Draft: 14 October 2013

CONSIDERATIONS FOR THE TIMING OF A SINGLE DOSE OF IPV IN THE ROUTINE IMMUNIZATION SCHEDULE

INTRODUCTION

In May 2012, the World Health Assembly declared the completion of polio eradication to be a global public health emergency and called for the development of a comprehensive polio endgame strategy. In response, the *Polio Eradication and Endgame Strategic Plan 2013-2018* was developed.

This plan contains four objectives, and objective 2 outlines the activities and timelines necessary to strengthen routine immunization, introduce at least one dose of inactivated poliovirus vaccine (IPV) into routine immunization schedule, and withdraw Sabin type 2 strains for the oral poliovirus vaccine (OPV).

The subsequent SAGE meeting (November 2012) recommended that all country should introduce at least one dose of IPV, prior to the OPV2 cessation, in order to a) prevent polio if exposed to a VDPV2 or WPV2, b) improve response to mOPV2 in an outbreak, c) reduce transmission of a reintroduced type 2, and d) boost immunity to WPV1 & 3[1].

This communication provides the key elements and supporting scientific data for the timing of the IPV dose.

GENERAL CONSIDERATIONS

There are a number of general considerations that may influence policy decisions for poliomyelitis prevention.

Schedule: The vast majority of OPV-using countries use one of three routine schedules: DTP/OPV at age 6, 10 and 14 weeks (AFRO and some Asian countries); at age 2, 3, and 4 months (China, Indonesia), or at age 2, 4, and 6 months (mostly PAHO, but also Bangladesh) [2, 3].

OPV immunogenicity: The immunogenicity of OPV varies greatly between industrialized and developing countries [3]. Even within developing countries, the immunogenicity of OPV shows major differences. For example, Northern India has very low immunogenicity [4-6], other tropical countries, such as Thailand [7] and Indonesia [8], have high immunogenicity.

In those countries with low immunogenicity, OPV is not "effective" in a substantial proportion of children until later doses in the series are given. This is in contrast to industrialized countries where much higher seroconversion rates are achieved with the initial dose of OPV.

Vaccine-associated paralytic poliomyelitis: No standardized global surveillance system exists for vaccine-associated paralytic poliomyelitis (VAPP), although countries may detect VAPP cases as part of their acute flaccid paralysis (AFP) surveillance system. Given the complexities of VAPP diagnosis

and classification [9], additional follow-up and review by national expert classification committees is necessary, and consequently, most data on VAPP come from industrialized countries.

Maternally-derived antibody: Newborns from many currently- OPV-using developing countries have a high prevalence of maternally-derived antibody against poliovirus [10-14] because their mothers are relatively more likely to have had recent exposure to wild poliovirus and/or OPV viruses.

SPECIFIC CONSIDERATIONS FOR THE TIMING OF AN ADDITIONAL IPV DOSE

Two considerations represent critical factors with respect to decisions about the timing of an additional IPV dose to the existing national OPV schedule: (1) Immunogenicity of IPV at possible age / schedule; and (2) coverage & drop out between DTP1-DTP3 Some countries have been concerned about VAPP as well in their decision making about IPV.

However, in the context of the new endgame strategy, there is a clear hierarchy for policy decision-making. Although VAPP and coverage & drop-out rates may be important in some countries, the over-riding objective is to ensure that the "highest possible immunity" can be achieved with the single additional dose of IPV, given in the context of an "unchanged OPV routine schedule", strictly additional to, and simultaneous with the OPV dose.

Immunogenicity: In general, the immunogenicity of IPV is inversely related to levels of maternally-derived antibodies [7, 14, 15]. In terms of seroconversion, early IPV administration at 6-8 weeks of age results in lower seroconversion rates [10]. Reviews of limited existing scientific data, a dose of IPV seroconverts between 32-39% against poliovirus type 2 at age 6-8 weeks, compared with 63% at age 16 weeks [3, 16, 17]. In terms of priming, one study of IPV birth dose administration in Israel provides limited evidence that IPV administered at birth is apt to induce immunologic memory, [18],

In Cuba, 98% of 4-month old infants in Cuba that didn't previously seroconvert with OPV responded with a priming immune response with one dose of IPV [16].

Please note that the additional IPV dose would be <u>co-administered with OPV and DTP</u> at the selected age.

<u>Interpretation</u>: A dose of IPV given at older age (14-16 weeks)appears to induce almost double the seroconversion rate compared with an early dose (6-8 weeks).

Coverage & drop out between DTP1-DTP3: Program evaluation data suggest that coverage varies by WHO Region, with the lowest in AFRO, and the highest in EURO, WPRO and PAHO. Drop-out rates between DTP1-DTP3 show similar patterns. Improving routine immunization coverage is a long-term health system development priority, as well as a key priority in the new Strategic Plan for Polio Eradication, 2013-2018 [18]. During the period, 2009-2011, only three countries had massive drop-out rates >35% between DTP1-DTP3 (Chad, Equatorial Guinea & Gabon), and the vast majority of countries had drop-out rates below 10% [WHO web].

