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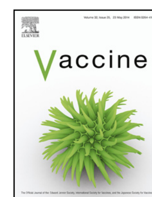

The transfer and decay of maternal antibody against *Shigella sonnei* in a longitudinal cohort of Vietnamese infants

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A B S T R A C T

Background: *Shigella sonnei* is an emergent and major diarrheal pathogen for which there is currently no vaccine. We aimed to quantify duration of maternal antibody against *S. sonnei* and investigate transplacental IgG transfer in a birth cohort in southern Vietnam.
Methods and results: Over 500-paired maternal/infant plasma samples were evaluated for presence of anti-*S. sonnei*-O IgG and IgM. Longitudinal plasma samples allowed for the estimation of the median half-life of maternal anti-*S. sonnei*-O IgG, which was 43 days (95% confidence interval: 41–45 days). Additionally, half of infants lacked a detectable titer by 19 weeks of age. Lower cord titers were associated with greater increases in *S. sonnei* IgG over the first year of life, and the incidence of *S. sonnei* seroconversion was estimated to be 4/100 infant years. Maternal IgG titer, the ratio of antibody transfer, the season of birth and gestational age were significantly associated with cord titer.
Conclusions: Maternal anti-*S. sonnei*-O IgG is efficiently transferred across the placenta and anti-*S. sonnei*-O maternal IgG declines rapidly after birth and is undetectable after 5 months in the majority of children. Preterm neonates and children born to mothers with low IgG titers have lower cord titers and therefore may be at greater risk of seroconversion in infancy.

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1. Introduction

Q3 The bacterial genus *Shigella* is a major contributor to the global burden of diarrheal disease. This genus of enteric pathogens is typically associated with disease in children under 5 years of age in industrializing regions [1], and is estimated to be responsible for 100,000 deaths annually [2]. *Shigella* infections are characteristically associated with dysentery (blood and mucus in the stool) and can be severe in young children [3,4]. Of the four *Shigella* species, *Shigella flexneri* and *Shigella sonnei* predominate worldwide [1]. *S. flexneri* is traditionally associated with disease in industrializing countries, whereas *S. sonnei* is more commonly isolated in industrialized regions. However, this distribution is changing. *S. sonnei* is globally emergent and replacing *S. flexneri* as the most common cause of bacterial dysentery [5,6]. This trend may be being exacerbated by resistance to common antimicrobials, with several recent reports of *S. sonnei* exhibiting resistance against fluoroquinolones and 3rd generation cephalosporins in the USA, Vietnam and elsewhere [7–9]. Improved sanitation and antimicrobial treatment remain the only current tools for prevention and control as there are no licensed *Shigella* vaccines [10].

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Neonates and infants are typically at increased risk from infectious agents such as *Shigella* due to immaturity of the immune system [11]. While neonates have some capacity for cell-mediated immunity [12], humoral immunity is very limited in early life [13]. Antibody responses in neonates are shorter, delayed in onset and of lower affinity than those observed in healthy adults [14]. The transfer of maternal IgG antibody to the fetus during pregnancy confers short-term passive immunity and represents a primary mechanism for protection against infectious diseases at birth [11]. Transport of maternal antibody across the placenta to fetal capillaries is mediated by the neonatal Fc receptor (FcRn) [15–17] and can be affected by factors such as gestational age, maternal IgG concentration and infection [18–21].

Maternally transferred IgG against *S. sonnei* in infancy has not been substantially investigated. Work conducted in Israel in the mid-1990s found that the concentration of anti-*S. sonnei* lipopolysaccharide (LPS) IgG present in umbilical cord plasma positively correlated with the concentration in maternal plasma [22]. IgG against LPS, specifically the O-antigen component, is the best described *S. sonnei* immune marker as it is the major bacterial surface antigen exposed to the immune system during infection. Although anti-*S. sonnei*-O IgG is not a definitive correlate of protective immunity [23], it is an indicator of some degree of acquired immunity; lack of *Shigella* serotype specific antibody is associated with an increased risk of symptomatic disease [24,25]. Furthermore, titers of anti-*S. sonnei*-O IgG rise significantly after symptomatic infection [22,26,27], with titers doubling 10 weeks post-infection [26,28]. Previous work from Vietnam in the late 1980s showed that anti-*S. sonnei*-LPS and anti-*S. flexneri*-LPS IgG rise dramatically from birth, peak at 3–4 years of age and then permanently plateau [29].

