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Recombinant Vaccine-derived Polioviruses in Healthy Children, Madagascar

To the Editor: Poliomyelitis outbreaks caused by pathogenic vaccine-derived polioviruses (VDPVs) are primarily a result of low polio vaccine coverage. Low coverage enables interhuman circulation of polioviruses (PVs) from the oral polio vaccine (OPV), and it enables genetic drift of the viruses and their subsequent reversion to neurovirulent phenotypes (1). Polio outbreaks associated with type 2 or 3 VDPVs (VDPV2s or VDPV3s) were reported in 2001–2002 and 2005 in Toliara Province in southern Madagascar (2,3). These VDPVs were found in patients with acute flaccid paralysis (AFP) and in healthy children who were contacts of the patients with AFP (2,4). The genomes of these VDPVs belong to several independent, complex mosaic recombinant lineages composed of sequences derived from vaccine polioviruses and other co-circulating species C human enteroviruses (human EV-C) (4,5). The 2001–2002 and 2005 outbreaks in Toliara Province were stopped after rapid and efficient OPV vaccination campaigns.

No polio cases have been detected in Madagascar since 2005. However, OPV coverage fluctuates in Toliara Province. In June 2011, to determine if VDPVs were circulating in the province, we collected fecal samples from 616 healthy residents <5 years of age (Madagascar Ethics Committee agreement 011-MSANP/CE). Sample extracts were used to inoculate human RD and HEp-2c cells and mouse L cells expressing the human poliovirus cellular receptor CD155 (L20B cells) (6). Of the 616 samples, 238 induced cytopathogenic effects in human cells, of which 20 also induced cytopathogenic effects

in L20B cells; the latter samples were confirmed by reverse transcription PCR molecular testing (7) to contain PV strains. All PV isolates originated from children who had not received OPV in the 30 days before samples were collected.

We sequenced the genomic regions encoding the capsid viral protein (VP1) of the 20 isolates

confirmed to contain PV strains: 3 type 2 PV isolates showed >0.5% nt sequence divergence from the type 2 OPV strain (Sabin 2) and were thus identified as potentially pathogenic VDPV2s. Two of these VDPV2s carried numerous mutations in the VP1 region (903 bp): isolates MAD-2593-11 (30 nt mutations) and MAD-2642-11 (33 nt mutations). The third

