Paediatrica Indonesiana

VOLUME 54 September • 2014 NUMBER 5

Original Article

Anti-*S. typhi* Vi IgG levels in children with and without typhoid vaccinations

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Abstract

Background Typhoid fever is endemic to Indonesia, with an annual incidence of 13/10,000 people. Vaccination has been shown to be an effective method to prevent typhoid fever. Of several vaccine types, the polysaccharide Vi vaccine is the most commonly used typhoid vaccine in developing countries. Results of previous studies remain inconclusive on the necessity of revaccination every 3 years.

Objective To compare the mean serum antibody titers of anti-*S. typhi* Vi IgG and the proportion of children with protective antibody levels between children with and without typhoid Vi vaccination.

Methods We conducted a cross-sectional study at Tuminting District, Manado from June to September 2012. Data was analyzed using independent T-test and Fisher's test. Serum anti-*S. typhi* Vi IgG levels were measured by *enzyme-linked immunosorbent assay* (ELISA) method.

Results Seventy-six subjects were divided into two groups: 38 children who had received the typhoid Vi vaccination more than 3 years prior to this study and 38 children who never had typhoid vaccinations as a control group. No statistically significant difference in age and gender was found between the two groups. The mean serum anti-Vi IgG level was 0.55 ug/mL (SD 0.58; 95%CI 0.36 to 0.74) in the vaccinated group, significantly higher than that of the control group [0.31 ug/mL (SD 0.42); 95%CI 0.17 to 0.44; P=0.038]. The proportion of children with protective anti-Vi antibody level was higher in the vaccinated group (23.7%) than in the control group (10.5%), however, this difference was not statistically significant (P=0.128).

Conclusion The mean serum anti-*S. typhi* Vi IgG antibody level in children who had been vaccinated more than 3 years prior to the study is higher than in children who had never received typhoid vaccinations. Nevertheless, the mean antibody titers are generally non-protective in both groups. Also, the proportion of children with protective antibody levels is not significantly different between the two groups. **[Paediatr Indones. 2014;54:284-8.]**

Keywords: *anti-S. typhi Vi IgG, Vi polysaccharide typhoid vaccine, typhoid fever, children*

Typhoid fever is an acute, life-threatening disorder commonly characterized by fever, headache, malaise, anorexia, spleen enlargement, and relative bradycardia.[1,2] Typhoid fever is recognized as a major health problem due to its rapid spread, especially in dense populations.[3,4] The *World Health Organization* (WHO) estimated the number of typhoid cases to be 21 million, with 216,000 deaths each year.[5] This disease is endemic to most developing countries in Asia, where an estimated 90% of typhoid-related deaths occur.[5] Indonesia is a typhoid-endemic region with a national typhoid fever incidence of 13/10,000 annually. In 2000, the total reported typhoid cases in Indonesia was 275,693. Based on surveillance data from 2001 to 2003, the annual incidence of typhoid fever was 63 to 119 culture-positive infections in a population of 100,000, with highest rates in children aged 5-14 years.[7] Data collected from Department of Pediatrics, Prof. Dr. R.D. Kandou General Hospital from 2007 to 2010 shows that the number of typhoid cases was 26 to 27 out of 1,000 inpatients.

The extent of the typhoid fever burden has

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raised the necessity for an effective prevention strategy, such as vaccination. To date, there are two, internationally-recommended typhoid vaccines: the Vi polysaccharide vaccine and the live-attenuated Ty21a vaccine.[8] The Vi polysaccharide vaccine has been most widely used in countries with a high incidence of typhoid.[9] Studies have reported that the cumulative efficacy of the Vi polysaccharide vaccine lasts only for 2 to 3 years, therefore, revaccination is needed every 3 years.[10] However, other studies with differing results have argued against the necessity of revaccination.[11-13] To date, no study has been conducted in Manado regarding the protective response of the typhoid vaccine, whereas, the contradictory results of previous studies implicitly indicated that the quality of response to typhoid vaccination were vary in different geographical areas. These differrences mainly related to degree of endemicity of each particular region. Accordingly, we conduct this study to compare the anti-*S. typhi* Vi IgG levels between children who had been vaccinated more than 3 years prior to the study and children who had not been vaccinated with the Vi polysaccharide typhoid vaccine.

