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Oral and Inactivated Poliovirus Vaccines in the Newborn: A review

Farrah J. Mateen, MD^{1,2,3}, Russell T. Shinohara, PhD⁴, and Roland W. Sutter, MD¹

¹Polio Eradication Initiative, World Health Organization, Geneva, Switzerland ²Department of Neurology, Johns Hopkins University, Baltimore, USA ³Departments of International Health, The Bloomberg School of Public Health Johns Hopkins University, Baltimore, USA. ⁴Biostatistics, The Bloomberg School of Public Health Johns Hopkins University, Baltimore, USA.

Abstract

Background—Oral poliovirus vaccine (OPV) remains the vaccine-of-choice for routine immunization and supplemental immunization activities (SIAs) to eradicate poliomyelitis globally. Recent data from India suggested lowerthanexpected immunogenicity of an OPV birth dose, prompting a review of the immunogenicity of OPV or inactivated poliovirus vaccine (IPV) when administered at birth.

Methods—We evaluated the seroconversion and reported adverse events among infants given a single birth dose (given 7 days of life) of OPV or IPV through a systematic review of published articles and conference abstracts from 1959-2011 in any language found on PubMed, Google Scholar, or reference lists of selected articles.

Results—25 articles from 13 countries published between 1959 and 2011 documented seroconversion rates in newborns following an OPV dose given within the first seven days of life. There were 10 studies that measured seroconversion rates between 4 and 8 weeks of a single birth dose of TOPV, using an umbilical cord blood draw at the time of birth to establish baseline antibody levels. The percentage of newborns who seroconverted at 8 weeks range 6-42% for poliovirus type 1, 2-63% for type 2, and 1-35% for type 3). For mOPV type 1, seroconversion ranged from 10-76%; mOPV type 3, the range was 12-58%; and for the one study reporting bOPV, it was 20% for type 1 and 7% for type 3. There were four studies of IPV in newborns with a seroconversion rate of 8-100% for serotype 1, 15-100% for serotype 2, and 15-94% for serotype 3, measured at 4-6 weeks of life. No serious adverse events related to newborn OPV or IPV dosing were reported, including no cases of acute flaccid paralysis.

Address correspondence or request for reprints to: Roland W. Sutter, Polio Eradication Initiative, World Health Organization CH-1211 Geneva 27, Switzerland; Tel +41 22 791 3262; Fax +41 22 791 1571, sutterr@who.int.

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Conclusions—There is great variability of the immunogenicity of a birth dose of OPV for reasons largely unknown. Our review confirms the utility of a birth dose of OPV, particularly in countries where early induction of polio immunity is imperative. IPV has higher seroconversion rates in newborns and may be a superior choice in countries which can afford IPV, but there have been studies of an IPV dose for newborns.

Keywords

poliomyelitis; polio vaccine; oral; vaccine; newborn; birth; immunogenicity; poliovirus vaccine; inactivated

Introduction

Oral poliovirus vaccine (OPV) is central to the goal of polio eradication in many countries where affordable and easily administered vaccination can facilitate the prevention of disease. Widespread use of trivalent oral poliovirus vaccine (tOPV), whether administered in routine immunization schedules or in supplemental immunization activities, has led to control and elimination of wild poliovirus in the industrialized world¹ and three World Health Organization Regions,²⁻⁴ and will hopefully, with the advent of more immunogenic monovalent and bivalent poliovirus vaccines, lead to global eradication in the near future.

tOPV is the vaccine-of-choice for the Global Polio Eradication Initiative (GPEI) because it provides superior mucosal immunity against subsequent infection and spread of wild poliovirus, spreads from vaccinees to close contacts (and thus immunizes some individuals not reached by immunization programs), can be rapidly administered by volunteers in the form of oral drops (important during mass vaccination campaigns), and is relatively affordable compared to inactivated poliovirus (0.15 versus 3.00 US dollars).^{5,6}

