVID and one with selective IgA deficiency.

Mexico/Brazil/United Kingdom

Polioviruses were isolated from one participant in Mexico and from three in Brazil; none of these four people had received OPV in the previous 6 months. All polioviruses were consistent with recently-acquired vaccine viruses with less than 1.0% variation from the parent vaccine viruses based on the nucleotide

sequence of the VP1 gene. Follow-up stool cultures obtained 2–4 months later were negative for polioviruses in three of the four originally positive participants, and the fourth was culture negative two months later. All samples were negative on culture and polymerase chain reaction for polioviruses.

Theoretical risk

The upper bound of the 95% confidence interval for observing zero persistent poliovirus excretors among the 306 participants with agammaglobulinaemia, CVID, or other severe deficiencies of IgG production was 1.0%.

Non-polio entoviruses

Non-polio enteroviruses were identified in 4/33 participants in Mexico and 15/95 in Brazil. These viruses were not further characterized. Decisions regarding follow-up cultures on these participants were deferred to their immunologists.

Discussion

We did not identify any individuals with long-term excretion of polioviruses. Most participants had received OPV and almost all had been exposed to household contacts who had received OPV. Polioviruses of recent vaccine origin were transiently found in four individuals in Mexico and Brazil, where OPV is recommended for all children. Given that these participants had not received OPV recently, the viruses were probably acquired from contacts. Most individuals with B-cell deficiency disorders who survive early childhood appear to eliminate polio vaccine viruses without developing long-term excretion. Nevertheless, 19 individuals with B-cell immune deficiency disorders have been reported to WHO with polio excretion for six or more months (D. Wood, personal communication, 2003) and some have excreted the virus for more than 10 years. There are limited data on the incidence and prevalence of agammaglobulinaemia and CVID in different countries, but these disorders have been identified in countries throughout the world. Undoubtedly, some chronic polio excretors have not been identified and only a very small percentage of the affected population has been studied. The incidence of agammaglobulinaemia has been estimated to be approximately 1 per 100 000 live births in the United States and Europe, but no estimates have been made for developing countries (J. Winkelstein, personal communication, 2003). No reliable estimates of the incidence of CVID can be made because of variability in case definitions used from different countries.

Patients with selective IgA deficiency can excrete polioviruses for up to six months (*18*). After studying 40 individuals with selective IgA deficiency we decided not to enroll additional such patients following consultations with immunologists and a review of the literature; there was no evidence to indicate that these patients are at increased risk of developing VAPP, and no cases of long-term persistent poliovirus or enterovirus infections have been reported. Similarly, we did not study patients with IgG subclass deficiency disorders that are not associated with increased risk of complications from enterovirus infections (*6*). We are currently completing studies of adults and children with HIV infection, children with leukaemia, and children in developing countries with recurrent infections or past history of acute flaccid paralysis from poliovirus infections. To date, we have not identified any additional persons with long-term polio virus excretion.

Investigators in Tunisia prospectively monitored 16 children with immune deficiency disorders, including six with CVID and three with X-linked hyper-IgM syndrome, following National Immunization Day Polio Campaigns (*19*). The immune-deficient children did not receive OPV, but four patients, including one with CVID, acquired the vaccine viruses from contacts. These patients shed the OPV viruses for 1–7 weeks. Also, most of the individuals with XLA and CVID in our study had received OPV, but none were chronic excretors. Thus, most patients with these disorders appear to have the ability to eliminate polioviruses.

Almost all participants with IgG deficiency disorders in our study were receiving replacement immunoglobulin therapy. Passive administration of immunoglobulins can prevent paralysis associated with wild-type polioviruses (*20*). Replacement immunoglobulin therapy may decrease the risk of paralytic complications from vaccine viruses in persons with B-cell immune deficiency, but the protection is incomplete as some patients with persistent poliovirus excretion were receiving replacement immunoglobulins at the time they developed paralysis (*8*) (D. Wood, personal communication, 2003). Replacement immunoglobulin therapy does not prevent or treat persistent enterovirus infections in persons with B-cell deficiency disorders (*6*, *21*). One patient developed persistent poliovirus excretion following immunoglobulin therapy (*22*).

