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Serological response following re-vaccination with *Salmonella typhi* Vi-capsular polysaccharide vaccines in healthy adult travellers

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ABSTRACT

An injectable Vi-capsular polysaccharide vaccine against typhoid fever is available but vaccine-induced immunity tends to wane over time. The phenomenon of immunotolerance or hyporesponsiveness has earlier been described for polysaccharide vaccines such as pneumococcal capsular polysaccharide vaccine and some publications also suggest a possible immunotolerance after revaccination with Vi-capsular polysaccharide vaccines.

In this study, post-immunisation antibody concentrations in adult travellers first vaccinated with a *Salmonella typhi* Vi-capsular polysaccharide vaccine (primary vaccination group) were compared with those having received one or more vaccinations previously (multiple vaccinations group). Vaccines administered were Typherix® (GlaxoSmithKline), Typhim Vi® (Sanofi Pasteur MSD) or Hepatyrix® (GlaxoSmithKline). Blood samples were obtained prior to vaccination (day 0) and on day 28 (−1/+14) after vaccination. Serum Vi-Antigen IgG concentrations were measured by ELISA.

Of the 85 subjects included in the per protocol data set, 45 (53%) belonged to the multiple vaccinations group. In both groups, geometric mean antibody concentrations (GMCs) were significantly higher after vaccination than before vaccination. Pre-vaccination GMCs were lower in the primary vaccination group than in the multiple vaccinations group (3.40 μg/ml versus 6.13 μg/ml, $P = 0.005$), while there was no significant difference in the post vaccination GMCs between groups (11.34 μg/ml versus 14.58 μg/ml, $P = 0.4$). In the multiple vaccinations group, vaccination was performed 18 to 57 months after the last vaccination (median 38 months) and there was a negative correlation between time since last vaccination and antibody concentration on day 0.

In conclusion, we were not able to demonstrate a relevant immunotolerance after multiple versus primary vaccination with *S. typhi* Vi-capsular polysaccharide vaccines.

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1. Introduction

In countries with limited food hygiene and sanitation infrastructure, typhoid fever still presents a major burden of disease and poses a risk to travellers to these regions [1,2]. Besides an oral *Salmonella typhi* Ty21a vaccine, injectable polysaccharide (PS) vaccines containing *S. typhi* Vi-capsular antigen are available. Protective efficacy of typhoid fever vaccines is not optimal and immunity tends to wane over time.

Large trials on the protective efficacy of the Vi-capsular polysaccharide vaccines were performed in areas where *S. typhi* is endemic [3–5]. A trial in Nepal demonstrated an efficacy of 72% of the Vi-capsular polysaccharide vaccines in preventing typhoid fever within 17 months of follow-up [4]. In another trial in South Africa, protective efficacy after 3 years was calculated as 55% while 64% of the vaccinees had an antibody concentration over 1 μg/ml at that time [3].

In non-endemic regions, protective efficacy can only be estimated indirectly by measuring vaccine-specific antibody

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concentrations. Estimated protective concentrations vary, probably due to different serologic assays and antibody standards [3,5,6]. Trials in non-endemic regions demonstrated a rapid decline of antibody concentration during the three years following vaccination [7–9]. A trial in the USA demonstrated a progressive decrease in the proportion of vaccinees with concentrations of ≥1 μg/ml from 87% after one month to only 35% after 3 years post-vaccination. Thus, in many industrialized countries it is recommended to re-vaccinate against typhoid fever after two or three years if extended protection is needed [10–12].

The phenomenon of immunotolerance, reflecting the overall lower increase in antibody concentration after re-vaccination compared to primary vaccination has been described for polysaccharide vaccines such as pneumococcal capsular polysaccharide vaccine or meningococcal serogroup C (MenC) vaccines [13,14]. Several immune mechanisms, including the depletion of the B-memory pool could be possible explanations for this phenomenon [14]. Recent findings also suggest a possible immunotolerance after re-vaccination with Vi-capsular *S. typhi* polysaccharide vaccines but results are controversial: Overbosch et al. observed a lower seroprotection and seroconversion after Vi-capsular re-vaccination than after the initial vaccination 3 years earlier [9]. Keitel et al., on the other hand, showed comparable results regarding antibody concentrations one month after primary immunization versus after re-immunization administered 27 or 34 month after primary immunization [7].

In the present study, anti Vi-capsular antibody concentrations have been assessed in travellers receiving their first vaccination (primary vaccination group) versus those having received one or more previous vaccinations (multiple vaccination group) with a Vi-capsular polysaccharide vaccine.

