



Immunogenicity to poliovirus type 2 following two doses of fractional intradermal inactivated poliovirus vaccine: A novel dose sparing immunization schedule



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ABSTRACT

Introduction: The polio eradication endgame strategic plan calls for the sequential removal of Sabin poliovirus serotypes from the trivalent oral poliovirus vaccine (tOPV), starting with type 2, and the introduction of ≥ 1 dose of inactivated poliovirus vaccine (IPV), to maintain an immunity base against poliovirus type 2. The global removal of oral poliovirus type 2 was successfully implemented in May 2016. However, IPV supply constraints has prevented introduction in 21 countries and led to complete stock-out in >20 countries.

Methods: We conducted a literature review and contacted corresponding authors of recent studies with fractional-dose IPV (fIPV), one-fifth of intramuscular dose administered intradermally, to conduct additional type 2 immunogenicity analyses of two fIPV doses compared with one full-dose IPV.

Results: Four studies were identified that assessed immunogenicity of two fIPV doses compared to one full-dose IPV. Two fractional doses are more immunogenic than 1 full-dose, with type 2 seroconversion rates improving between absolute 19–42% (median: 37%, $p < 0.001$) and relative increase of 53–125% (median: 82%), and antibody titer to type 2 increasing by 2–32-fold (median: 10-fold). Early age of administration and shorter intervals between doses were associated with lower immunogenicity.

Discussion: Overall, two fIPV doses are more immunogenic than a single full-dose, associated with significantly increased seroconversion rates and antibody titers. Two fIPV doses together use two-fifth of the vaccine compared to one full-dose IPV. In response to the current IPV shortage, a schedule of two fIPV doses at ages 6 and 14 weeks has been endorsed by technical oversight committees and has been introduced in some affected countries.

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1. Introduction

Indigenous wild poliovirus type 2 was last detected in Northern India in 1999, and declared as eradicated by the Global Certification Commission in September 2015 [1]. The Global Polio Eradication Initiative (GPEI) prepared a strategic action plan which called for the sequential removal of Sabin serotypes from the trivalent oral poliovirus vaccine (tOPV), and the introduction of inactivated poliovirus vaccine (IPV) [2]. By May 2016, Sabin type 2 was successfully withdrawn globally when tOPV was replaced with bivalent OPV (bOPV), containing poliovirus types 1 and 3. The switch was preceded by a phased introduction of one dose of IPV in the

routine immunization schedule. Countries were prioritized for IPV introduction based on the historical risk profile of generating circulating vaccine-derived polioviruses.

The Strategic Advisory Group of Experts (SAGE) on Immunization has recommended introduction of at least one dose of intramuscular IPV at age ≥ 14 weeks, with bOPV at ages 6, 10 and 14 weeks, to provide an immunity base to type 2 poliovirus after cessation of Sabin type 2 [3]. The immunity base against type 2 should decrease the paralytic consequences of poliovirus type 2 exposure and improve immunological response to type 2 containing poliovirus vaccine administered in the event of a type 2 poliovirus outbreak. IPV introduction (in previously OPV-only using countries) has increased global IPV demand, stand-alone as well as that used in combination vaccines, from about 80 million doses in 2013 to about 200 million doses in 2016. The supply commitments by IPV manufacturers were expected to meet the increased demand

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through expanded production; however, the quantity of IPV promised by the manufacturers has repeatedly been reduced (currently <50% of initial commitments). These supply reductions have led to at least 49 countries either having to delay IPV introduction or experience a stock-out of IPV after introduction [4]. IPV supply constraints are expected to last until 2018–2019.

Fractional IPV (fIPV), in which one-fifth (0.1 ml) of the full dose of intramuscular IPV (0.5 ml) is administered intradermally, is a potential option to stretch limited supplies of IPV. Here we present a literature review and comparative analysis of poliovirus type 2 immunogenicity between two doses of fIPV and one full-dose IPV.

Based on promising preliminary evidence from the data presented in this review, in 2012, SAGE recommended that development of fIPV be prioritized [5]. Since then, in response to the IPV supply constraints, a new schedule of two fIPV doses at ages 6 and 14 weeks in addition to bOPV at ages 6, 10 and 14 weeks was developed and endorsed by advisory committees [6].

2. Methods

PubMed database was searched for studies published from January 01, 1959 onwards. Search terms used were: inactivated poliovirus vaccine; fractional inactivated poliovirus vaccine; and intradermal inactivated poliovirus vaccine. Assessment was limited to studies that assessed enhanced potency IPV (eIPV), henceforth called IPV, and studies using original potency IPV were excluded from the review. Studies were selected for review if they assessed immunogenicity of fractional one-fifth intradermal IPV in infants who had received no prior poliovirus vaccine and did not administer type 2 OPV with IPV. Among studies selected for review, primary assessment was restricted to those that compared immunogenicity of one full-dose of intramuscular IPV to two doses of intradermal fIPV.

