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Monovalent type 1 oral poliovirus vaccine among infants in India: Report of two randomized double-blind controlled clinical trials☆

T. Jacob John[a], Hemant Jain[b], Kanithi Ravishankar[c], A. Amaresh[c], Harish Verma[d], Jagadish Deshpande[e], Mark A. Pallansch[f], Ajit Pal Singh[g], Meghana Sreevatsava[h], Anthony Burton[h], Pradeep Malankar[h], Arani Chatterjee[g], Roland W. Sutter[h,*]

[a] *Vellore,[1] India*
[b] *MGM Medical College, Indore, India*
[c] *Niloufer Hospital, Hyderabad, India*
[d] *National Polio Surveillance Project, World Health Organization, New Delhi, India*
[e] *Enterovirus Research Centre, Mumbai, India*
[f] *Centers for Disease Control and Prevention, Atlanta, USA*
[g] *Panacea Biotec Ltd., New Delhi, India*
[h] *World Health Organization, Geneva, Switzerland*

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ABSTRACT

Background: To provide the polio eradication initiative with more immunogenic oral poliovirus vaccines (OPVs), we evaluated newly developed monovalent type 1 OPV (mOPV1) among infants in India.
Methods: Two double-blind randomized controlled clinical trials compared two mOPV1s (mOPV1 A and mOPV1 B) versus trivalent OPV (tOPV X) given at birth (trial I), or assessed two products of higher-potency mOPV1 (mOPV1 C and mOPV1 D) versus regular-potency mOPV1 (mOPV1 B) or tOPV Y given at birth and at 30 days (trial II).
Results: In trial I, 597 newborns were enrolled, 66 withdrawn or excluded, leaving 531 (88.9%) subjects for analysis. Seroconversion to poliovirus type 1 was 10.4% for mOPV1 A, 15.6% for mOPV1 B and 10.2% for tOPV X. In trial II, 718 newborns were enrolled, 135 withdrawn or excluded, leaving 583 (81.2%) subjects for analysis. Seroconversion to poliovirus type 1 following a birth dose was 15.1%, 19.7%, 18.0% and 10.6%, following the 30-day dose 87.1%, 89.2%, 84.4%, or 55.9%, and cumulative for both doses 90.4%, 90.3%, 89.5% and 61.9% for mOPV1s B, C, and D and tOPV Y, respectively.
Conclusions: In both studies, seronconversion rates were unexpectedly low to poliovirus type 1 after mOPV1 or tOPV given at birth but high for all formulations of mOPV1 given at age 30 days. The cause for low immunogenicity of OPV at birth in India is not known.

1. Introduction

The Global Polio Eradication Initiative (GPEI) of the World Health Organization (WHO) has made enormous strides towards the goal of worldwide polio eradication, following the resolution calling for it by the World Health Assembly in 1988 [1]. With the use of trivalent oral poliovirus vaccine (tOPV) in routine immunization and additional campaigns of supplementary immunizations, the number of countries endemic with wild poliovirus (WPV) dropped from over 125 in 1988 to 4 (India, Nigeria, Pakistan, and Afghanistan) in 2006 and thereafter [2]. In 1999, WPV type 2 was eradicated globally [2]. Interrupting the remaining WPV transmission in these countries in Asia and Africa has proved to be extremely difficult due to a variety of environmental and programmatic challenges, including low immunogenic efficacy of tOPV for poliovirus types 1 and 3, particularly in India [3,4].

The problem of lower efficacy of tOPV in developing, tropical countries compared to industrialized countries has been known for decades [5,6], but it was overcome in most countries and also in most states in India by repetitive supplementary immunization campaigns. The exact reason(s) for this anomaly is not

☆ Voluntary and informed consent for participation of children in this study was obtained from parents or guardians in accordance with ethical principles, including the Declaration of Helsinki, and the additional requirements of local and national authorities. The study was approved by the Drug Controller General (India), the institutional review boards of MGM Medical College and Niloufer Hospital, the Institutional Review Board of the Centers for Disease Control and Prevention, and the Ethical Review Committee of the World Health Organization.

