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CONSIDERATIONS FOR VACCINATION RECOMMENDATIONS FOR TRAVELLERS FROM POLIO-INFECTED COUNTRIES

INTRODUCTION

Following the discussion at the World Health Organization (WHO) Executive Board meeting in January 2014, the WHO Director-General requested that the Strategic Advisory Group of Experts on Immunization (SAGE) review the scientific evidence regarding polio vaccination recommendations for travellers arriving from polio-infected countries. This communication summarizes the key elements and the supporting scientific data for the vaccination recommendations, including a) the recommended population for vaccination, and b) the recommended vaccinations.

Considerations for the recommended target population to be vaccinated prior to travel from polio-infected countries

Role of older age groups in international spread of poliovirus:

Poliovirus importation into polio-free areas is assumed to occur frequently. However, most of these importation events are silent (i.e., not leading to paralytic cases) and the transmission is self-limiting because of high population immunity. Occasionally these events are detected and reported (i.e., Paris, Strasbourg, Geneva, etc.).

A subset of these importations may lead to establishment of circulation that manifest as outbreaks. Between 2004 and 2013, 179 importation events resulted in more than reported 3,500 paralytic cases. Of these, 27 (15%) were associated with long-distance travel (i.e., transmission between non-contiguous countries or across oceans) where adult travellers would be expected to much more likely to be involved[1,2,3,4], although no definitive information about the transmission path and specific individuals who imported virus were available.

Furthermore, there are several lines of evidence that support the potential importance of adult travellers in harbouring and propagating poliovirus infection, including: 1) stool surveys demonstrate that adults can be infected and excrete poliovirus: 2) duration and titre of poliovirus excretion among adults is similar to that of children because mucosal immunity wanes relatively rapidly (i.e., <12 months); and 3) adults travellers constitute the vast majority of international travel and occasionally infected adult travellers are identified[5].

[1] Afif H., Sutter R.W., Kew O.M., et al.: Outbreak of poliomyelitis in Gizan, Saudi Arabia: co-circulation of wild type 1 polioviruses from three separate origins. J Infect Dis. 175 (suppl 1):S71-S75 1997

[2] Kidd S, et al. 2011 Poliomyelitis outbreaks in Angola genetically linked to India: risk factors and implications for prevention of outbreaks due to wild poliovirus importations. Vaccine 29, 3760–3766

[3] Smorodintsev A.A., Davidenkova E. F., Drobyshevskaya Y.A. et al. Results of a study of the reactogenic and immunogenic properties of live anti-poliomyelitis vaccine. Bull World Health Organ. 1959;20:1053–1074.

[4] Yakovenko M et al Euro Surveill. 2014 Feb 20;19(7)

[5] Kubli D., Steffen R., Schar M. (1987) Importation of poliomyelitis to industrialised nations between 1975 and 1984: evaluation and conclusion for vaccination reccomendations. Br. Med. J. 295:169–171.

There is epidemiological evidence that older persons (those over 15 years of age) have participated in poliovirus transmission. In 2009, two investigations conducted in UP and Bihar in India on the prevalence of asymptomatic WPV infection found that 60% of silent transmission (measured by excretion of wild poliovirus in stool) was among those over 5 years of age[6]. In addition, a stool survey conducted in Southern Israel in July 2013 among a convenience sample of ~2,000 individuals found an excretion rate of 3.3% among children 0-18 years, with a higher rate of excretion in cohorts not given tOPV in the past (0-9 years age band). An excretion rate of 0.5% was documented among adults >18 years, and 1.4% (2 out of 147) among >45 years[7]. Numerous studies found that older children and adults can become infected and excrete poliovirus if challenged with an OPV virus or if in contact with children who excrete poliovirus[8]. For example, the 1965 Virus Watch studies by Fox and associates that investigated OPV virus introductions from the community into families also demonstrated that adults can not only become infected but also infect others (e.g., of the introducers, 66% were <5, 11% were older children, and 22% were adult parents[9]. Also in Israel, an OPV challenge study in 2007 indicated that 1.1% of 99 mothers of OPV- challenged children excreted virus on day 7 after challenge of their children. Similarly, 2.1% of 145 siblings of challenged children excreted by day 7, declining to 1.4% and 0.7% by days 14 and 21, respectively, after challenge. This illustrates the potential for adults, even those previously vaccinated or exposed such that they benefit from lifelong protection from paralysis, to become infected in the course of poliovirus transmission among children[10].

