18 October 2012

Scientific evidence in support of:

Note for the Record: 5th Meeting of the SAGE Working Group, World Health Organization, Geneva, September 3-4, 2012

Statements under 2.2 (pages 2-3)

2.2 *Use of IPV to manage risks associated with OPV2 cessation.* OPV2 cessation will expose the global population to a new, exceptional era in the history of vaccination, in which there will be a low, but real risk of type 2 polio outbreaks due to circulating vaccine-derived polioviruses, long-term VDPV excretors and reintroduction from containment failures (the last WPV type 2 cases, which occurred in northern India in 2002-2003, were associated with the introduction of a laboratory strain).

The risks of new cVDPV2 emergences extend into the period immediately following OPV2 cessation, because some OPV2 viruses may be circulating silently in populations with relatively low population immunity at the time of cessation. The possibility of sustained transmission of a type 2 virus increases with increasing population susceptibility following cessation of all routine and supplemental use of OPV2. IPV, which is trivalent and includes serotype 2, will be the only poliovirus vaccine available for type 2 protection. At least 1 dose of IPV should be introduced into routine immunization programmes prior to or at the time of OPV2 cessation to yield the following expected benefits:

a) the prevention of paralytic polio in individuals successfully vaccinated with IPV who get exposed to a cVPDV type 2, Sabin type 2 (VAPP) or wild poliovirus type 2;

b) improved immunological response in individuals previously vaccinated with IPV when receiving mOPV2 vaccination given in response to a WPV2 or cVDPV2 outbreak that occurs after OPV2 cessation;

c) reduced transmission of cVDPV2 or WPV2 should they be introduced (i.e. there is evidence to suggest that IPV reduces the titer of fecal virus excretion and duration of shedding and is equivalent to OPV in decreasing oropharyngeal shedding);

d) boosting of immunity to wild polioviruses type 1 and 3 in vaccine recipients, which may further accelerate wild poliovirus eradication.

For countries at particular risk of cVPDV emergence, the suggested minimum 1-dose IPV policy may need to be complemented with additional measures (e.g. pre-OPV2-cessation boosting with tOPV SIAs to maximize population immunity to serotype 2 or introduction of a 2nd IPV dose, potentially with catch-up campaigns).

a) the prevention of paralytic polio in individuals successfully vaccinated with IPV who get exposed to a cVPDV type 2, Sabin type 2 (VAPP) or wild poliovirus type 2;

Supporting evidence:

- *Efficacy against Sabin virus (i.e., surveillance for vaccine-associated paralytic poliomyelitis [VAPP])*:
    - the most convincing evidence emanates from countries that used sequential schedules of one or more doses of IPV followed by OPV to prevent vaccine-associated paralytic poliomyelitis (VAPP) [1].
    - in the United States, after introduction of a sequential schedule of IPV followed by OPV in 1997, no case of VAPP was reported in infants that had received at least a single dose of IPV [2].
    - in Hungary, a country that has traditionally reported the highest rates of VAPP in the world, not a single VAPP case was reported, after introduction of a single dose of IPV in 1992, suggesting that a dose of IPV is highly efficacious in preventing VAPP [3-6, & WHO unpublished data].
    - WHO is aware of only single case of VAPP in a child that had received a dose of IPV in the modern era (with enhanced-potency IPV) [WHO unpublished data].
- *Efficacy against wild poliovirus*:
    - there are data on one-dose efficacy generated in a case-control study in Senegal that reported 36% effectiveness (95% confidence interval 0-67%) in preventing paralysis during an outbreak of poliomyelitis caused by poliovirus type 1 [7].
- *Immunogenicity of a single dose of IPV in naïve infants:wild poliovirus*:
    - a single dose of IPV administered to naïve infant s aged 4 months reported that 63% seroconverted against type 2 (compared to 47% of infants that received fractional-dose IPV [0.1. ml intradermally, 1/5 of a full dose] and that 98.3% of infants that didn't seroconvert did actually respond with a priming immune response (compared to 94.0% in the fractional-dose IPV group). [Data presented to SAGE WG. WHO unpublished data from Cuba, 2012]

Summary:

The data suggest high efficacy (close to 100%) of a single dose of IPV against VAPP and somewhat lower efficacy against wild poliovirus. The biological plausibility seems established with the recent data from Cuba on one-dose IPV seroconversion and priming. Given that indigenous wild poliovirus type 2 has been eliminated since 1999 globally, the challenge to IPV-induced type 2 immunity will be primarily Sabin type 2 poliovirus.

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b) improved immunological response in individuals previously vaccinated with IPV when receiving mOPV2 vaccination given in response to a WPV2 or cVDPV2 outbreak that occurs after OPV2 cessation;

Supporting evidence:

- a single dose of IPV will effectively close the immunity gaps to poliovirus type 2 in previously OPV-vaccinated children. In Cote d'Ivoire and India studies one IPV dose in seronegative infants closed the immunity gaps against type 2 completely [8, 9].
- Data suggest that IPV and OPV are interchangeable. A study from the United States with arms of IPV followed by OPV and OPV followed by IPV reported similar results in terms of seroconversion [10, 11].
- in seropositive individuals, a dramatic boosting of antibody titers is seen (~60-70%) against type 2 after a single IPV dose [12,13].
- a single dose of IPV in immunologically-naïve infants in Cuba aged 4 mos seroconverted 63% against type 2 (compared to 47% after a fractional dose). [Data presented to the SAGE WG. WHO unpublished data from Cuba, 2012. Submitted for publication].
- data from Cuba showed that 98.3% (94.0% following a fractional IPV dose) infants who didn't seroconverted after a single dose of IPV responded with a priming response to poliovirus type 2. [Data presented to the SAGE WG. WHO unpublished data from Cuba, 2012. Submitted for publication].
- OPV after IPV results in closing of immunity gaps and substantial boosting of antibody titers [10-12, 14-15].
- new data from India demonstrate that a single dose of IPV in infants and children (aged 6-11 mos, 5 and 10 yrs) with a history of multiple doses of OPV boosts intestinal mucosal immunity, and reduces excretion prevalence after a challenge by 51-81%. [Data presented to the SAGE WG. WHO unpublished data from India, 2012. Submitted for publication].