However, tOPV is associated with rare cases of vaccine-associated paralytic poliomyelitis (VAPP) (approximately 2-4 cases per 1 million in a birth cohort in developing countries)⁷ and the immunogenicity of a schedule of 3 to 4 doses of tOPV varies widely in developing countries.⁸⁻¹⁰ The low immunogenicity of OPV requires multiple doses to be given each year to children who are less than five years old in areas where poliomyelitis is most difficult to eradicate. To correct for the low immunogenicity of tOPV, the GPEI has recommended the development, licensure, and massive use of monovalent type 1 OPV (mOPV1), monovalent type 2 (mOPV2), monovalent type 3 (mOPV3), and bivalent (type 1 and 3) OPV (bOPV) in the last 5 years.^{11,12}

Since 1985, the World Health Organization has recommended OPV at the time of birth as well as at 6, 10, and 14 weeks as a safe and effective means of protection against poliomyelitis in resource-poor regions.¹³ The birth dose was initially referred to as “zero-dose tOPV” and is not usually counted as part of the three-dose routine tOPV schedule in developing countries. At the time, the recommendation for a birth dose derived from clinical data from the developing world, including China¹⁴ and India¹⁵ as well as theoretical considerations.^{16,17} The administration of tOPV at birth is especially important to consider because this dose can provide early protection to newborns in endemic settings and may be the only vaccine received by children who later become lost to medical services. In addition,

given that most newborns have maternally-derived antibody against polioviruses, a birth dose of tOPV is associated with the lowest risk of serious adverse events (i.e. VAPP).

As part of a policy review on the routine administration of tOPV in newborns, a systematic review of the published literature of OPV and IPV at birth was performed to determine whether there is continued justification for a birth dose in the routine immunization schedule of tOPV.

Methods

Search Strategy

In August 2011, a search was performed in PubMed and Google Scholar for all articles which present the original research results of newborn OPV administration. Key search terms included “newborn,” “birth,” “poliomyelitis,” “vaccination” “immunization,” and “oral poliovirus vaccine.” Articles describing the results of clinical studies in humans in any language were included. Commentaries, opinions, and reviews were excluded. Studies that had a sample size of less than 20 babies were also excluded. The reference lists of included articles were used to identify other articles and non-indexed work including abstracts from conference proceedings.

Evaluation of Articles

All articles were scrutinized for pre-determined characteristics to ensure they were relevant to the study question. *Newborn dosing* is defined here as a dose of vaccine within the first 7 days of life in a non-premature, healthy neonate. *Seroconversion* was the primary endpoint of analysis and defined as the percentage of all vaccinees who received newborn dosing of OPV or IPV and developed serum antibodies to poliovirus as a result of the vaccination. Reports were also analyzed for serious adverse events following OPV and IPV administration in the newborn period, including VAPP in the case of OPV.

Included articles were categorized based on study characteristics. Year of publication, country of study origin and its development status (based on classification from the World Economic Situation and Prospects)¹⁸, study design, sample size, type of oral poliovirus vaccine (monovalent, bivalent, or trivalent), manufacturer of the vaccination, total number of doses administered, and time of blood draw to estimate serology were collected.

Assessment of Seroconversion

To allow for precise estimation of baseline serological status, it was noted whether an umbilical cord blood sample or a maternal antibody titre at the time of birth was performed. Umbilical cord blood sampling was considered a higher form of data quality in providing seroconversion estimates. Using maternal antibody titre, estimation of seroconversion was considered acceptable in this study if the following criteria were met: an increase by four-fold from the expected decline in baseline maternal antibodies or a serological titre was equal or greater than 1:8 (assuming a maternal antibody half-life of 28).¹⁹

The percentage of infants with seroconversion and the age at which the blood draw occurred after the newborn dose were recorded for each poliovirus type in each study. For monovalent

vaccinations, only seroconversion related to the virus type immunized was recorded, although some naturally acquired immunity may have occurred to other types during the study timeframe in some children. In the presentation of seroconversion rates, the first blood draw which measured serum antibodies in the infant, following the newborn dose, was used to measure seroconversion rates. Blood draws must have occurred between 28 days and 4 months. Studies which included a first serum blood draw beyond 4 months or measured serum antibodies to poliovirus for the first time after multiple vaccine doses were excluded from this analysis.

A nonparametric (Kruskal-Wallis) test was performed to compare the seroconversion rates between countries with different income levels (categorized as low, middle, or high by World Bank income level at the time of the study).