2. Materials and methods

The study was conducted at the pre-travel clinic of the Section Tropical Medicine of the University Medical Center Hamburg-Eppendorf, Germany, between January 2012 and June 2013. All subjects had sought pre-travel consultation and vaccination against typhoid fever was indicated following recommendations of the German Society for Tropical Medicine and International Health [10]. In brief, travellers to tropical/subtropical areas with limited hygiene and sanitation conditions staying more than 4 weeks (Indian subcontinent: any travel duration) were offered typhoid fever vaccination as well as all travellers inquiring maximum protection. Subjects over 18 years of age with (multiple vaccinations group) or without (primary vaccination group) previous parental typhoid fever vaccination were included after providing written informed consent. Exclusion criteria included concurrent febrile illness, severe chronic disease, relevant allergies, illness/medication associated with immunosuppression and past history of typhoid fever. Subjects with previous vaccination must have received their last vaccination with *S. typhi* Vi-capsular polysaccharide vaccine not more than 5 years ago.

After inclusion, subjects received a single dose of typhoid fever vaccination composed of purified Vi polysaccharide into the right or left deltoid muscle. Vaccines administered were Typherix® (GlaxoSmithKline), Typhim Vi® (Sanofi Pasteur MSD) or Hepatyrix® (GlaxoSmithKline). Each dose of monovalent typhoid vaccine (Typherix® and Typhin Vi®) consisted of 0.025 mg *S. typhi* Vi-polysaccharide antigen, Hepatyrix® additionally contained 1440 ELISA units of inactivated hepatitis A virus. Blood samples were obtained via venipuncture on day 0 prior to vaccination and on day 28 (−1/+14) after vaccination.

Sera were prepared immediately from all blood samples and stored at −20 °C until shipment for serologic analyses. Laboratory personnel performing serum antibody analyses were blinded to study group allocation of respective serum samples. Serum Vi-antigen IgG concentrations were measured by an in-house ELISA as described before [15]. Vi-polysaccharide (Typhim) at a concentration of 1 μg/ml was used to coat plates and incubated at room temperature for 3 h. Plates were blocked with carbonate/bicarbonate buffer and non-fat dry milk at 4 °C overnight. Vi-standard and experimental samples were diluted 2-fold beginning at a starting dilution of 1:50. Samples were added to ELISA plates and incubated at 37 °C for 1 h. A Vi-standard curve was performed on each ELISA plate using a pooled serum sample from study participants with elevated Vi-specific IgG responses. The pooled serum sample had an anti-Vi IgG concentration of 13.60 μg/ml as determined by comparison to the FDA anti-Vi IgG reference sample R1, 2011 [6]. Plates were washed and a goat-anti human IgG-AP secondary antibody was added to plates at a dilution of 1:10,000. After incubating for 1 h at 37 °C, plates were washed and AttoPhos® (alkaline phosphatase fluorescent) substrate was added allowed to incubate at room temperature for 1 h. The Vi-standard curve on each plate was used to calculate the anti-Vi IgG μg/ml concentration in each experimental sample assayed on the same plate.

The study was approved by the ethics committee of the Physicians' Chamber Hamburg, Germany. Statistics software SPSS 17.0 was used to analyse data. A *P*-value <0.05 was considered as statistically significant. Paired *t*-test was used for comparing findings between day 0 and day 28. Independent *t*-test was used to analyse differences between groups. A antibody concentration of 4.3 μg/ml was seen as protective for our data according to data published earlier [6].

3. Results

Of the 102 subjects enrolled, 85 (83%) were included in the per protocol data analysis. A total of 11 subjects were excluded because of protocol deviations: Six were excluded because the last vaccination was more than 5 years ago, 5 subjects were excluded as serum samples were obtained outside the protocol-specified time window. Of the remaining 91 participants, 6 were lost to follow up and did not present for post-vaccination visit on day 28.

The median age was 33 years (range 18–79), 45% were male (Table 1). Most subjects presented with plans to travel to South-East Asia (Table 2). Eighty-one subjects (95%) were born and raised in Germany, 4 (5%) originated from typhoid fever-endemic regions (Cameroon, Chile, Ecuador, Venezuela). Seventy-five percent of the subjects had visited typhoid fever-endemic countries in the last 5 years.

Of the 85 subjects, 40 subjects (47%) were vaccinated for the first time with *S. typhi* Vi-capsular polysaccharide vaccines

Table 1
Demographic characteristics of subjects with and without previous *Salmonella typhi* Vi-capsular polysaccharide vaccination.

Characteristics	Primary vaccination group (*n* = 40)	Multiple vaccinations group (*n* = 45)	Total (*n* = 85)
Median age (range)	28.5 (18–65)	28.0 (18–79)	28.0 (18–79)
Male	18 (45%)	20 (44%)	38 (45%)
Previous travel to regions for which a vaccination against typhoid fever would have been recommended	19 (48%)	45 (100%)	64 (75%)
Born and raised in typhoid fever-endemic regions	2 (5%)	2 (4%)	4 (5%)

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