Summary:

- since levels of antibody (after mucosal exposure of live poliovirus) are predictive of likelihood of excretion, a single dose of IPV should substantially decrease prevalence, titer, and length of poliovirus excretion.
- and more importantly could allow rapid (within 3 days) boosting of immune response (both humoral and mucosal).

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c) reduced transmission of cVDPV2 or WPV2 should they be introduced (i.e. there is evidence to suggest that IPV reduces the titer of fecal virus excretion and duration of shedding and is equivalent to OPV in decreasing oropharyngeal shedding);

Supporting evidence:

Intestinal mucosal immunity:

General:

- Introduction of IPV in advance of Sabin type 2 cessation would decrease the proportion of population naïve to poliovirus and boost both humoral and mucosal immunity.
- convincing evidence suggests that mucosal exposure with live poliovirus is necessary to obtain an IgA response after IPV booster vaccination. In subjects that were naturally immune (to wild poliovirus), a single booster dose of IPV resulted in strong increases of IgA levels within a week in 93%, 94% and 83% against poliovirus types 1, 2, and 3, respectively [16,179].

After sequential (OPV and IPV) vaccination:

- in sequential schedule of OPV and IPV, nearly a high proportion of infants formed local neutralizing and IgA antibody responses [18].
- IPV was administered at age 9 months in infants with a history of 5 doses of OPV in Oman [19]. Infants were then challenged with monovalent type 3 poliovirus vaccine (mOPV3) 6 months later. In the IPV group, 12.7% subjects excreted virus compared with 17.0% and 16.4% in the two tOPV groups, respectively.
- new data from India demonstrate that a single dose of IPV administered to infants and children (aged 6-11 mos, 5 and 10 yrs) with a history of multiple OPV doses dramatically boosts intestinal mucosal immunity, and reduces excretion prevalence after a bOPV challenge by 54-72% against type 1, and 51-81% against type 3 The effect is largest in children age 10 yrs and considerably larger than with a supplemental dose of bOPV. [Data presented to the SAGE WG. WHO unpublished data from India, 2012].

After IPV vaccination only:

- after 2 doses of IPV, the excretion prevalence is similar to unvaccinated control groups (>90% excrete after a challenge) by day 7, but virus titer in stool is 0.5 log10 lower by day 7 [12]; a follow-up study suggested that excretion period is shortened by half (median 10-12 days compared with >20 days in unvaccinated controls), and titers are ~0.5-1 $\log_{10}$ (3-10-fold decrease) lower at day 7 [Data presented to the SAGE WG. WHO unpublished data from Cuba, 2012].
- After 3 doses, the responses appear to be similar to those after 2 doses of IPV [12, 20].

Oropharyngeal mucosal immunity:

- after 3 doses of IPV, oropharyngeal shedding is rare, and appears to be similar to OPV-induced immunity [21].
- no data are available of oropharyngeal shedding after a single dose of IPV.

Summary:

- in infants whose mucosal surfaces had been exposed to live poliovirus (for example, after OPV vaccination), resistance to excretion following a challenge (e.g., OPV) depends on levels of type-specific antibody (the higher the antibody levels, the less likely to excrete). WHO unpublished data from Cuba, 2012. Netherlands.
- a dose of IPV (after multiple doses of OPV) closes the immunity gaps (both humeral and mucosal) and substantially boosts antibody titer [8-13].
- as shorter excretion duration with lower viral titer likely equates with lower transmission), the addition of a single dose of IPV would be expected to have a substantial effect on population transmission.
- the lower prevalence of excretion, the shorter length of excretion duration, and the lower stool titers of poliovirus among IPV-vaccinated infants should curtail endemic or epidemic spread of poliovirus.

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d) boosting of immunity to wild polioviruses type 1 and 3 in vaccine recipients, which may further accelerate wild poliovirus eradication.

Supporting evidence:

- in the schedule proposed for OPV2 cessation, 3 doses of bOPV (birth, 6, and 10 weeks) would be administered prior to simultaneous bOPV (4^{th} dose)/IPV (single dose) administration (at 14 weeks), so both the humoral and mucosal immunity against type 1 and 3, respectively, should be expected to very robust. These are the viruses that still circulate in the remaining polio-endemic countries.
- solid evidence from multiple studies demonstrates that a single dose of IPV in previously OPV-vaccinated children closes the immunity gaps to all three serotypes (including types 1+3) [examples: 10-11, 12, 14-15].
- similarly the evidence suggest rapid and massive increase in antibody titers [10-11, 12, 14-15].

Summary:

- the combination of these effects (closure of immunity gaps, and boosting antibody titers) after a dose of IPV in infants who had previously received multiple doses of OPV, should decrease excretion prevalence after poliovirus exposure, and therefore, accelerate eradication.

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