Results

Characteristics of Included Studies

Twenty-five published reports of 26 separate studies^{14,20-43} fit the study inclusion criteria including 21 articles published in English, 2 articles published only in Spanish, 1 article in press, and 2 conference proceedings papers. The most common reason for a study which included a birth dose to be excluded from this analysis was a lack of complete reporting of the seroconversion rate following the birth dose alone.

Articles were highly concentrated in two time periods: 1959-1969 (n=8), surrounding the time of development of the Sabin vaccine, and 1985-present (n=17), following the resolution to eradicate poliomyelitis globally (table 1). More recent publications derive from developing countries, particularly in countries where wild-type poliovirus remains endemic (e.g. Pakistan), whereas earlier articles derived nearly exclusively from sites in high income countries (e.g. United States of America, New Zealand). Overall 13 countries were represented.

Study design was as follows: randomized trial (n=17, 65%), prospective cohort study (n=4, 15%), randomized trial with poor follow up (n= 2, 8%), prospectively followed case series (n=2, 8%), and one small, nonrandomized, controlled trial (n=1, 4%). Eleven studies reported on the efficacy of the monovalent vaccine (usually MOPV but also including CHAT 1). Fourteen studies reported the seroconversion rates of tOPV and a single study reported the results of bivalent (bOPV) vaccine administration.

Sample size of the included studies ranged from 21 to 302 newborns. The total number of newborn infants studied in all combined reports is 5257. Thirteen published studies have sample sizes less than 100 newborn infants in a study arm assessing seroconversion of newborn OPV dosing and all six of the IPV studies have sample sizes less than 100 newborns.

Twenty of the reported studies have used umbilical cord blood samples to estimate newborn antibody levels at the time of birth prior to newborn vaccination (20/24, 83%). There were six studies of TOPV which included both an umbilical cord blood sampling and a 30-day

blood draw for antibody levels. An additional four TOPV studies included both an umbilical cord blood sampling and a blood draw between 31 and 60 days. Eight published studies looked at the relationship between a TOPV dosing schedule that included a newborn dose and other schedules.

Seroconversion Rates following OPV

Seroconversion rate (as measured between birth and 4 to 8 weeks) was measured in 10 TOPV studies with umbilical cord blood measurements of maternal antibodies taken at the time of birth. Seroconversion rates ranged from 6-42% for tOPV for poliovirus type 1, 2-63% for type 2, and 1-35% for type 3 (table 2, figures 1, 2, and 3). For mOPV type 1, seroconversion ranged from 10 to 76%. In the one study reporting bOPV, seroconversion to type 1 poliovirus was 20% for type 1 and 7% for type 3. For mOPV type 2, seroconversion to poliovirus type 2 was measured in one study and was 4%. Seroconversion to mOPV for poliovirus type 3 was studied twice and was 12% and 58%. Seroconversion rates in the four studies that did not use an umbilical cord sample were reported to be overall higher (range 28-86% for type 1, 51-94% for type 2, and 14-76% for type 3).

Seroconversion rate of TOPV (including only studies with an umbilical cord draw, table 2) was also studied by income level of the country where the study occurred. When testing for a significant difference between low, middle, and high income countries, no difference in seroconversion rates was observed for TOPV for type 1 ($p=0.16$), type 2 (0.058), or type 3 poliovirus (0.062). A difference in seroconversion rates was however observed by country income level for type 1 poliovirus monovalent vaccine (0.036).

Seroconversion Rates Following IPV

Seroconversion from a newborn dose of IPV was measured in 4 separate studies, including 3 in Israel and 1 in India (Table 4). Only 3 studies estimated seroconversion of the newborn dose in 8 weeks. Seroconversion to poliovirus type 1 was between 8 and 100%; for type, 15-100%; and for type 3, 15-94%.

Adverse Events

Fifteen studies reported on adverse events. There were no reported adverse events related to OPV or IPV dosing in the newborn period including no reports of acute flaccid paralysis after OPV administration. Although newborn fatalities were reported in some clinical trials, causes were attributed to other events and illnesses, not related to the administration of OPV.

