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A randomized, observer-blinded, equivalence trial comparing two variations of Euvichol®, a bivalent killed whole-cell oral cholera vaccine, in healthy adults and children in the Philippines ☆

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ABSTRACT

Background: To contribute to the global demand for oral cholera vaccine (OCV), the production of Euvichol® was scaled up with elimination of thimerosal. To demonstrate the equivalence of the variations, a study was carried out in the Philippines.

Methods: Healthy male and female adults and children in Manila were randomized to receive two doses of Euvichol® two weeks apart from either the 100L (Comparator) or the 600L (Test) variation. Primary and secondary immunogenicity endpoints were respectively geometric mean titer (GMT) of vibriocidal antibodies (two weeks post second dose) and seroconversion rate (two weeks after each dose) against O1 Inaba, Ogawa, and O139 serogroups. The GMT of vibriocidal antibodies against O1 Inaba, Ogawa, and O139 two weeks post first dose was also measured. To show the equivalence of two variations of Euvichol®, the ratio of GMT and the difference of seroconversion rate between Test and Comparator vaccines were tested with equivalence margin of [0.5, 2.0] for GMT ratio and of 15% for seroconversion rate, respectively. Safety assessment included solicited reactogenicity within 6 days after each dose and unsolicited and serious adverse events.

Results: A total of 442 participants were enrolled. For the overall population, equivalence between Test and Comparator was demonstrated for vibriocidal antibody response against O1 Inaba and Ogawa serotypes and O139 serogroup in both modified intention-to-treat (mITT) and per protocol analysis, since the 95% confidence intervals (CI) of GMT to any serotypes were within the lower and upper boundary [0.5, 2.0]. Seroconversion rates after two doses also showed equivalence for O1 Inaba, Ogawa, and O139. The vaccine was safe and well tolerated, similarly between the two groups.

Abbreviations: ADR, Adverse Drug Reaction; AE, Adverse Event; CI, Confidence Interval; CV, Coefficient of Variation; GAVI, Gavi, The Vaccine Alliance; GMR, Geometric Mean Ratio; GMT, Geometric Mean Titer; GTFCC, Global Task Force for Cholera Control; IRB, Institutional Review Board; IVI, International Vaccine Institute; KMFDS, Korea Ministry of Food and Drug Safety; LEU, Lipopolysaccharide ELISA Unit; mITT, modified Intention-To-Treat; NCH, National Children's Hospital; OCV, Oral Cholera Vaccine; PP, Per Protocol; PT, Preferred Term; RITM, Research Institute for Tropical Medicine; SAE, Serious Adverse Events; SOC, System Organ Class; UPT, Urine Pregnancy Test; WHA, World Health Assembly; WHO, World Health Organization.

☆ All authors attest they meet the ICMJE criteria for authorship.

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Conclusion: The study results support the equivalence of the 600L Euvichol® to the 100L formulation in healthy children and adults. The 600L Euvichol® is safe and immunogenic in adults and children.
ClinicalTrials.gov registration number: NCT02502331.

1. Introduction

With estimated 1.3–4.0 million cholera cases and 21,000–143,000 annual deaths in endemic countries [1], the World Health Organization (WHO) recommends oral cholera vaccine (OCV) use for control of both endemic and epidemic cholera [2,3]. Following the 2011 World Health Assembly [4], an OCV stockpile has been established in 2013 for emergency responses [5]. To be utilized through the stockpile, vaccines must be WHO-prequalified (WHO PQ) [4]. Three WHO PQ OCVs are currently available: Dukoral®, Shanchol™, and Euvichol®. Shanchol™ and Euvichol® were developed following the same technology transfer from the International Vaccine Institute (IVI) initially to Shantha Biotechnics Ltd. (India) and subsequently to EuBiologics Co., Ltd. (Republic of Korea). The IVI's formulated OCV is a whole-cell killed liquid formulation containing O1 (Inaba and Ogawa) and O139 serogroups of *Vibrio cholerae*, inactivated by heat or formalin. In Shanchol™, thimerosal was added as a preservative. Euvichol® was originally developed in 100L formulation in order to be equivalent to Shanchol™ in terms of quality, safety and immunogenicity, thus containing the same active ingredients as well as thimerosal as preservative. Both Shanchol™ and Euvichol® are presented as single-dose vials, with two doses being administered with a 2-week interval to all persons 1 year of age and older [6,7]. Euvichol® obtained WHO PQ in December 2015 following a Phase III trial which showed non-inferiority to Shanchol™ [8,9]. To meet the increasing OCV global demand [1,10], as recently illustrated by the massive outbreak in Yemen [11], the manufacturing process of Euvichol® was scaled-up to 600L fermenter. Thimerosal was no longer added since not required for a single-dose vaccine [12]. The Korea Ministry of Food and Drug Safety (KMFDS) as well as WHO evaluated the process changes as minor, and thimerosal-free Euvichol® (600L) variation received WHO PQ in September 2016.