People with CVID often do not develop signs or symptoms of immune deficiency until they are young adults (*23*). Most individuals with CVID in our study had been repeatedly exposed to OPV before the onset of their immune deficiency. At the time of exposure to polioviruses their immune systems may have been intact. The study may not be an accurate reflection of all persons with B-cell immunodeficiency disorders since severely affected individuals may have died at an early age or developed paralysis following exposure to polioviruses.

OPV is often transmitted to close contacts within the first few weeks after vaccination via respiratory and/or gastrointestinal tract secretions (*1*, *3*, *4*, *14*). Pharyngeal excretion of polio vaccine viruses occurs, but only transiently in immunologically intact individuals (*3*). No prospective studies have been done or could be done on persons with known B-cell deficiency disorders, but no persons with persistent respiratory excretion of polioviruses have been identified. Persistent intestinal excretion in industrialized countries with high levels of sanitation may represent a low risk of transmission.

The eradication of wild polioviruses from circulation should be completed within the next few years. As originally envisioned, eradication was to be followed by stopping vaccination against polioviruses. However, identification of persistent poliovirus excretors and outbreaks of vaccine-derived polioviruses in Haiti, the Dominican Republic, the Philippines, and Madagascar in recent years have forced a reassessment of this strategy (*7*, *14*, *24*). Many industrialized countries have switched to IPV to reduce the risks associated with OPV; these countries will continue to use IPV for years after the last cases of wild-type virus have been identified (*25*). The higher cost of IPV is a barrier to the use of this vaccine in all developing countries. Nevertheless, an increasing number of combination vaccines that include IPV may allow more countries to switch to IPV (*26*).

Of the 19 patients identified in the past 40 years with polio excretion for more than 6 months, all but three have spontaneously stopped excreting, or died (D. Wood, personal

communication, 2003). Therefore, the risk of reintroduction of neurovirulent polioviruses from individuals with immune deficiency disorders in industrialized countries appears to be very low, but not zero.

Persistent poliovirus excretors could be a source of transmission or neurovirulent viruses to close contacts. Immunologists caring for patients with XLA, CVID, and severe combined immunodeficiency disorder (SCID) should encourage their patients to have a stool culture for polioviruses. If a poliovirus is identified extra efforts should be made to assure that IVIG is administered in a timely manner. Pleconaril is an antiviral agent with known effectiveness against some polioviruses and may be of value in efforts to eliminate the persistent excretion (*21*, *22*). ■

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Conflicts of interest: none declared.

Résumé

Recherche des porteurs de poliovirus chez les sujets atteints d'immunodéficience primaire au Brésil, aux Etats-Unis d'Amérique, au Mexique et au Royaume-Uni

Objectif Estimer la proportion de sujets excrétant des poliovirus sur le long terme chez les personnes présentant une immunodéficience liée aux lymphocytes B.

Méthode Les auteurs ont recherché activement les cas d'excrétion chronique de virus parmi 306 personnes connues pour avoir une carence en immunoglobulines G (IgG) au Brésil, aux Etats-Unis d'Amérique, au Mexique et au Royaume-Uni et chez 40 autres ayant une carence en immunoglobulines A (IgA) aux Etats-Unis d'Amérique. Les participants ou leurs tuteurs légaux ont donné par écrit leur consentement éclairé et les études ont été officiellement approuvées. Des échantillons de selles ont été prélevés pour tous les participants et mis en culture pour rechercher les poliovirus. Le calcul de l'intervalle de confiance pour la proportion de participants présentant une excrétion persistante repose sur la loi binomiale.