Discussion

This review documented great variability in birth dose performance in developing countries, similar to the performance of a routine immunization schedule in the developing world.⁴⁴ The level of variability of a birth dose performance should not be surprising, given that there is also a large variability in the performance of a routine immunization against poliomyelitis in developing countries.⁸ In addition, it highlights the poor immunogenicity of a birth dose with tOPV, mOPV1 or bOPV in India for reasons that remain unclear.

The consistently low seroconversion of a birth dose of OPV in India is unlikely due to such factors as concurrent gastrointestinal infections, high levels of maternally-derived antibody, concomitant breast-feeding, or interference among the Sabin strains.^{37,45,46} There is unpublished information from India that suggest that this inhibitory effect is relatively short-lived, probably less than a week (T Cherian, TJ John, personal communication to RW Sutter, 2009). A dose of OPV given at 30 days of age results in consistently high seroconversion rates in India. Therefore the reason(s) why newborns in India do not seroconvert are speculative. Genetic factors or immaturity of the immune system are unlikely to be responsible (because the inhibitory effect is said to be transient). It may be valuable to instead focus attention on potential factors related to maternal status and the amniotic fluid. The microbiome of the gut may also be an important factor in vaccine uptake and seroconversion but has not been studied in large numbers of newborns to date. The role of the microbiome and OPV seroconversion rates is the topic of study in current clinical trials.

OPV vaccine is given to millions of newborns each year in regions where the risk of poliomyelitis persists. Almost all newborns who receive low levels of passive antibody transfer from their mothers, and are therefore protected against poliomyelitis until this maternally-transferred immunity wanes. Immunogenicity of OPV is quite good outside of India, making continued use of OPV at the time of birth a continuing goal in the program for eradication. From this review, it is apparent that a birth dose will never lead to immunity in all newborns vaccinated. Multiple subsequent routine vaccination doses are still necessary. Notably, there have been no serious adverse events reported from any of the studies that have considered newborn dosing over the past approximately 50 years.

This study had limitations. First, given that there is no standard time to measure seroconversion and the number and timing of subsequent doses of OPV have differed by study, the results of seroconversion are variable and may not be directly comparable. Importantly, the definition of seroconversion may be a source of variation in the final estimates. The studies that had a longer time to first blood draw to estimate seroconversion (closer to the 16-week cutoff point for this review) could overestimate the seroconversion from the vaccine due to secondary exposure to the vaccine in countries using OPV. Secondary exposure to OPV can impact a newborn's immunity since up to 50 percent of immunized babies excrete live weakened poliovirus when studied.⁴⁷ Second, the definition of the half-life of maternal antibodies may have varied. The use of a definition with a half-life longer than 4 weeks may lead to underestimation of the seroconversion rate in newborns. Third, the type of vaccination preparation and producer usually differ by study with some vaccines made in a non-standardized fashion in individual labs in early reports. Overall, the included studies had different primary aims, locations, vaccine manufacturers, and methods of evaluation. Therefore, comparisons between studies must be scrutinized with caution.

In spite of the attempt to make newborn dosing with OPV ubiquitous in countries where poliomyelitis is endemic, there remain little data on the precise seroconversion rates from a single newborn dose. The highest level of certainty can be provided from studies which include an umbilical cord blood sample at the time of birth. This represents the level of antibody in the newborn rather than estimation based on the maternal antibody level. Although a majority of studies provided an umbilical cord blood sample for a baseline

measurement, including all monovalent vaccine studies, many large trivalent OPV studies did not. The level of seroconversion provided by the newborn dose alone remains difficult to analyze fully based on the heterogeneity of available studies.

The administration of IPV at birth has been studied infrequently. Due to the well-characterized interference of maternally derived antibodies with IPV, few studies examined IPV at birth. Reported publications include at least some premature newborns in multiple reports. In general, IPV has superior conversion rates to OPV when studied and may be a valuable treatment in combination with OPV in some countries and as replacement for OPV in countries which can afford to reliably implement IPV at the time of birth for the long term. There are no reports of VAPP following IPV, making it a superior option for the end-game of polio eradication. Nonetheless, there remains insufficient evidence to recommend an IPV birth dose. The only two studies to look at IPV seroconversion within 4 weeks of life included babies who were prematurely (30-35 weeks). Only one study has been performed on healthy newborns in a low income setting, including a total of 50 babies.