The objectives of this study were to assess safety and immunogenicity and to demonstrate the equivalence of the already WHO PQ formulation (100L fermenter, with thimerosal) to the scaled-up formulation (600L fermenter, thimerosal-free).

This study was conducted in the Philippines, where the incidence rate of cholera was estimated at 1/10,000 with 2430 annual cases [1].

2. Materials and methods

The clinical study (ClinicalTrials.gov NCT02502331) was approved by the Philippines Food and Drug Administration and by the Institutional Review Boards (IRB) of the National Children's Hospital (NCH), the Research Institute for Tropical Medicine (RITM), and of IVI. The study was conducted in accordance with the ICH E8 Guideline for Good Clinical Practice and the ethical principles of the Declaration of Helsinki.

2.1. Study design, vaccines and participants

This was a randomized, observer-blinded, equivalence, multicenter study to assess and compare the safety and immunogenicity of the scaled-up formulation of Euvichol® (Test vaccine: 600L fermenter and thimerosal-free) with the originally licensed formulation (Comparator vaccine: 100L fermenter with thimerosal) [9].

Participants were healthy Filipino adults and children, recruited at the NCH and the RITM clinical sites in Manila. Written informed consent was obtained from eligible adult participants and from the parents or legal guardians of participants aged 1–17 years. Assent was also obtained from 7 to 17 years old children according to the 2011 Philippines National Ethics Guidelines.

Participants were stratified into adults (18–40 years old) and children (1–17 years old) cohorts and were enrolled in May-June 2016. Subjects with gastrointestinal symptoms occurring up to one week before study initiation, history of cholera or cholera vaccination as well as pregnant or lactating women were excluded. A urine pregnancy test (UPT) by urine HCG was performed at screening and, subsequently, at each of the three scheduled visits, in all women who reached the age of menarche, excluding those who had hysterectomy or bilateral ovariectomy. Women with bilateral tubal ligation underwent a UPT at each visit.

Eligible participants were randomized to one of two (Test or Comparator) vaccine groups, so that the same number of participants was randomly allocated to each of the two vaccine groups. The formulation of Euvichol® was reported previously [9]. Both vaccine variations were presented in single dose glass vials and administered orally by oral syringe in two doses (1.5 mL each) two weeks apart. Vaccines were stored at +2–8 °C. Participants were instructed not to eat one hour before and after dosing while water intake was allowed.

Screening and enrollment with randomization took place at Day 0, when enrolled participants received the first dose. The second dose was administered after two weeks (Visit 2, Day 14) with a window period of +/−3 days. Participants were followed up for two weeks after the second dose (Visit 3, Day 28 +/−3 days), observed for 30 min following vaccination, and given diary cards at Visits 1 and 2, in order to record any solicited and unsolicited adverse events (AEs) occurring up to 6 days following each vaccination. Adverse events, serious adverse events (SAEs) and concomitant medications were monitored until Day 28, end of the study. On Day 7 and Day 21 (+3 days if necessary), adult participants and parents or legal guardian of children participants were interviewed through phone call or home visit by study staff for AE monitoring. At the end of study, women of childbearing age were followed up for 3 months through monthly phone call or home visit to assess if any pregnancy had occurred.

2.2. Sample size, randomization and blinding

Adults (18–40 years) and children (1–17 years) participating were recruited in 1:1 ratio at the two sites. The 1–17 years age cohort was further stratified into 1–5 years (82 subjects) and 6–17 years (162 subjects) age groups to achieve balance and proportionate representation among vaccine groups (not statistically powered), so that the number of participants within each of the two children sub-cohorts is very similar in Test vs. Comparator groups. The sample size was calculated within each age strata of adults and children separately (244 children and 198 adults, respectively) to provide 90% power to show equivalence of the serotype-specific geometric mean titers (GMT) of vibriocidal

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