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Needle adapters for intradermal administration of fractional dose of inactivated poliovirus vaccine: Evaluation of immunogenicity and programmatic feasibility in Pakistan

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ABSTRACT

Administration of 1/5th dose of Inactivated poliovirus vaccine intradermally (fIPV) provides similar immune response as full-dose intramuscular IPV, however, fIPV administration with BCG needle and syringe (BCG NS) is technically difficult. We compared immune response after one fIPV dose administered with BCG NS to administration with intradermal devices, referred to as Device A and B; and assessed feasibility of conducting a door-to-door vaccination campaign with fIPV. In Phase I, 452 children 6–12 months old from Karachi were randomized to receive one fIPV dose either with BCG NS, Device A or Device B in a health facility. Immune response was defined as seroconversion or fourfold rise in polio neutralizing antibody titer 28 days after fIPV among children whose baseline titer $\leq$362. In Phase II, fIPV was administered during one-day door-to-door campaign to assess programmatic feasibility by evaluating vaccinators' experience. For all three poliovirus (PV) serotypes, the immune response after BCG NS and Device A was similar, however it was lower with Device B (34/44 (77%), 31/45 (69%), 16/30 (53%) respectively for PV1; 53/78 (68%), 61/83 (74%), 42/80 (53%) for PV2; and; 58/76 (76%), 56/80 (70%), 43/77 (56%) for PV3; $p < 0.05$ for all three serotypes). Vaccinators reported problems filling Device B in both Phases; no other operational challenges were reported during Phase II. Use of fIPV offers a dose-saving alternative to full-dose IPV.

1. Background

The Global Polio Eradication Initiative (GPEI) is getting ever closer to reaching its goal, with only 34 cases of polio caused by wild poliovirus (WPV) reported from 3 endemic countries (Afghanistan, Pakistan and Nigeria) as of December 20, 2016 [1]. Complete poliovirus eradication, however, requires the disappearance of not only WPVs but of all polioviruses from human populations: including those resulting from use of oral poliovirus vaccine (OPV). The Polio Eradication & Endgame Strategic Plan 2013–2018 provides a framework for interruption of WPV transmission in remaining endemic foci and lays out plans for the new polio endgame, which includes the withdrawal of Sabin strains contained in OPV vaccine, starting with type 2, and the introduction of inactivated poliovirus vaccine (IPV), for risk mitigation purposes [2]. The last case of poliomyelitis caused by type 2 wild poliovirus was reported in 1999 and this serotype is now considered to be eradicated [3].

The switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) without type 2 poliovirus has been conducted in a globally synchronized manner in April 2016. As of December 2016, there were no countries still using type 2 containing OPV, except for outbreak control: in case of outbreaks of type 2 circulating vaccine derived poliovirus (cVDPV2) or wild poliovirus in the post switch era, WHO maintains a stock of monovalent type 2 OPV (mOPV2) reserved for outbreak response [4].

At least one dose of inactivated poliovirus vaccine (IPV) has been planned to be introduced globally in routine immunization of all countries in 2015 and 2016 to provide immunity against type 2 polioviruses. In addition to IPV use in routine immunization, IPV, together with mOPV2, are tools to be used in campaigns as a response to cVDPV 2 outbreaks [5]. However, as of June 2016, there

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was acute IPV shortage that affected 43 countries and caused either delayed IPV introduction or stock-outs in countries that had already introduced IPV [6,7]. This global shortage is likely to last at least until end 2018.

Intradermal administration of 1/5th of full IPV dose (0.1 mL instead of 0.5 mL), referred to as fractional IPV (fIPV) has demonstrated good safety and immunogenicity [8–15]; and can be considered as an alternative to full-dose, intramuscular IPV in routine immunizations, and in outbreak response IPV campaigns [16].

Use of full-dose IPV in campaigns (combined with OPV) has been successfully demonstrated in Kenya, Nigeria and in high risk areas of Pakistan and Afghanistan to accelerate eradication or to control polio outbreaks [17]. The fIPV intradermal administration in campaigns is however, technically difficult with BCG needles and syringes (considered a "classical" intradermal administration performed by insertion of a 26–27 gauge needle nearly parallel to and solely into the skin to raise a visible bleb), requires additional training, and may result in poor intradermal injection. Therefore, new intradermal administration methods are being explored. Needle-free jet injectors, various needle adaptors, or intradermal syringes have been developed to ease intradermal administration and improve injection quality [7].

This study was conducted in two phases; in Phase I, we assessed the usability and immune response following fIPV administration with two novel ID adaptors (Device A: Intradermal Adapter by HELM/West Pharmaceutical Services Inc., Exton, USA and Device B: Star Intradermal Syringe by Star Syringe Ltd, East Sussex, UK) and compared this response with the one achieved with traditional BCG syringe which served as a reference. In Phase II we evaluated the feasibility of conducting a door-to-door campaign with intradermal fIPV administered using BCG NS and the two novel devices.