Although this analysis did not reveal uniform seroconversion rates following a birth dose, there are many reasons to continue with a birth dose recommendation in locations where early inducement of immunity against poliomyelitis is beneficial. This included induction of mucosal immunity at an early stage, a possible decreased incidence of VAPP by initiating OPV at the time of high maternal antibody exposure, access to care, and a “priming” effect in which subsequent doses of OPV may have higher seroconversion rates as compared to when a birth dose was not given. In accordance with this work, newborn dosing was again endorsed in a WHO June 2010 position paper on polio vaccination.⁴⁸

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HIGHLIGHTS

We reviewed the literature on the birth dose of poliovirus vaccines.

Both oral and inactivated poliovirus vaccines were studied. Seroconversion was assessed in 26 studies from 13 countries (1959-2011). There is great variability in the seroconversion following a birth dose of OPV. The utility of a dose of poliovirus vaccine at birth is confirmed.

Figure 1.

Forest plots showing seroconversion and confidence intervals (bars), weighted by sample size (boxes) for poliovirus serotype 1.

Figure 2.

Forest plots showing seroconversion and confidence intervals (bars), weighted by sample size (boxes) for poliovirus serotype 2.

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TABLE 1

OVERVIEW OF LOCATION, YEAR, AND QUALITY ASSESSMENT OF INCLUDED STUDIES (N=25)

Study Number	Primary Author's Last Name	Year of Publication	Country of Study	Vaccine Studied (OPV or IPV)	Type of Study
1	Prem	1959	United States	OPV	Prospective cohort study
2	Krugman	1960	United States	OPV	Randomized trial
3	Pagano	1962	United States	OPV	Randomized trial with poor follow up
4	Campillo-Sainz	1962	Mexico	OPV	Randomized trial
5	Sabin	1963	United States	OPV	Prospective case series
6	Sabin	1963	United States	OPV	Small controlled trial
7	Ordenez	1966	Mexico	OPV	Randomized trial
8	Farmer	1969	New Zealand	OPV	Prospective case series
9	Banfi	1974	Chile	OPV	Randomized trial
10	De-Xiang	1986	China	OPV	Randomized trial
11	Swartz	1989	Israel	IPV	Prospective cohort study
12	Weckx	1992	Brazil	OPV	Randomized trial
13	Khare	1993	India	OPV	Randomized trial with poor follow up
14	Sutter	1993	Oman	OPV	Prospective cohort study
15	Osei-Kwasi	1995	Ghana	OPV	Randomized trial
16	Linder	1995	Israel	IPV	Randomized trial
17	Bhaskaram	1997	India	OPV	Randomized trial
18	Jain	1997	India	OPV, IPV	Randomized trial
19	WHO Collaborative	1997	Brazil	OPV	Prospective cohort study
20	Linder	2000	Israel	IPV	Randomized trial
21	Parent du Chatelet	2003	Pakistan	OPV	Randomized trial
22	El-Sayed	2008	Egypt	OPV	Randomized trial
23	Sutter	2010	India	OPV	Randomized trial
24	John, I	2011	India	OPV	Randomized trial
25	John, II	2011	India	OPV	Randomized trial
26	Waggie	2011	South Africa	OPV	Randomized trial

Table 2

Prevalence of seroconversion following immunization schedules that include a single newborn dose of OP V with an umbilical blood draw performed at birth