Methods

We conducted a descriptive, analytic, cross-sectional study at Tuminting District, Manado from June to September 2012. Subjects were included by consecutive sampling. Inclusion criteria for the vaccinated group were healthy children, aged 5 to 12 years, who had been vaccinated with the Vi polysaccharide typhoid vaccine more than 3 years prior to the study. Proof of vaccination was obtained by subjects' *Kartu Menuju Sehat* (KMS) or other medical records. Children with poor nutritional status were excluded. The control group consisted of children who had not received any typhoid vaccination. All children who met the inclusion criteria for the two groups underwent serum antibody level examinations for anti-*S. typhi* Vi IgG. Serum anti-*S. typhi* Vi IgG levels were measured by *enzyme-linked immunosorbnet assay* (ELISA) method. Serum antibody level of >1 μg/mL anti-*S. typhi* Vi IgG was considered to be protective against disease.

Subjects' characteristics were assessed by descriptive analysis. Comparisons of the two groups were analyzed using independent T-test for mean serum antibody levels and Chi-square test for the proportion of children with protective anitbody levels.

Results

During the study period, 76 subjects were divided into two groups: children with a history of Vi polysaccharide typhoid vaccination more than 3 years prior to our study (n=38) and children without a prior history of typhoid vaccination (n=38). Characteristics of subjects are shown in **Table 1**.

Independent T-test results on mean anti-*S. typhi* Vi antibody levels between the two groups are shown in **Table 2,** while Chi-square test results to compare the proportion of children with protective anti-*S.*

Table 1. Subjects' characteristics

Variables	Typhoid Vi vaccination n=38	No typhoid vaccination n=38
Gender		
• Males, n (%)	24	17
• Females, n (%)	14	21
Mean age (SD), years	8.18 (1.67)	8.39 (1.57)
Mean BMI (SD), kg/m^2	18.72 (4.72)	16.53 (4.41)

Table 2. Comparison of anti-*S. typhi* Vi IgG levels between the vaccinated and unvaccinated groups

Groups	anti-*S. typhi* Vi IgG level (µg/mL)			P value
	Mean	SD	95% CI	
Typhoid Vi vaccination	0.55	0.58	0.36 to 0.74	0.038
No typhoid vaccination	0.31	0.42	0.16 to 0.44	

typhi Vi antibody levels between the two groups are shown in **Table 3**.

The levels of anti-S.typhi Vi IgG in children who had been vaccinated were significantly higher compared to those who had no vaccination (**Table 2**).

The proportion of children with protective antibody levels was not statistically significant different between the two groups (**Table** 3).

Table 3. Proportion of children with protective anti-*S. typhi* Vi IgG levels (>1 µg/mL)

Groups	Protectivity of *S. typhi* Vi antibody		P value
	Protective	Not protective	
	n	n	
Typhoid Vi vaccination	9	29	0.128
No typhoid vaccination	4	34	

Discussion

The Vi polysaccharide subunit vaccine is a homopolymer of galacturonic acid, which is extracted from the bacteria *Salmonella typhi*.[1] This vaccine is a T-cell independent vaccine with long and repetitive epitopes which allow crosslinking with immunoglobulin receptors located on the surface of B cells. Immunoglublin binding to B cells' surface receptors result in B cells activation, which in turn allowing proliferation and differentiation into antibody-secreting plasma cells. The primary immune response is induced at the time of first exposure to the antigen. Antibodies formed in the primary immune response are mostly IgM and IgG, generally at lower titers than that formed during a secondary immune response. A secondary immune response is more adequately developed after exposure to the same antigen, hence, this type of immunological response is expected following booster immunization.. As such, the Vi polysaccharide as a T-cell independent antigen activates only a primary immune response without a booster effect, so immunological memory is not developed.[14-15]