2. Methods

The study was conducted in four low-income areas in and around Karachi (4 peri-urban, contiguous coastal villages: Rehri Goth, Bhains Colony, Ali Akber Shah and Ibrahim Hydri) where the Aga Khan University's Department of Paediatrics and Child Health has well-established Demographic Surveillance System (DSS) which captures population size, pregnancies and births. The population of the study area according to the last census from 2015 is 294,171. Each area has a Primary Health Center (PHC) operated by the Department of Paediatrics and Child Health research program, which also provides Expanded Programme on Immunizations (EPI) services.

Phase I was an un-blinded randomized controlled trial. Children aged 6–12 months living in the target area were enrolled after their guardians provided informed consent. Exclusion criteria were acute illness at the time of enrolment, requiring emergent medical care/hospitalization, refusal of blood testing, contraindication for ID injection or suspicion of immunodeficiency disorder.

The selection of participants was performed using simple random sampling from lists generated by DSS which contained lists of households with age eligible children. Teams of community health workers (CHWs) visited selected households to confirm eligibility and administer informed consent.

Vaccination history with OPV received through routine immunization was assessed from vaccination cards, when cards were not available by parental recall. OPV doses received through SIAs were estimated by the number of SIA rounds that were conducted in the study area during the life of each child. The majority of the SIA rounds in this area were conducted using bivalent OPV vaccine.

All enrolled children received one dose of fIPV (0.1 mL) between November and December 2015; prior to fIPV administration they were randomized into three study arms: in arm A they received fIPV with Device A; in arm B they received fIPV with Device B; and in arm C they received fIPV with regular BCG needle and syringe (BCG NS). The bleb diameter was measured by marking the outer rims of the bleb with a pen and recording the distance between the marks in millimeters with a ruler. Bleb diameter is often interpreted as the extent of intradermal localization of the antigen. Vaccine loss as indicated by liquid on the surface of the skin was measured by applying filter paper to collect liquid on the skin surface immediately after fIPV injection. The wet spot on the filter paper was then circled and the circle diameter compared to a reference template graded 0–5. Vaccine loss was graded using the following: grades 0, 1, and 2 indicated a $\leq$10% of vaccine loss, or $\leq$10 μl of a 0.1 ml dose volume. Wetness grades 3, 4, and 5 indicated >10–$\leq$20%, >20–$\leq$40%, and >40% vaccine loss, respectively [7]. Successful intradermal injection was defined as injection resulting in a bleb with diameter $\geq$5 mm and wetness $\leq$10%.

Only one attempt for intradermal injection was allowed, even if deemed unsuccessful by the vaccinator (i.e. no bleb or high volume of vaccine spilled).

Device A is a novel injection guide designed for use with 1 mL staked needle disposable syringes. The ID Adapter can help make ID injection easier and more consistent by guiding the angle and limiting the depth of needle insertion [18]. Device B enables simple consistent accurate intradermal (ID) injection without requiring the difficult Mantoux technique, while at the same time facilitating access to all vial sizes and ampoules without any additional devices or manipulation. The device also meets or exceeds WHO global public health standards for auto-disable technology and US standards for needle stick protection [19].

Peripheral blood (2 mL) was collected at the time of enrollment (prior to the study vaccine administration) and 28 days after immunization using venipuncture. Blood specimens collected at the sites were allowed to clot, centrifuged to separate serum, and transported to the Infectious Disease Research Laboratory (IDRL) at the Aga Khan University where they were stored at −20 °C until shipment to the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA, where the anonymized blinded sera were tested for presence of poliovirus neutralizing antibodies using standard neutralization assays [20–23].

Seropositivity was defined as reciprocal titers of poliovirus neutralizing antibodies $\geq$8; seroconversion was defined as the change from seronegative to seropositive (from reciprocal titer of <8–$\geq$8); and boosting was defined as $\geq$4-fold increase in titers. In this study, "immune response" refers to either boosting or seroconversion. The analysis of immune response was restricted to infants with a baseline serological titer of $\leq$362 to ensure that a 4-fold boosting response could be achieved since the highest tested titer was $\geq$1:1448.

Subjective assessment of each device was performed by each vaccinator after completion of Phase I; vaccinators were asked to rank and compare the methods of intradermal vaccination and to assess each component of the injection process (process of filling with vaccine, delivery and safety) using a self-administered questionnaire.

Adverse events following vaccination were identified by site investigators and reviewed by the principal investigator. Children were observed for 30 min following the administration of the vaccine for immediate adverse events; parents were instructed to immediately report back to the health centers if adverse events occurred. Serious adverse events were reported for review by the Data and Safety Monitoring Board and by the Ethical Review Committees of the Aga Khan University and the World Health Organization. Druing observations, the study staff were aware of arm allocation of the observed children.

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