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A Japanese study to assess immunogenicity and safety of a typhoid Vi polysaccharide vaccine☆

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ABSTRACT

Background: Although typhoid fever is rare in Japan, imported cases have been reported occasionally in travelers returning from endemic areas. To achieve licensing of a typhoid Vi polysaccharide vaccine (Typhim Vi®) and make it widely available in Japan, this study was conducted at the request of the Japanese Ministry of Health Labor and Welfare to assess the immunogenicity and safety of this vaccine when given as a single dose (the recommended schedule of administration) in a Japanese population.
Methods: In this multi-center, open-label, non-comparative, intervention study performed in Japan, 200 healthy volunteers (188 adults [≥18 years of age], 7 adolescents [12–17 years of age] and 5 children [2–11 years of age]) were administered Typhim Vi®. Immunogenicity was assessed 28 days after vaccinations using an ELISA method of anti-Vi antibody detection. A 4-fold increase in anti-Vi titer was considered as the threshold for seroconversion for anti-Vi antibodies. Safety was assessed up to 28 days following vaccination.
Results: Overall, 92.0% (95% confidence interval [CI]: 87.3–95.4%) of participants achieved seroconversion 28 days after a single dose of typhoid Vi polysaccharide vaccine. GMTs of Vi antibody titers increased from 6.6 (95% CI: 5.8–7.4) prior to vaccination to 157.3 (95% CI: 135.1–183.2) on Day 28 after vaccination. The geometric mean of individual anti-Vi antibody titer ratios (Day 28/Day 0) was 23.9 (95% CI: 20.3–28.3). There were no immediate adverse events and no adverse events led to the discontinuation of participants from the study. Across all age groups, pain and myalgia were the most frequently reported injection site and systemic reactions, respectively. Most of these reactions were mild in intensity and resolved within 7 days.
Conclusions: A single dose of typhoid Vi polysaccharide vaccine, Typhim Vi®, demonstrated good safety and immunogenicity profile in a Japanese population.

1. Introduction

Typhoid fever remains a global public health concern and a major cause of morbidity in developing countries in particular [1]. It is a systemic illness caused by *Salmonella enterica* serotype *Typhi* [1]. The disease is spread via the fecal–oral route as a result of inadequate sanitation, poor personal and food-related hygiene [1].

Typhoid is rare in countries with high sanitation standards and in most developed countries the disease occurs most often among international travelers to and from endemic areas [2,3]. South Central/Eastern Asia has the highest incidence of the disease (>100 per 100,000 cases annually), with the rest of Asia, Latin America, the Caribbean and Oceania (excluding Australia and New Zealand) considered to have a medium incidence of the disease (10–100 per 100,000 annually) [2]. Developed countries have much lower incidences of typhoid fever (<10 per 100,000 annually) [2]. Crude and adjusted global estimates for typhoid fever range from 11 to 21 million cases annually [4,5], with the number of related deaths

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estimated to be around 200,000 [4,6]. Typhoid fever in Japan is rare with <100 cases reported in a typical year [7]. However, >18 million Japanese travel overseas annually and the main destinations are in Asia (i.e. India, Indonesia and China) [8]. Most cases of typhoid fever in Japan are imported cases in travelers returning from endemic areas such as India, Indonesia, Nepal and the Philippines [7].

Currently typhoid fever can be effectively treated with antibiotic drugs, but the increasing rates of antibiotic resistance suggest that it is important to consider a more preventative medicine approach. Such an approach might entail the targeted vaccination of high-risk populations, combined with the longer-term solutions of provision of safe water and improved sanitation [9].

A number of typhoid Vi polysaccharide vaccines that provide protection against the disease are available and have been demonstrated in clinical trials to have good safety and immunogenicity profiles [10]. For travelers to South Asia and other endemic countries, the World Health Organization (WHO) and other national health bodies recommend vaccination against typhoid [11–13]. At present there are no typhoid vaccines licensed in Japan and as such the rate of vaccination among Japanese travelers is generally low [14]. As a result Japanese travelers may be more at risk of acquiring enteric fever while traveling through endemic countries [15]. This situation leads some physicians to personally import the typhoid vaccine so that they can vaccinate individuals prior to their travels.

This clinical study was conducted to assess the immunogenicity and safety of a single dose of a typhoid vaccine (Typhim Vi®), so as to achieve registration of this vaccine in Japan and make it widely available. Typhim Vi®, a typhoid Vi polysaccharide vaccine, was selected because at the time the study was initiated, it was the only typhoid vaccine with a single dose schedule (for subjects ≥2 years of age) [12] and, it was and still is (as of September 2015), the only typhoid vaccine prequalified by WHO [16,17]. WHO prequalification of vaccines is a system that evaluates the safety, efficacy and manufacture of vaccines to ensure that vaccines meet the requirements for global supply through the United Nations [18].