<u>Interpretation</u>: Drop-out rates from DTP1-DTP3 do not constitute a major consideration with respect to the timing of the introduction of an additional IPV dose to a national immunization schedule.

Vaccine-associated paralytic poliomyelitis: Our review of VAPP suggests different epidemiology for developing and industrialized countries. In industrialized countries, VAPP occurs primarily in early

infancy associated with the first dose of OPV. In contrast, in some developing countries, VAPP is associated with subsequent doses of OPV, with the age distribution concentrated among 1-4 year old children [20]. This difference in epidemiology most likely reflects the low immunogenicity of OPV in some tropical developing countries [4-6], which delays the actual immunizing dose to later in life [20, 21], and the prevalence of maternally-derived antibody in recently polio-endemic countries, which also impedes OPV vaccine "takes".

In Iran, a total of 12 cases of VAPP were reported between 2005-present, with an age distribution of >5-25 months, mostly among immunodeficient individuals, and associated with Sabin type 2 (97%) (personal communication, Shahmahmoodi, 2013; data shared with SAGE WG).

In India, further analysis suggested that <10% of VAPP cases occur prior to age 12 weeks. The most recent analysis refined this estimate to only 6.4% of VAPP cases occurring before age 12 weeks. Data from India [21, and unpublished data] and Iran [personal communication, S Shahmahmoodi, 2013] suggest that early IPV administration (age 6-8 weeks) would only further decrease the risk of VAPP by <10% compared with later IPV administration (age 14-16 weeks).

Countries that adopted sequential schedules using IPV followed by OPV rapidly eliminated VAPP, and introducing IPV as a first dose offers the greatest potential to reduce VAPP, as long as interference with maternal antibodies does not impact take rates for IPV. Theoretically, in developing countries, 25-40% of VAPP could be prevented by OPV2 withdrawal, although uncertainty remains about the actual magnitude of the change.

For OPV-using countries with a documented VAPP age distribution similar to that of industrialized countries, early administration of IPV (age 6-8 weeks) or a sequential schedule of IPV followed by OPV may represent the best option. For example in Thailand, 55% (6/11) of VAPP cases reported during 2001-2012 followed the administration of the first dose of OPV ; and a further 18% (2/11) followed the administration of a second dose of OPV [personal communication, Dr Piyanit, MOH/Thailand]. For countries with distribution of VAPP cases that occur at relatively older ages, later introduction of IPV will most likely offer the best chance of minimizing the impact of maternal antibodies and increasing take rates.

Interpretation: OPV administration (delayed to age14-16 weeks) should prevent the vast majority of VAPP (>90%) in most tropical developing countries. However countries with a demonstrated VAPP burden following the first dose of OPV may wish to consider relatively earlier introduction of IPV.

PROPOSED RECOMMENDATIONS

Given these considerations, weighting the evidence, and quantifying the trade-offs, the SAGE WG made the following preliminary recommendations during their October 2013 meeting (to be endorsed by the full SAGE in November 2013):

- _All countries should introduce at least one dose of IPV into their immunization schedules by the third quarter of 2015._
- _In OPV-only using countries which are introducing one dose of IPV, IPV should be administered in addition to the 3-4 doses of OPV in the primary series. The dose should be administered during the immunization contact at or after 14 weeks._

- *The timing of the IPV dose is as follows:*

    o *6, 10, 14 weeks or 2, 3, 4 months schedule: add IPV dose at the DPT3/OPV3 (or OPV 4 in countries administering a birth dose of OPV) contact;*

    o *2, 4, 6 months schedule: add IPV dose at the DPT3-OPV3 contact (although the DPT2-OPV2 can be considered).*

- *For children starting the routine immunization schedule late (age >14 weeks) the IPV dose should be administered at the first immunization contact. The minimum age for IPV is 14 weeks.*

- *When communicating this recommendation, the following should be highlighted:*

    o *IPV is an additional dose to OPV and not a replacement (the combined schedule gives the optimal immunity);*

    o *The primary :purpose of IPV introduction is to mitigate the cVDPV type 2 following OPV2 withdrawal (it will also prevent VAPP due to OPV types 1 and 3.);*

    o *The immunization visit in which DTP3 and OPV3 (OPV4 if there is a birth dose) are administered was selected over DTP1/OPV1 because of the gains in immunogenicity of IPV at 14 weeks compared to earlier administration. The later visit gives time to allow decrease in the levels of maternally-derived transplacental polio antibodies in the infant, which can interfere with an immune response to IPV; and*

    o *The potential risk of an IPV only schedule should be explained to any country considering such a change (including the evidence from Israel, an IPV only using country, of prolonged transmission of wild poliovirus type 1 probably related to the inferior intestinal immunity IPV induces compared to OPV)*

Countries with documented VAPP risk prior to 4 months of age may decide to consider alternative schedules as outlined in the previous WHO position paper [22].

REFERENCES

1. World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, November 2012: conclusions and recommendations. Wkly Epidemiol Rec 2013;88:1-16.

2. WHO website on immunization.

3. Thompson KM, Pallansch MA, Duintjer Tebbens RJ, Wassilak SGF, Cochi SL. Pre-eradication national vaccine policy options for poliovirus infection and disease control. Risk Analysis 2013; 33(4):516-543.