Although the underlying immunological mechanism of response to the Vi polysaccharide typhoid vaccine is well known, the protective efficacy of this vaccine may vary depending on typhoid endemicity of particular geographical region. Previous studies remain inconclusive on the need for vaccination or revaccination with the Vi polysaccharide typhoid vaccine.[11,12] In our study, the mean anti-*S. typhi* Vi IgG level of the vaccinated group was not in protective range. Study conducted by Acosta *et al.*[10] showed similiar result through different ways. Acosta *et al.* studied the protective efficacy of typhoid vaccination by calculating the incidence of typhoid fever (diagnosed clinicaly and serologicaly) from 80,000 post-vaccinated subjects. This study found that in the second year after vaccination the protective efficacy of the *S. typhi* Vi polysaccharide subunit vaccine was high (85%), but in the third year the efficacy decreased to 55%. Our study has shown that the drop in anti-*S. typhi* Vi IgG level 3 years or more after vaccination is responsible for the reduction in protective efficacy of *S. typhi* Vi subunit vaccine which shown by Acosta. Similarly, Froeschele *et al.*[16] in 2010 found that serum antibody levels induced by a single dose of *Typhim Vi*® vaccine decreased after 3 years, hence, revaccination every 3 years is recommended.

The mean anti-Vi IgG level was significantly higher in the vaccinated group than in the unvaccinated group (P=0.038). However, antibody levels in both groups were generally less than the protective level of <1 μg/mL, suggesting a need for typhoid revaccination every 3 years as recommended by previous studies.

In the unvaccinated control group, 10.5% of children had protective antibodies against typhoid. Despite the negative history of vaccinations, we suggest a role of environmental antigen exposure in developing antibodies among people at risk for such exposure. However, our results emphasize that vaccination should not be replaced by environmental antigen exposure. This finding is in contrast with a study conducted in a highly endemic area in South Africa.[11] They compared anti-Vi antibody levels between children who had received the *S. typhi* Vi polysaccharide subunit vaccine 10-12 years earlier and a control group who had not received the vaccine.

They found no significant difference in anti-Vi antibody levels between the two groups. Furthermore, 58% of subjects in each group had protective anti-Vi antibody levels (> 1 μg/mL). Similarly, Tacket *et al.* studied 10 volunteers in non-endemic areas (North America) who received the Vi subunit vaccine. With periodic checking, anti-Vi antibody levels in this group persistently increased in 9/10 volunteers, even 36 months after vaccination. Therefore, they concluded that without revaccination, anti-Vi antibody levels increased even after 3 years. Factors influencing the persistence of antibody levels remain unclear.[12]

Proportion of children with protective anti-Vi antibody levels in vaccinated group was higher compared to unvaccinated group, although this difference was not statistically significant (P=0.128). These results emphasize the need for vaccination and revaccination in children in endemic areas. Zhou *et al.*[17] showed that children who were revaccinated 3 years after the first dose of *S. typhi* Vi polysaccharide subunit vaccine had significantly increased anti-Vi antibody titers. A review by Guzman *et al.*[1] stated that high-risk populations such as children in endemic areas, travelers and microbiology laboratory officials will benefit from an effective typhoid vaccination.

A limitation of this study was not obtaining antibody levels to *S.typhi* at more time points. Interval between vaccination and time of anti-S. typhi IgG levels measurement in vaccinated group also not calculated in this study. Another drawback lies to its cross-sectional design which make us unable to determine factors that contributed to a small proportion of children in both groups which have protective levels of immunity against *S. typhi*. Also, we were unable to control factors indirectly related to typhoid antigen exposure, such as hygiene and socioeconomic status.

Although several studies recommend revaccination with the Vi polysaccharide typhoid vaccine every 3 years, other studies suggest that the need for revaccination largely depends on factors that are not yet clearly known in a particular region. We found that the serum anti-*S. typhi* Vi IgG level was higher in children who had received typhoid vaccinations more than 3 years prior to the study, than in children who had not received typhoid vaccinations. Nevertheless, mean antibody titers in both groups were non-protective and the proportion of children with protective antibody levels was not significantly different between the groups. These findings provide evidence for health practitioners to recommend typhoid vaccinations as well as revaccinations every 3 years in children over 2 years of age, especially those at higher risk for typhoid fever infections.

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