There is some scientific evidence to show that there is no significant difference in the duration of poliovirus excretion between adults and infants. The stool study in Bihar suggested similar titres of poliovirus found in stool in children and adults[11]. A more recent study in Moradabad, India also demonstrated that the titter and duration of poliovirus excretion after the OPV challenge is similar across age groups (6-11 months, 5-6 years and 10-11 years)[12].

Lastly, there have been several documented cases of adult poliovirus excretors travelling long distances. WHO and other public health authority records indicated that 175 cases of poliomyelitis were imported to industrialized countries between 1975 and 1984, including 34 travellers above 20 years old[13]. There are more recent documented cases of adults, who are travelling long distance with wild poliovirus excretion (e.g. three cases from Mexico, Nepal, and Zaire to the U.S. between 1980 and 1989[14], one case from Pakistan to Australia in 2007[15], and one case from Xinxiang to

[6] Mach O et al. Prevalence of Asymptomatic Poliovirus Infection in Older Children and Adults in Northern India: Analysis of Contact and Community Enhanced Surveillance, 2009. Journal of Infectious Diseases. In press.
[7] Unpublished data
[8] Duintjer Tebbens RJ, Pallansch MA, Chumakov KM, Halsey NA, Hovi T, Minor PD, Modlin JF, Patriarca PA, Sutter RW, Wright PF, Wassilak SGF, Cochi SL, Kim J-H, Thompson KM. Expert review on poliovirus immunity and transmission. Risk Analysis 2013;33(4):544-605
[9] Fox JP, Hall CE, Viruses in Families, PSG Publishing Co, Inc, Littleton, Massachusetts, 1980, page 194.
[10] Schwartz et al. Intestinal immunity following a combined enhanced inactivated polio vaccine/oral polio vaccine programme in Israel. Vaccine. 2007.
[11] Mach O et al., ibid.
[12] Jafari H et al. in prep (WHO Moradabad study)
[13] Kubli D et al., ibid.
[14] Strebel Pm, Sutter Rw, Cochi Sl, et al. Epidemiology of poliomyelitis in the United States one decade after the last reported case of indigenous wild virus-associated disease. Clin Infect Dis 1992; 14: 568-579
[15] Stewardson AJ, Roberts JA, Beckett CL, Prime HT, Loh PS, Thorley BR, Daffy JR: Imported case of poliomyelitis, Melbourne, Australia, 2007.Emerg Infect Dis 2009, 15(1):63-65

Beijing in 2011[16]). These data suggest the high likelihood that older individuals participate in the international importation of poliovirus.

Considerations for the recommended vaccinations for travellers from polio-infected countries

There are a number of general considerations that may influence policy decisions for the recommended vaccinations for travellers from polio-infected countries.

Rapidity of humoral and intestinal immunity induced by IPV and OPV: Analysis of kinetics of antibody response has shown that the majority of naïve individuals develop serum IgG within 4 weeks of vaccination with IPV or OPV[17]. An early study in the USSR in 1959 with 70 seronegative children demonstrated almost all the children responded to OPV by day 21 with a significant increase in antibody titre (i.e. average GMT of 130.0-306.4)[18]. There are several studies demonstrating that OPV or IPV-primed individuals given a supplementary dose of either vaccine show an increase in antibody titres in as early as 7 days: Studies in both Oman[19] and Cuba[20] showed a peak boosting response with IPV within 7 days among OPV or IPV-primed individuals. Another more recent study in Cuba in 2013[21] showed that among individuals who had an immune response by 21 days, antibodies rose in 5-10% of individuals within 3 days and in more than 90% within 7 days after administration of the boosting dose of IPV. The kinetics analysis also suggested that induction of intestinal immunity is quicker (i.e. one to two weeks after vaccination)[22] although the available evidence from clinical research on the rapidity of mucosal immunity is limited. A study in Japan with four naive subjects who received tOPV in 2001 showed that secretory IgA (sIgA) appeared in naive infants as early as 7 days after administration of either the first dose or second dose of tOPV[23]. Another study from the Netherlands (1999) also demonstrated the rise of sIgA within 7 days after a booster dose of IPV among adults previously immunised with OPV[24].