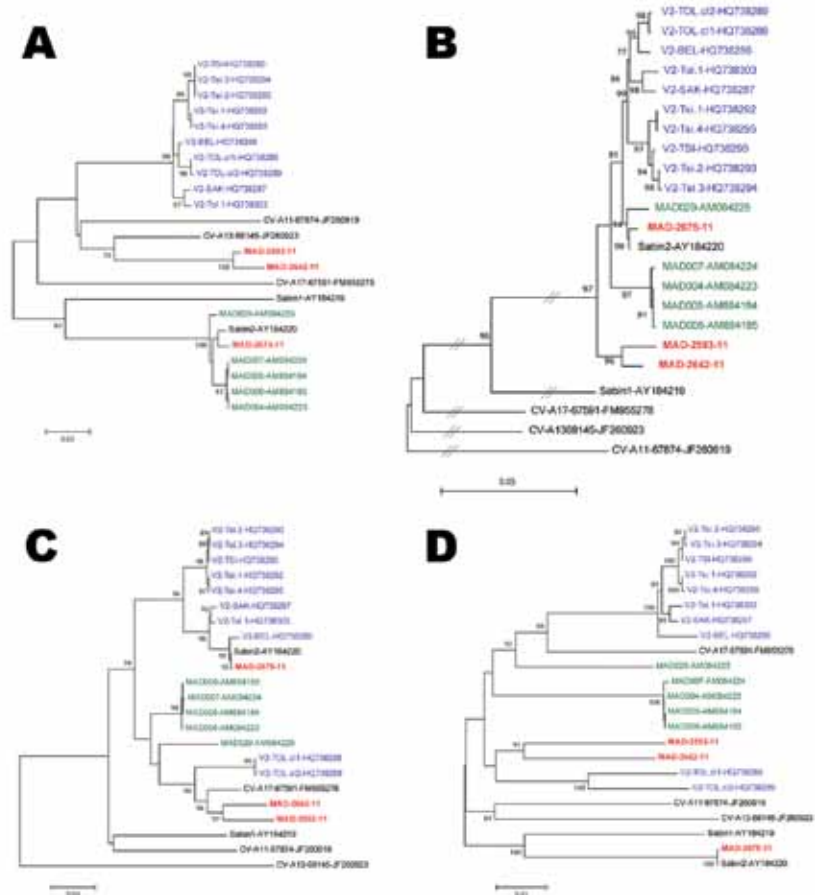


Figure. Phylogenetic trees showing genetic relationships between sequences of vaccine-derived poliovirus (VDPV) isolates. The trees are based on nucleotide sequence alignments of various subgenomic regions. Multiple sequence alignments were performed with CLC Main Workbench 5.7.2 software (CLC bio, Aarhus, Denmark). Phylograms were constructed with MEGA4 (<http://mega-software.net/mega4/mega.html>), using the Jukes-Cantor algorithm for genetic distance determination and the neighbor-joining method. The robustness of the resulting trees was assessed with 1,000 bootstrap replications. A) Tree built from 712-bp fragments of the 5'-untranslated region (nt 36–747, with reference to Sabin 2 nucleotide numbering). B) Tree built from 2,637-bp fragments of the P1 region (nt 748–3,384). C) Tree built from 1,725-bp fragments of the P2 region (nt 3,385–5,109). D) Tree built from 2,259-bp fragments of the P3 region (nt 5,110–7,368). Names (isolate name-accession no.) are VDPV isolates recovered in Madagascar in 2011, 2005, and 2001–2002, respectively. Sequences of other isolates (CV-A11, 13, and 17) from Madagascar were also used. The percentage of bootstrap replicates is indicated at nodes if >70%. The length of branches is proportional to the number of nucleotide differences (percent divergence). Scale bars indicate genetic distances. A color version of this figure is available online (wwwnc.cdc.gov/EID/article/1916/13-0080-F1.htm).

VDPV2, MAD-2675–11, carried 6 nt mutations. The nucleotide differences between Sabin 2 and MAD-2593–11 (3.3%) and MAD-2642–11 (3.6%) suggest that these VDPV2s had been multiplying or circulating for \approx 3.0 years, and the differences between Sabin 2 and MAD-2675–11 suggest it had been multiplying or circulating for \approx 0.5 year. Almost complete genomic sequencing, from nt 36 to nt 7,420 (Sabin 2 numbering), was subsequently performed (EMBL accession nos. HF913426–HF913428).

Isolate MAD-2675–11 was shown to be a mutated Sabin 2 PV, but isolates MAD-2593–11 and MAD-2642–11 displayed mosaic recombinant genomes composed of sequences derived from Sabin 2 and other human EV-Cs. Both recombinants had the 5′-untranslated region (UTR), the nonstructural P2–P3 regions, and the 3′-UTR derived from non-PV human EV-C. The 2 recombination sites were similarly located in each of these recombinant genomes (approximately at nt 760 and nt 3,368) at the 2 extremities of the structural genomic P1 region. Although these recombinants appeared to be related, they had different non-PV human EV-C sequences in the P2–P3 region and the 3′-UTR (6.0%–20.0% nt sequence difference). The phylogenetic relationship of these isolates to the previous Madagascar VDPV2s was assessed: the 2011 isolates originated from 2 novel, independent events (Figure). The 2011 VDPVs had lost the major attenuating determinants in the 5′-UTR (guanine to adenine at nt 481) and VP1 region (isoleucine to threonine at codon 143) regions (δ). This finding strongly suggests that the 2011 VDPVs had regained a degree of neurovirulence.

Although there is currently no evidence of AFP cases linked to these new VDPVs, their detection in 3 children and their genetic characteristics strongly suggest insufficient OPV coverage in Toliara

Province. We could obtain proof of vaccination (vaccination card) for only 27% of the participants. To prevent a third poliomyelitis outbreak, the Ministry of Health of Madagascar organized house-to-house OPV vaccination campaigns within Toliara Province in October and December 2011 and in January 2012. No polio cases have been reported in the province since then, suggesting that VDPV circulation was limited or stopped by these campaigns.