* Corresponding author at: Polio Eradication Department, World Health Organization, 20, Avenue Appia, CH-1211 Geneva 27, Switzerland. Tel.: +41 22 791 4682; fax: +41 22 791 1571.
E-mail address: sutterr@who.int (R.W. Sutter).

[1] Formerly with Christian Medical College.

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known, but most probably environmental and not genetic factors are involved [5,6]. Children in higher socio-economic families in India may have similar responses to tOPV as have children from industrialized countries [7]. In low income countries the lack of sewage and drainage systems, overcrowded conditions, micronutrient deficiencies, altered intestinal microbiota, and recurrent enteric infections with pathogenic bacteria and viruses may all be contributory. However, in northern India the problem is worse and children who had received 10 doses of tOPV were found to participate in continued wild poliovirus types 1 and 3 transmission and even to develop paralytic disease [3,4].

In order to provide the GPEI with a more immunogenic vaccine for use in these problem areas, in 2004 the Advisory Committee for Polio Eradication (ACPE) endorsed the development of monovalent type 1 oral poliovirus vaccine (mOPV1) initiated by WHO [8]. Following this mandate mOPV1 vaccine was developed and licensed by a French pharmaceutical company in <6 months. Moreover, in 2004 the India Expert Advisory Group (IEAG) on polio eradication recommended the licensing of mOPV1 for use in supplementary immunization in WPV-endemic and surrounding states/districts, particularly in northern India [9]. Consequently an Indian manufacturer obtained license for the production of mOPV1 from imported Sabin virus bulks. The IEAG had also requested an immunogenicity trial comparing mOPV1 with tOPV [10].

An exploratory trial in India had shown 2–3 times higher seroconversion rates to mOPV1 and mOPV3 than to tOPV, all containing high potency (approximately 10-times the minimal potency requirements) [11]. A review of mOPV trials showed significantly higher rates of seroconversion after mOPV1 than after tOPV [12]. In 2005, an epidemiologic study in northern India found 3 times higher protective efficacy in children vaccinated with mOPV1 than with tOPV [3,4].

To assess the immunogenicity of mOPV1 in India, we conducted a randomized controlled clinical trial. The results of this trial I demonstrated low seroconversion following a birth dose, but high rate of infection by Sabin strain type 1 used as challenge dose at day 30. After reviewing possible risk factors for the low immunogenicity, and noting the later high vaccine virus take rate, we decided to initiate a second trial (trial II) with mOPV1 administered at birth and a second dose at 30 days. We combined the findings of both trials in this report to allow full interpretation of all results.

2. Subjects and methods

The field work for both studies was carried out at two institutions (M.G.M. Medical College, Indore, Madhya Pradesh State and Niloufer Hospital, Hyderabad, Andhra Pradesh State) during December 2005 to March 2006 (trial I) and July 2007 to January 2008 (trial II). In each study, we calculated a sample size of 139 per study arm to demonstrate significantly higher responses of $\geq$|20%| to mOPV1 compared with tOPV (alpha = 0.05, beta = 0.1 [two-tailed test]). We assumed a tOPV seroconversion rate of 40% to derive at the most conservative sample size. In the first trial, we inflated the sample size to 200 per arm, and adjusted it downwards in the second trial to 180, based on actual attrition in trial I.

In both trials, expectant mothers were approached during antenatal visits or during admission for delivery, informed about the study, invited to participate, and if agreeable, to sign the informed consent form to enroll the newborn in the study. Inclusion criteria were healthy newborns with a birth weight $\geq$2.5 kg, Apgar scores $\geq$9 at 5 min, residence <30 km from the study site, and not planning to travel during the study period. Newborns were excluded if they required hospitalization or were at risk of immunodeficiency, such as a family member with a history of immunodeficiency.