Résultats Les auteurs n'ont trouvé aucun sujet présentant une excrétion prolongée de poliovirus. Le vaccin antipoliomyélitique buccal (VPO) avait été administré à la plupart des participants et presque tous avaient été en contact dans leur foyer avec des sujets vaccinés par le VPO. Des poliovirus d'origine vaccinale récente ont été retrouvés de manière transitoire chez quatre sujets au Brésil et au Mexique où la vaccination par le VPO est recommandée pour tous les enfants.

Conclusion Bien que l'excrétion chronique de poliovirus soit possible chez le sujet immunodéficient, elle semble rare.

Resumen

Búsqueda de portadores del poliovirus entre personas afectadas por una inmunodeficiencia primaria en los Estados Unidos, México, el Brasil y el Reino Unido

Objetivo Estimar la tasa de excretores crónicos de poliovirus entre las personas con trastornos de inmunodeficiencia de células B.

Métodos Se llevó a cabo una búsqueda activa de excretores crónicos entre 306 personas con deficiencia demostrada de inmunoglobulina G (IgG) en los Estados Unidos, México, el Brasil y el Reino Unido, y entre 40 personas con deficiencia de IgA en los Estados Unidos. Se obtuvo el consentimiento o asentimiento informado de los participantes o de sus representantes legales, así como la autorización oficial pertinente para realizar el estudio. Se recogieron muestras de heces de los participantes para determinar en cultivo la presencia de poliovirus. A partir de la distribución binomial se calculó el intervalo de confianza del porcentaje de pacientes con excreción persistente del poliovirus.

Resultados Ninguno de los individuos resultó ser excretor crónico del poliovirus. La mayoría de los participantes habían recibido vacuna antipoliomielítica oral (OPV), y casi todos habían estado expuestos a contactos familiares que habían recibido OPV. Se encontraron transitoriamente poliovirus de origen vacunal reciente en cuatro personas de México y el Brasil, donde se recomienda administrar OPV a todos los niños.

Conclusión Aunque se puede dar una excreción crónica de poliovirus entre las personas con inmunodeficiencia, el fenómeno parece ser infrecuente.