Massive OPV immunization campaigns worldwide have greatly decreased the frequency of poliomyelitis caused by wild-type PVs. However, after the disease has been eliminated in developing countries, low polio vaccine coverage frequently enables the emergence of VDPVs or the reintroduction of wild-type PV from disease-endemic countries; both scenarios threaten the success of the poliomyelitis eradication program (9,10). More than 640 polio cases caused by circulating VDPVs have been reported in 21 developing countries. We have shown that even in the absence of polio cases, potentially pathogenic circulating VDPVs can be detected in fecal samples collected from children living in areas with fluctuating and often low polio vaccine coverage. Thus, such sampling can help determine whether vaccine campaigns should be implemented in areas where polio could reemerge. In Madagascar, vaccination appears to have cleared emerging VDPVs and to have prevented polio cases in children.

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References

1. Kew OM, Sutter RW, de Gourville EM, Dowdle WR, Pallansch MA. Vaccine-derived polioviruses and the endgame strategy for global polio eradication. *Annu Rev Microbiol.* 2005;59:587–635. <http://dx.doi.org/10.1146/annurev.micro.58.030603.123625>
2. Rakoto-Andrianarivelo M, Gumedé N, Jegouic S, Balanant J, Andriamamonjy SN, Rabemanantsoa S, et al. Reemergence of recombinant vaccine-derived poliovirus outbreak in Madagascar. *J Infect Dis.* 2008;197:1427–35. <http://dx.doi.org/10.1086/587694>.
3. Rousset D, Rakoto-Andrianarivelo M, Razafindratsimandresy R, Randriamanalina B, Guillot S, Balanant J, et al. Recombinant vaccine-derived poliovirus in Madagascar. *Emerg Infect Dis.* 2003;9:885–7. <http://dx.doi.org/10.3201/eid0907.020692>
4. Rakoto-Andrianarivelo M, Guillot S, Iber J, Balanant J, Blondel B, Riquet F, et al. Co-circulation and evolution of polioviruses and species C enteroviruses in a district of Madagascar. *PLoS Pathog.* 2007;3:e191. <http://dx.doi.org/10.1371/journal.ppat.0030191>
5. Joffret ML, Jegouic S, Bessaud M, Balanant J, Tran C, Caro V, et al. Common and diverse features of cocirculating type 2 and 3 recombinant vaccine-derived polioviruses isolated from patients with poliomyelitis and healthy children. *J Infect Dis.* 2012;205:1363–73. <http://dx.doi.org/10.1093/infdis/jis204>.

6. Department of Immunization, Vaccines and Biologicals, World Health Organization. Isolation and identification of polioviruses. In: Polio laboratory manual. 4th edition. WHO/IVB/04.10. 2004. p. 87–100 [cited 2013 Apr 11]. <http://who.int/vaccines/en/polio/lab/WHO-Polio-Manual-9.pdf>
7. Kilpatrick DR, Nottay B, Yang CF, Yang SJ, Mulders MN, Holloway BP, et al. Group-specific identification of polioviruses by PCR using primers containing mixed-base or deoxyinosine residue at positions of codon degeneracy. *J Clin Microbiol.* 1996;34:2990–6.
8. Macadam AJ, Pollard SR, Ferguson G, Skuce R, Wood D, Almond JW, et al. Genetic basis of attenuation of the Sabin type-2 vaccine strain of poliovirus in primates. *Virology.* 1993;192:18–26. <http://dx.doi.org/10.1006/viro.1993.1003>
9. Centers for Disease Control and Prevention. Update on vaccine-derived polioviruses—worldwide, April 2011–June 2012. *MMWR Morb Mortal Wkly Rep.* 2012;61:741–6.
10. Burns CC, Shaw J, Jorba J, Bukbuk D, Adu F, Gumedé N, et al. Multiple independent emergences of type 2 vaccine-derived polioviruses during a large outbreak in northern Nigeria. *J Virol.* 2013 Feb 13. [Epub ahead of print]. <http://dx.doi.org/10.1128/JVI.02954-12>

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Hepatitis E Outbreak, Dadaab Refugee Camp, Kenya, 2012

To the Editor: Hepatitis E virus (HEV) is transmitted through the fecal-oral route and is a common cause of viral hepatitis in developing countries. HEV outbreaks have been documented among forcibly displaced persons living in camps in East Africa, but for >10 years, no cases were documented among Somali refugees (1,2). On August 15, 2012, the US Centers for Disease Control and Prevention

(CDC) in Nairobi, Kenya, was notified of a cluster of acute jaundice syndrome (AJS) cases in refugee camps in Dadaab, Kenya. On September 5, a CDC epidemiologist assisted the United Nations High Commissioner for Refugees (UNHCR) and its partners in assessing AJS case-patients in the camp, enhancing surveillance, and improving medical management of case-patients. We present the epidemiologic and laboratory findings for the AJS cases (defined as acute onset of scleral icterus not due to another underlying condition) identified during this outbreak.