An understanding of the nature and duration of maternal antibody protection in infancy is important for determination of an appropriate vaccination schedule when *Shigella* vaccines eventually become available. Additionally, although IgG titers against *S. flexneri* and *Shigella dysenteriae* type I in Vietnam were found to be high in children and adults in the early 1990s [27,29], exposure to *Shigella* has not been measured in a contemporary Vietnamese population. As *S. sonnei* is now the predominant *Shigella* species in Vietnam [30], we hypothesized there would be substantial evidence of population exposure and *S. sonnei* maternal antibody transfer in this rapidly industrializing country. Therefore, we aimed to quantify maternal anti-*S. sonnei*-O antibody decay using the largest sample size to date, with over 500 paired mother and infant plasma samples. We also investigated transplacental IgG transfer and determined the incidence of *S. sonnei* seroconversion in infancy in southern, urban Vietnam.

2. Methods

2.1. Ethical approval

Written informed consent was required from all enrolled families. Ethical approval was granted from Hung Vuong Hospital, Oxford Tropical Research Committee as well as the London School of Hygiene & Tropical Medicine for the main cohort study. Ethical approval was also granted from the Hospital for Tropical Diseases in HCMC and OxTREC for the studies collecting acute and convalescent plasma samples from culture-positive *Shigella* and *Salmonella* cases for ELISA validation.

2.2. Study population

The birth cohort population and methodology has been described previously in detail [31]. Briefly, mothers delivering at Hung Vuong obstetric hospital in Ho Chi Minh City (HCMC) were invited to enroll during either an antenatal visit in the final month of pregnancy or at the time of hospital admission for delivery. Children born between January and December 2013 in HCMC were included in the analysis presented here. Pregnant women were eligible if they lived in district 8 of HCMC (a previously identified endemic hotspot for *Shigella* [30]), were aged 16 years or older and were HIV seronegative at the time of birth. Mothers answered a baseline questionnaire and blood (umbilical cord and venous) samples were collected in EDTA tubes. After delivery, infants were recalled regularly for routine follow up visits. A 1 ml EDTA blood sample was collected at the 4, 9 and 12 month visits. All blood samples were separated into cells and plasma and stored at −20 °C until required.

2.3. *S. sonnei* anti-O antigen ELISA

Antibody (IgG and IgM) against *S. sonnei* O-antigen were measured using an enzyme-linked immunosorbent assay (ELISA) in maternal, umbilical and longitudinally collected infant plasma samples. Purified *S. sonnei* O-antigen was extracted as previously described [32] and provided by Sclavo Behring Vaccines Institute for Global Health (Siena, Italy). For the ELISA assays, 96-well microtiter plates (Maxisorb; NUNC) were coated overnight with 0.5 mg/ml *S. sonnei* O-antigen in PBS pH 7.0 at 4 °C, plates were then washed and blocked in PBS containing 5% skimmed milk powder for 2 h. After washing, 100 μl of each plasma sample (diluted at 1:200 in PBS containing 1% skimmed milk) were added and plates were incubated for 2 h at room temperature. IgG and IgM against *S. sonnei* O-antigen were detected by incubation with alkaline phosphatase directly conjugated anti-human IgG/IgM for 1 h. Plates were developed by p-nitrophenyl-phosphate solution (Sigma) and were read at absorbance 405 nm and 490 nm by an ELISA platereader (Microplate reader, Biorad). Each plate contained a 2-fold serially diluted pool of anti-*S. sonnei*-O antigen human plasma (primary concentration 1:200). A standard curve was generated from the corresponding optical density (OD) and ELISA units using a 4-parameter logistic regression fit. One ELISA unit (EU) was defined as the reciprocal dilution of the standard plasma that gave an absorbance value equal to 1 in this assay. The ELISAs were done in duplicate. Antibody (IgG and IgM) units in the cohort members' plasma were calculated relative to this standard each time the assay was performed. Acute and convalescent plasma samples for the ELISA validation were derived from pediatric culture-positive *S. sonnei* and *Salmonella* dysentery cases presenting to either the Hospital for Tropical Disease in HCMC as part of another ongoing study.

2.4. Statistical analyses

Geometric mean titers (GMT) were calculated to summarize anti-*S. sonnei*-O IgG in maternal and cord plasma. Paired *t*-tests were used to compare $\log_{10}$ titers between paired maternal/cord samples. Analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons was used to compare maternal and cord log-transformed antibody titers within categorical groups. The ratio of maternal transfer was compared across groups using the Kruskal–Wallis (KW) test with Dunn's test for multiple comparisons [33]. Linear mixed effects modeling was used to assess the trajectory of infant $\log_{10}$ titers from birth to 20 weeks to account for within-participant association over time. The half-life of IgG titer was calculated as the time at which the predicted IgG titer would decrease by 50% from the cord blood titer. The population half-life was derived using the formula:

$$\frac{-\log_{10}(2)}{b_1}$$

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