References

1. Benyesh-Melnick M, Melnick JL, Rawls WE, Wimberly I, Oro JB, Ben-Porath E, et al. Studies of the immunogenicity, communicability and genetic stability of oral poliovaccine administered during the winter. *American Journal of Epidemiology* 1967;86:112-36.
2. Melnick JL, Benyesh-Melnick M, Brennan JC. Studies on live poliovirus vaccines. Its neurotropic activity in monkeys and its increased neurovirulence after multiplication in vaccinated children. *JAMA* 1959;171:1165-72.
3. Gelfand HM, Potash L, LeBlanc DR, Fox JP. Revised preliminary report on the Louisiana observations of the natural spread within families of living vaccine strains of poliovirus. In: *Live poliovirus vaccines: papers presented and discussions held at the first international conference on live poliovirus vaccines*. Special Publication No. 44. Washington (DC): Pan American Sanitary Bureau; 1959.
4. Fox JP, Gelfand HM, LeBlanc DR, Potash L, Clemmer DI, LaPenta D. The spread of vaccine strains of poliovirus in the household and in the community in southern Louisiana. In: *International Poliomyelitis Congress, ed. Poliomyelitis: papers and discussions presented at the fifth international poliomyelitis conference*. Philadelphia: Lippincott; 1961:368-83.
5. Sutter RW, Cochi SL, Melnick JL. Live attenuated poliovirus vaccines. In: Plotkin SA, Orenstein WA, editors. *Vaccines*, 3rd ed. Philadelphia: WB Saunders; 1999:364-408.
6. Modlin JF. Coxsackieviruses, echoviruses, and newer enteroviruses. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 5th ed. Philadelphia (PA): Churchill-Livingstone; 2000. pp. 1904-19.
7. Wood DJ, Sutter RW, Dowdle WR. Stopping poliovirus vaccination after eradication: issues and challenges. *Bulletin of the World Health Organization* 2000;78:347-57.
8. Kew OM, Sutter RW, Nottay BK, McDonough MJ, Prevots DR, Quick L, et al. Prolonged replication of a type 1 vaccine-derived poliovirus in an immunodeficient patient. *Journal of Clinical Microbiology* 1998;36:2893-9.
9. Buttinelli G, Donati V, Fiore S, Marturano J, Plebani A, Balestri P, et al. Nucleotide variation in Sabin type 2 poliovirus from an immuno-deficient patient with poliomyelitis. *Journal of General Virology* 2003;84:1215-21.
10. John TJ, Walker DH. Enterovirus infections, including poliomyelitis. In: Guerrant RL, Walker DH, Weller PF, editors. *Tropical infectious diseases, principles, pathogens, and practice*. Philadelphia: Churchill Livingstone; 1999. pp. 1123-32.
11. Minor P. Characteristics of poliovirus strains from long-term excretors with primary immunodeficiencies. *Developmental Biology* 2001;105:75-80.
12. Minor PD, Ferguson JA, Icenogle JP. Antigenic and molecular evolution of the vaccine strain of type 3 poliovirus during the period of excretion by a primary vaccinee. *Journal of General Virology* 1986;67:693-706.
13. Dunn G, Begg NT, Cammack, N, Minor PD. Virus excretion and mutation by infants following primary vaccination with live oral poliovaccine from two sources. *Journal of Medical Virology* 1990;32:92-5.
14. Sutter RW, Tangermann RH, Aylward RB, Cochi SL. Poliomyelitis eradication: progress, challenges for the end game, and preparation for the post-eradication era. *Infectious Disease Clinics of North America* 2001;15:41-64.
15. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immuno-deficiencies). *Clinical Immunology* 1999;93:190-7.
16. *Manual of the virological investigation of poliomyelitis*. Geneva: World Health Organization; 1997. WHO document WHO/EPI/GEN/97.01.
17. Liu HM, Zheng DP, Zhang LB, Oberste MS, Pallansch MA, Kew OM. Molecular evolution of a type 1 wild-vaccine poliovirus recombinant during widespread circulation in China. *Journal of Virology* 2000;74:11153-61.
18. Savilahti E, Klemola T, Carlsson B, Mellander L, Stenvik M, Hovi T. Inadequacy of mucosal IgM antibodies in selective IgA deficiency: excretion of attenuated polio viruses is prolonged. *Journal of Clinical Immunology* 1988;8:89-94.
19. Triki H, Barbouche MR, Bahri O, Bejaoui M, Dellagi K. Community-acquired poliovirus infection in children with primary immunodeficiency in Tunisia. *Journal of Clinical Microbiology* 2003;41:1203-11.
20. Hammon WD, Coriell LL, Wehrle PF, Stokes J. Evaluation of Red Cross gammaglobulin as a prophylactic agent for poliomyelitis. 4. Final report of results based on clinical diagnosis. *JAMA* 1953;151:1272-85.
21. Halliday E, Winkelstein J, Webster AD. Enteroviral infections in primary immunodeficiency (PID): a survey of morbidity and mortality. *The Journal of Infection* 2003;46:1-8.
22. Buttinelli G, Donati V, Fiore S, Marturano J, Plebani A, Balestri P, et al. Nucleotide variation in Sabin type 2 poliovirus from an immuno-deficient patient with poliomyelitis. *Journal of General Virology* 2003;84:1215-21.
23. Cunningham-Rundles C, Bodian C. Common variable immuno-deficiency: clinical and immunological features of 248 patients. *Clinical Immunology* 1999;92:34-48.
24. 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.
25. Halsey NA. Commentary: Poliomyelitis and unnecessary injections. *International Journal of Epidemiology* 2003;32:278-9.
26. Halsey NA. Combination vaccines: defining and addressing current safety concerns. *Clinical Infectious Diseases* 2001;33 Suppl 4:S312-8.