Frequency and duration of poliovirus excretion: A review of cross-sectional and longitudinal studies of wild or Sabin poliovirus excretion concluded that live polioviruses are excreted by a majority of previously unvaccinated infants and young children for 3-4 weeks following the onset of paralysis (i.e. 4-6 weeks after exposure). The duration of excretion data among the studies was consistent despite numerous differences in design, and the cumulative excretion rates for Sabin strains were similar to those for wild type. However, it should be noted that studies for WPV were measured relative to onset of paralysis and the ones for Sabin were measured relative to the time of challenge. This

[16] Luo, H. M. et al. Identification and control of a poliomyelitis outbreak in Xinjiang, China. N. Engl. J. Med.2013; 369, 1981–1990

[17] Ogra PL, Karzon DT, Righthand F, MacGillivray M. Immunoglobulin response in serum and secretions after immunization with live and inactivated poliovaccine and natural infection. N Engl J Med 1968; 279: 893–90

[18] Smorodintsev A.A., Davidenkova E. F., Drobyshevskaya Y.A. et al. Results of a study of the reactogenic and immunogenic properties of live anti-poliomyelitis vaccine. Bull World Health Organ. 1959;20:1053–1074.

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[24] Herremans TM, Reimerink JH, Buisman AM, Kimman TG, Koopmans MP (1999) Induction of mucosal immunity by inactivated poliovirus vaccine is dependent on previous mucosal contact with live virus. J Immunol 162: 5011–5018

would suggest longer excretion for WPV than Sabin. However, there is no study that provides a direct comparison of Sabin vs. WPV[25].

The frequency and duration of viral shedding appears reduced among infants with high levels of serum neutralizing antibody due to prior OPV, IPV or natural infection[26]. Numerous studies found that the duration of faecal excretion of poliovirus by infants who have recently received OPV is less than that of infants who have received IPV, suggesting a significant role of local immunity in reducing intestinal replication of poliovirus[27,28].

Duration of intestinal immunity: Intestinal immunity against poliovirus induced by OPV wanes as early as 12 months after vaccination. Two OPV challenge studies indicated that children and adults previously exposed to live poliovirus (OPV or WPV) frequently shed poliovirus following OPV administration more than 10 years after the last vaccination[29,30]. However, the time frame for most challenge studies is such that OPV is provided either more than 10 years after the last vaccination (for older children or adults), or 1-3 months after the last vaccination for younger children (under 18 months); few studies have examined shedding in relation to the time since last vaccination[31]. A retrospective analysis of AFP surveillance data in India showed that the odds of excreting virus increased significantly (1.5-2.0 times) in the group which received a challenge dose of OPV more than six months (average time 9-15 months depending on serotype) following the last exposure to the OPV[32]. Shedding of poliovirus after OPV challenge was found to increase with age in a recent study in India in a manner consistent with waning of immunity after leaving the age group eligible for supplementary immunisation activities (shedding among 10 year old children > 5 year old children > 6-11 months old infants) (Jafari et al.)