4. Grassly NC, Fraser C, Wenger J, Deshpande JM, Sutter RW, Heymann DL, Aylward RB. New strategies for the elimination of polio from India. Science 2006; 314:1150-1153.

5. Grassly NC, Wenger J, Durrani S, Bahl S, Deshpande JM, Sutter RW, Heymann DL, Aylward RB. Protective efficacy of a monovalent oral type 1 poliovirus vaccine. Lancet 2007;369:1356-62.

6. Estívariz CF, Jafari H, Sutter RW, John TJ, Jain V, Agarwal A, Verma H, Pallansch MA, Singh AP, Guirguis S, Awale J, Burton A, Bahl S, Chatterjee A, Aylward RB. Immunogenicity of poliovirus vaccines administered at age 6-9 months in Moradabad District, India: A randomized controlled phase 3 trial. Lancet Infectious Diseases 2012;12:128-35.

7. WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines. Combined immunization of infants with oral and inactivated poliovirus vaccines: Results of a randomized trial in the Gambia, Oman, and Thailand. Bull WHO 1996;74:253-268 and J Infect Dis 1997;175(suppl1):S215-S227.

8. World Health Organization. Polio eradication: surveys of routine immunization coverage and seroprevalence against polioviruses, Yogjakarta Province, Indonesia. Wkly Epidemiol Rec 2008;83:45-48.

9. Sutter RW, Brink EW, Cochi SL, Kew OM, Orenstein WA, Biellik RJ, Hinman AR. A new epidemiologic and laboratory classification system for paralytic poliomyelitis cases. Am J Public Health 1989;79:495 498.

10. El-Sayed N, El-Gamal Y, Abbassy AA, Seoud I, Salama M, Kandeel A, Hossny E, Shawky A, Abou Hussein H, Pallansch MA, van der Avoort HGAM, Burton T, Sreevatsava M, Malankar P, Wahdan MH, Sutter RW. Monovalent type 1 oral poliovirus vaccine in newborns. N Engl J Med 2008;359:1655-65.

11. John TJ, Jain H, Amaresh A, Ravishankar K, Varma H, Deshpande J, Pallansch MA, Singh AP, Sreevatsava M, Burton A, Malankar P, Chatterjee A, Sutter RW. Monovalent type 1 oral poliovirus vaccine in India: Report of two randomized double-blind controlled clinical trials. Vaccine 2011;29:5793-801.

12. Sutter RW, John TJ, Jain H, Agarkhedkar S, Ramanan PV, Verma H, Deshpande J, Singh AP, Sreevatsava M, Malankar P, Burton A, Chatterjee A, Aylward RB. Trial of bivalent type 1 and 3 oral poliovirus vaccine. Lancet 2010; 376:1682-88.

13. Caceres VM, Sutter RW. Sabin monovalent oral polio vaccines: Review of past experiences and their potential use after polio eradication. Clin Infect Dis 2001;33:531-41.

14. Mateen FJ, Shinohara RT, Sutter RW. Oral and Inactivated poliovirus vaccine in the newborn period: A systematic review. Vaccine 2013,31:2517-24 (http://dx.doi.org/10.1016/j.vaccine.2012.06.020).

15. Samuel BU, Cherian T, Sridharan G, Mukundan P, John TJ. Immune response to intradermally injected inactivated poliovirus vaccine. Lancet 1991;338(8763):343-4.

16. Resik S, Tejeda A, Sutter RW, Diaz M, Sarmiento L, Alemañi N, Garcia G, Fonseca M, Hung LH, Kahn A-L, Burton A, Landaverde M, Aylward RB. Priming after a fractional dose of inactivated poliovirus vaccine. N Engl J Med 2013;368:416-24.

17. Estivariz CF, Pallansch MA, Anand A, Wassilak SG, Sutter RW, Wenger JD, Orenstein WA. Polio vaccination strategies as we move towards poliovirus eradication. Current Opinion in Virology 2013 Online publication complete: 10-JUN-2013 DOI information: 10.1016/j.coviro.2013.05.007.

18. Swartz TA, Handsher R, Stoeckel P, Drucker J, Caudrelier P, Van Wezel AL, Cohen H, Salk D, Salk J. Immunologic memory induced at birth by immunization with inactivated polio vaccine in a reduced schedule. Eur J Epidemiol 1989;5:143-5.

19. Global Polio Eradication Initiative. Polio Eradication & Endgame Strategic Plan 2013-2018. World Health Organization, 2013.

20. Kohler KA, Banerjee K, Hlady WG, Andrus JK, Sutter RW. Vaccine-associated paralytic poliomyelitis in India, 1999: decreased risk despite massive use of oral polio vaccine. Bull WHO 2002;80:210-6.

21. Kohler KA, Banerjee K, Sutter RW. Further clarity on vaccine-associated paralytic polio in India. Bull Wrld Hlth Organ 2002;80:987 (letter).

22. World Health Organization. Polio vaccines and polio immunization in the pre-eradication era: WHO position paper. Wkly Epidemiol Rec 2010;85:213-28.