In terms of statistical methods, we compared the proportion with seroconversion in the 2-dose fIPV and single full-dose arms. In all of the studies, blood for serological assessment was collected 4 weeks after the fIPV/IPV dose, except in a study in Cuba in which blood was collected 4 months after the first full-dose IPV [7]. For the antibody titer distribution, we were able to obtain subject-specific titer values and compared the two study arms using the Wilcoxon rank-sum test. For median antibody titers, 95% confidence intervals were calculated using bootstrapping with 10,000 replications [8]. In addition, for each study arm we prepared the reverse cumulative antibody titer distribution curves. All statistical analyses were conducted in R (version 2.92) [9].

3. Results

Three studies comparing fIPV and full-dose IPV did not meet selection criteria and were therefore excluded [10–12]. Four studies were identified that compared two fIPV doses to one full-dose IPV. Two additional studies were identified that assessed immunogenicity of two fIPV doses though did not compare it to one full-dose IPV. Also three additional studies assessed immunogenicity of full-dose IPV at age 14 weeks, the standard recommended full-dose schedule.

Table 1 lists the nine studies that were identified. Studies were implemented from 1992 to 2015. In India two studies reported 70–89% type 2 seroconversion with two doses of fIPV at ages 6 and 14 weeks [13,14]. Fig. 1 displays, by study, the reverse cumulative antibody curves 4-weeks after one full-dose IPV compared with 4-weeks after two fIPV doses and demonstrates in all studies that two fIPV doses induce more robust antibody titers than a single full dose.

In Cuba, type 2 seroconversion with fIPV at age 6 and 10 weeks was 19% higher compared to IPV at age 6 weeks (55% vs 36%; $p < 0.001$), a relative increase of 53% [15]. Median titers were 2-fold higher with two fIPV doses compared to one IPV dose. In Bangladesh, type 2 seroconversion with fIPV at ages 6 and 14 weeks was 43% higher compared to IPV at age 6 weeks (81% vs 38%; $p < 0.001$), a relative increase of 113% [16]. Type 2 median antibody titers after two fIPV doses were 16-fold higher compared to one IPV dose. This study also assessed immunologic priming with IPV, a seroconversion response assessed one week after administration of a second dose of IPV/fIPV among those who did not seroconvert after the first dose. Overall, after one fIPV dose, 78% of participants either seroconverted or were primed.

In Oman, type 2 seroconversion with fIPV at ages 2 and 4 months was 40% higher compared to IPV at age 2 months (72% vs 32%; $p < 0.001$), a relative increase of 125% [17]. The median antibody titer was 5-fold higher with two fIPV doses compared to one IPV dose. In a second study in Cuba, type 2 seroconversion with fIPV at ages 4 and 8 months was 35% higher compared to IPV at age 4 months (98% vs 63%; $p < 0.001$), a relative increase of 56% [7]. Type 2 median antibody titers were 32-fold higher after two fIPV doses compared to one IPV dose. After one fIPV dose at age 4 months 97% of participants had either seroconverted or were primed.

Overall, two doses of fIPV were more immunogenic with higher seroconversion (absolute increase median: 37%, range: 19–42%; relative increase median: 84%, range: 53–125%) and higher antibody titers (median: 10-fold; range: 2–32-fold) than one full-dose IPV given at the age of first fIPV dose.

Three studies from India and Latin America reported 69–80% type 2 seroconversion after one full-dose IPV at age 14 weeks with median titers of 18–36 [18–20].

4. Discussion

In April 2016, in light of global IPV shortage SAGE recommended that countries consider an IPV schedule of two fractional doses (0.1 ml each) at ages 6 and 14 weeks in lieu of one full-dose (0.5 ml) at age 14 weeks [21]. The WHO position paper on polio states that “in the context of an IPV shortage, countries could consider instituting a 2-dose fractional dose schedule which could ensure that all eligible infants receive IPV, is dose-sparing and results in better immunogenicity than a single full dose of IPV”. The data presented here formed the basis of the advisory committee recommendation of two fIPV doses at ages 6 and 14 weeks as an alternative to one full-dose of IPV at age ≥ 14 weeks in addition to bOPV at ages 6, 10 and 14 weeks. Two fIPV doses, 4 weeks to 4 months apart are more immunogenic for type 2 poliovirus (and for types 1 and 3; data not shown) than one IPV dose administered at the age of first intradermal dose. The type 2 immunogenicity of two fIPV doses were related directly to the age at first administration and the interval between the doses, starting later and having a longer interval was more immunogenic, consistent with the “prime-boost” concept for inactivated vaccines.

Two fIPV doses use two-fifth of the amount of vaccine compared to one full-dose IPV. Therefore, each full-dose IPV, which would have been used to vaccinate one child can now be used to vaccinate at least two infants, stretching limited supplies of IPV. Fractional IPV does not require modification of existing IPV vaccine vial or its contents to make IPV compatible to draw the vaccine in devices for intradermal injection. Multi-dose IPV vial policy permits use of vials up to 28 days from the date of first use and this will minimize wastage particularly in immunization sessions, in which the number of vaccine recipients is less than the maximum number of fIPV doses that could be withdrawn from an IPV vial.

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