Ability of IPV/OPV to boost intestinal immunity among those previously vaccinated with OPV: Two randomized controlled studies indicated that IPV has a greater effect than OPV in boosting intestinal immunity among OPV-primed individuals. A study in Moradabad, India demonstrated that a single dose of IPV administered to infants and children (aged 6-11 months, 5-6 years and 10-11 years) with a history of multiple OPV doses significantly boosts intestinal immunity, and reduces prevalence of excretion after a bivalent OPV challenge. The relative reduction in excretion between IPV and control group were remarkably consistent across the age groups. For poliovirus type 1 the decrease in excretion in any stool sample after challenge in the IPV group compared to the control group was 38.8% (14.4% vs 8.8%) in the 6-11-month, 65.6% (24.1% v 8.3%) in the 5-year, and 74.2% (52.4% vs 13.5%) in the 10-year age group; the corresponding decreases for poliovirus type 3 were 71.1% (13.5% vs 3.9%) in the 6-11-month, 52.4% (25.0% vs 11.9%) in the 5-year, and 75.7% (51.4% vs 12.5%) in the

[25] Duintjer Tebbens RJ, ibid.
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[32] Grassly NC, Jafari H, Bahl S, Sethi R, Deshpande JM, Wolff C, Sutter RW and Aylward RB (2012). Waning intestinal immunity following vaccination with oral poliovirus vaccines in India. J Infect Dis 205: 1554-1561

10-year age group[33]. It also reduced overall viral titre shed (4.1 vs. 3.6 in log10 CCID 50 in type 1, and 4.1 vs. 3.4 in type 3) and length of overall excretion (8.7 vs. 7 days in type 1 and 12.9 vs. 10.5 days in type 3). This reduction effect is largest in children aged 10-11 years and is considerably larger than that of a supplemental dose of bOPV (which reduced excretion prevalence by 51.7% and 48.8% against types 1 and 3 respectively in the 10-11 year old group). Also, a recent study in South India demonstrated that IPV can boost both intestinal and humoral immunity better than bivalent OPV among 1-4 year-olds who last received OPV 7-10 months previously[34]. However, there is insufficient information as to whether the intestinal immunity boosted by IPV lasts as long as or longer than for OPV.

Conclusion

The evidence reviewed in this paper reaffirms the scientific basis for the current advice on polio vaccination for international travellers, as outlined in the WHO document *International Travel and Health (ITH) 2013* , as well as the updated recommendations on the vaccines of choice for, and timing of, additional doses. This evidence and its implications for vaccination recommendations for travellers is summarized as follows (key changes highlighted):

- Epidemiological and observational evidence indicate that older children and adults have participated in poliovirus transmission and the international spread of poliovirus. Therefore, travellers of <u>all ages</u> within the recommended population (i.e. residents of polio-infected countries and long-term visitors) should be vaccinated before travelling from polio-infected countries.

- The risk of poliovirus exportation through excretion is reduced among individuals 4 weeks after receiving a supplementary dose of IPV or OPV, so travellers from the recommended populations should receive at least one additional dose of <u>OPV or IPV</u> at least <u>4 weeks</u> before departure:

    - By 4 weeks following administration of IPV or OPV, most naive individuals will have developed sufficient serum and mucosal antibodies (in case of OPV) to protect against shedding and transmission of infection. A boosting dose of IPV/OPV can induce humoral and intestinal immunity as early as 7 days post vaccination.

    - Even if a traveller is infected with wild poliovirus or a cVDPV at the time of vaccination, most poliovirus excretion from natural infection is over in 3-4 weeks.

- A recent analysis using data from the polio endemic country indicates that the Intestinal mucosal immunity appears to wane within 12 months after the vaccination with OPV. This suggests that a traveller should be <u>vaccinated within 12 months before departure to ensure adequate intestinal immunity</u>.

- In children whose intestinal mucosal immunity has waned, one dose of polio vaccine (OPV or IPV) will decrease prevalence of poliovirus excretion (50-75%), decrease viral titre and shorten duration of excretion. This suggests that additional vaccination with <u>OPV or IPV</u> should decrease the risk of travellers importing poliovirus into polio-free areas.

[33] Jafari H et al., ibid.
[34] John J et al in prep (CMC IPV study)