Dadaab refugee camp is located in eastern Kenya near the border with Somalia. It has existed since 1991 and is the largest refugee camp in the world. Dadaab is composed of 5 smaller camps: Dagahaley, Hagadera, Ifo, Ifo II, and Kambioos. As of December 2012, a total of 460,000 refugees, mainly Somalis, were living in the camps; >25% were recent arrivals displaced by the mid-2011 famine in the Horn of Africa (3). Overcrowding and poor sanitation have led to outbreaks of enteric diseases, including cholera and shigellosis (4); in September 2012, an outbreak of cholera occurred simultaneously with the AJS outbreak.

During July 2–November 30, 2012, a total of 339 AJS cases were reported from the camps and 2 nearby villages: 232 (68.4%) from Ifo II, 57 (16.8%) from Kambioos, 26 (7.7%) from Ifo, 12 (3.5%) from Dagahaley, 10 (3.0%) from Hagadera, and 1 each (0.6%) from the nearby Kenyan villages of Biyamadow and Darkanley. The epidemic curve of the outbreak is shown in the Figure.

Of the 339 AJS case-patients, 184 (54.3%) were female. The overall median age was 23.5 years (range 1 month–91 years). The median age among female and male residents was 24 years and 20 years, respectively. Among the 134 women of reproductive age (15–49 years), 72 (53.7%) reported being pregnant; the median gestational age was 17.4 weeks (range 8.7–35.3 weeks). Death was reported for 10 of the 339 case-patients (case-fatality ratio 2.9%), 9 of whom were postpartum mothers (case-fatality ratio 12.5%) and 1 a 2-year-old child.

Serum samples were obtained from 170 (50.1%) AJS case-patients for testing at the Kenya Medical Research Institute/CDC laboratories in Nairobi, Kenya. Of the 170 samples, 148 were tested for hepatitis E virus (HEV) IgM by using an ELISA

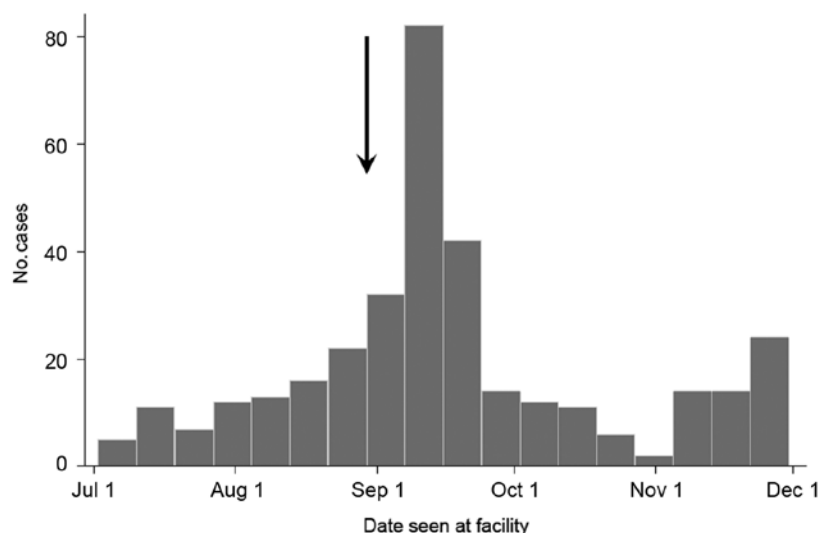


Figure. Cases of acute jaundice syndrome, Dadaab, Kenya, July–November 2012. The arrow indicates the point at which outbreak control measures (e.g., construction of new latrines and hygiene messaging) were initiated by health authorities.