2. Methods

2.1. Study design and participants

This was a multi-center, open-label, non-comparative, intervention study performed at four centers in Japan between 26 May and 28 Sep 2012 (https://www.clinicaltrials.gov/; [NCT01608815]). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on the Harmonization-Good Clinical Practice. The study was approved by each study site's institutional review board, and all participants or their parents/guardians provided written informed consent/assent before entering the study.

Eligible participants were healthy volunteers aged 2 years or older. Female participants of childbearing potential, had to use an effective method of contraception starting at least 4 weeks before vaccination until at least 4 weeks after vaccination.

Exclusion criteria: pregnancy (known pregnancy or a positive serum and/or urine pregnancy test) or breast feeding; history of typhoid fever or *Salmonella typhi* infection; previous vaccination against *S. typhi*; known or suspected congenital or acquired immunodeficiency or receipt of immunosuppressive therapy; bleeding disorder; systemic illness; receipt of any vaccine within the 4 weeks before the trial vaccination (except for influenza vaccination, which may have been received at least 2 weeks before the study); receipt of blood or blood-derived products in the past 3 months that might have interfered with assessment of the immune response or known systemic hypersensitivity to one of the vaccine component in the past.

2.2. Vaccine

The typhoid Vi polysaccharide vaccine Typhim Vi® was provided in pre-filled syringes that contained 0.5 mL of vaccine (Sanofi Pasteur Inc., France [Batch G0528-1]). Each dose of 0.5 mL was formulated to contain 25 μg of purified Vi capsular polysaccharide. The vaccine was administered intramuscularly into the deltoid region at Day 0.

2.3. Immunogenicity assessments

Blood samples (5 mL) were collected in dry sterile capped plastic tubes for estimation of antibody titer against Vi antigen prior to vaccination and 28 days post-vaccination. The blood was allowed to clot before separation of serum by centrifuging at 3000 rpm for 10 min. The serum samples were stored at −20 °C or lower until analysis.

Anti-Vi antibodies were measured by ELISA (VaccZyme™ Human Anti-S typhi Vi IgG Enzyme Immunoassay Kit; The Binding Site Group Ltd., Birmingham, UK) by Sanofi Pasteur Central Laboratories. Diluted serum samples (100 μL) were added to wells of antigen-coated microtitre test plates and incubated in the dark at 18–24 °C for 30 min. Each well was washed 3 times with 300 μL of wash buffer. 100 μL purified peroxidase labeled rabbit anti-human IgG (γ chain specific) conjugate was added to each well and the plates incubated in the dark at 18–24 °C for 30 min. The wells were washed an additional three times, tetramethylbenzidine substrate added and incubated at room temperature in the dark for 30 min. The substrate reaction was then stopped with 100 μL 3M phosphoric acid and plates were read spectrophotometrically at 450 nm. The assay was calibrated against an affinity purified preparation of pooled human antiserum to typhi Vi. The quantity of IgG antibodies in the affinity purified preparation was confirmed against the European Reference Material ERM®-DA470 (Institute for Reference Materials and Measurements, Belgium). The anti-typhi Vi units assigned to this assay were determined based upon the quantity of IgG (EU/mL) in the binding site's affinity purified reference material. The lower limit of quantification for the assay was 7.4 ELISA units/mL (EU/mL).

2.4. Safety

Participants were kept under observation for 30 min after the vaccination to assess the occurrence of any immediate adverse events/reactions. Participants or their parents/guardians were provided with diary cards, digital thermometers and flexible rulers to record solicited systemic and injection site reactions, as well as other unsolicited adverse events/reactions. Solicited injection site reactions (pain, erythema and swelling) and solicited systemic reactions (fever, headache, malaise and myalgia) were recorded daily for 7 days after vaccination along with any action taken to manage each event. Body temperature was measured daily for 7 days after vaccination. Unsolicited adverse events were recorded for 28 days after vaccination. Serious adverse events were recorded throughout the study. Participants or their parents/guardians were contacted by telephone 8 days (Day 8 ± 2 days) after vaccination to remind them to record all safety information in the diary card. Diary cards were collected from participants when they returned for follow-up at visit 2 (Day 28 + 7 days).

Participants or their parents/guardians graded the intensity of non-measurable solicited reactions and unsolicited adverse reactions using a three-point grading scale of increasing severity: grade 1, no interference with activity; grade 2, some interference with activity; and grade 3, significant, prevents daily activity. Adverse reactions of injection site erythema, swelling and pain were graded on the three-point scale during statistical analysis according to age