Primary author Name (year)	Study country	No. given newborn dose	Comparison of Newborn Dose with other Schedule?	Poliovirus Type 1 (% Sero-converted)	Poliovirus Type 2	Poliovirus Type 3	Time of First Estimation of Seroconversion (weeks of life)
Trivalent Vaccine							
Waggie (2011)	South Africa	184	Yes	39	63	21	4
Sutter (2010)	India	168	No	15	25	4	4
John (2011) I	India	176	No	10	14	2	4
John (2011) II	India	160	No	11	17	1	4
El-Sayed (2008)	Egypt	190	No	32	62	17	4
Bhaskaram (1997)	India	51	Yes	6	2	2	6
Jain (1997)	India	25	Yes	14	18	7	6
Khare (1993)	India	52	Yes	42	39	35	6
Sutter (1993)	Oman	53	No	42	70	23	12
Weekx (1992)	Brazil	27	Yes	22	59	9	8
De-Xiang (1986)	China	200	Yes	41	43	32	4
Furner [*] (1969)	New Zealand	22	No	27	36	45	12
Krugman (1960)	USA	115	Yes	7	43	12	12
Prem (1959)	USA	23	Yes	30	4	43	4-15
Bivalent Vaccine (1+3)							
Sutter (2010)	India	148	No	20		7	4
Monovalent Vaccine							
Waggie (2011) Type 1 GSK	South Africa	192	Yes	73			4
Waggie (2011) Type 1 Panacea	South Africa	191	Yes	76			4
Waggie (2011) Type 3	South Africa	195	Yes			58	4
Sutter (2010) Type 1	India	168	No	20			4
Sutter (2010) Type 2	India	170	No		4		4

Primary author Name (year)	Study country	No. given newborn dose	Comparison of Newborn Dose with other Schedule?	Poliovirus Type 1 (% Sero-converted)	Poliovirus Type 2	Poliovirus Type 3	Time of First Seroconversion (weeks of life)
Sutter (2010) Type 3	India	165	No			12	4
John (2011) I, PT Biofarma	India	182	No	10			4
John (2011) I, Imported Sanofi-Pasteur	India	173	No	16			4
John (2011) II, PT Biofarma	India	146	No	15			4
John (2011) II, Sanofi-Pasteur higher potency	India	144	No	10			4
John (2011) II, Sanofi-Pasteur in France	India	133	No	18			4
El-Sayed (2008)	Egypt	231	No	55			4
Banfi (1974)	Chile	110	No	49			12
Ordenez (1966)	Mexico	115	No	35			12
Sabin (1963)A	USA	21	Yes	14			12
Sabin (1963)B	USA	122	No	32			12
Pagano (1962)	USA	64	No	59			NP
Krugman (1960)	USA	109	Yes	31			12

* Extrapolated from provided data

† Average

Key to Abbreviations: N/A=Not available, NP=Not provided

‡ Recalculated, see reference Halsey & Galzka 1985 Bull WHO

Table 3

Prevalence of Seroconversion from Immunization Schedules including a single newborn dose of TOPV in Published Articles without an Umbilical Blood Draw performed at birth (1959-2011)

Primary author Name (year)	Study Country	No. given newborn dose	comparison of Newborn Dose with other Schedule?	Poliovirus Type 1 (% Sero-converted)	Poliovirus Type 2	Poliovirus Type 3	Time of First Estimation of Seroconversion (wks of life)
Trivalent Vaccine							
Parent du Chatelet (2003)	Pakistan	302	Yes	86	94	70	6
WHO Collaborative (1995)	Brazil	195	No	28	51	14	6
Osei-Kwasi (1995)	Ghana	200	Yes	84	91	76	6
Campillo-Sainz (1962)	Mexico	49	Yes	90	61	90	16

Table 4

Prevalence of Seroconversion from Immunization Schedules including Newborn Dose of IPV in Published Articles with an Umbilical Blood Draw at Birth (1959-2011)

Primary author Name (year)	Study Country	No. given newborn dose	Comparison of Newborn Dose with other Schedule?	Poliovirus Type 1 (% Sero-converted)	Poliovirus Type 2	Poliovirus Type 3	Time of First Estimation of Seroconversion (wks of life)
Swartz (1989), A	Israel	48	No	64	81	86	14
Swartz (1989), B	Israel	50	No	79	77	75	14
Swartz (1989), C	Israel	49	No	67	76	67	14
Linder (1995)*	Israel	39	Yes	8	15	28	4
Jain (1997)	India	50	Yes	24	32	15	6
Linder (2000)*	Israel	50	Yes	100	100	94	4

Table 4 Legend: A= 160-32-128, B=80-16-64, C=40-8-32,

* =includes infants with a gestational age of 30-35 weeks