In trial I, after delivery, cord blood was collected and infants were randomized to receive either of two products of mOPV1 (mOPV1 A and mOPV1 B) or tOPV X. At age 30 days, blood and stool samples were collected and a challenge dose of mOPV1 (identical to the one given earlier) was administered to all infants. A second stool sample was collected 7 days after the mOPV1 challenge dose.

In trial II, after delivery, cord blood was collected and infants were randomized to receive either tOPV Y or one of three mOPV1 formulations (B, C and D). At 30 days, blood samples were collected and the subjects received a second dose of the identical vaccine as administered at birth. A third blood sample was collected at 60 days.

For trial I, all study vaccines were produced by Panacea Biotec Ltd. (New Delhi, India) using imported bulks from 3 sources. The bulk source for mOPV1 A was from PT Bio Farma (BF), Bandung, Indonesia and for mOPV1 B was Sanofi Pasteur Serum & Vaccines (SP), Lyon, France. Each mOPV1 (A and B) was formulated to contain at least 10^6 median cell culture infectious dose ($CCID_{50}$) Sabin poliovirus strain type 1 per dose. The tOPV bulk was from Chiron (now Novartis), Siena, Italy; tOPV X was formulated to contain at least 10^6, 10^5, and $10^{5.8}$ $CCID_{50}$ of Sabin poliovirus types 1, 2, and 3, respectively, per dose.

For trial II, three vaccines were produced by Panacea Biotec using imported bulks from Sanofi Pasteur Serum & Vaccines for mOPV1 (B and C, see below) and from PT Bio Farma for tOPV Y. The mOPV1 D was produced by Sanofi Pasteur Serum & Vaccines and had been used in a previous trial in Egypt [13]. The regular-potency mOPV1 (mOPV1 B) was formulated to contain at least 10^6 $CCID_{50}$ Sabin poliovirus strain type 1 per dose. The higher-potency mOPV1s (C and D) were formulated to contain at least $10^{6.7}$ $CCID_{50}$ of poliovirus type 1. The tOPV Y was formulated to contain at least 10^6, 10^5, and $10^{5.8}$ $CCID_{50}$ of Sabin poliovirus types 1, 2, and 3, respectively, per dose. mOPV1 B was identical with regards to bulk source and potency in both trials.

All vaccines were shipped in 10-dose vials on dry ice from the manufacturer to the study sites where they were stored in deep freezer (−20 °C). Each vaccine vial label contained a serial number that coded for the study arm assignment. However, because the vial shape used by Sanofi Pasteur was different from the vial shape of the three vaccines produced by Panacea Biotec, the mOPV1 D vaccine could not be blinded. One dose was taken for vaccination from the vial and the rest of vaccine in the vial was stored frozen and returned to the manufacturer after the study was completed.

In trial I, subjects were randomized to receive mOPV1 A, mOPV1 B, or tOPV X. The investigators were blinded to the identity of vaccines. The vaccines were administered within 48 h after birth and the exact time was recorded. At 30 days of age (with allowed delay of no more than 2 days) all subjects received a dose of mOPV1, by study number, so that every infant got the same vaccine as was given at birth. Infants who got tOPV X at birth got mOPV1 B.

In trial II, subjects were randomized to receive mOPV1 B, C, D or tOPV Y. Again, the investigators were blinded to the identity of vaccines (except mOPV1 D). The vaccines were administered as soon as possible after birth and the exact time was recorded. At 30 days of age (with allowed delay of no more than 2 days) all subjects received a second dose of the identical product they had received at birth, by study numbers, so that each infant received the same vaccine as was given at birth (the mOPV1 arms received the identical mOPV1 vaccine and the tOPV Y arm received tOPV Y).

In both trials, the pre-release potency of the vaccines was assessed by the manufacturer (Panacea Biotec) and by the National Control Laboratory at the Central Research Institute (Kasauli, India) and results from both laboratories are given below. In trial I, the potency data from the manufacturer were in line with expected potency values; mOPV1 A ($10^{6.18}$ $CCID_{50}$ and $10^{6.16}$ $CCID_{50}$ of