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Early-life and contemporaneous nutritional and environmental predictors of antibody response to vaccination in young Gambian adults

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ABSTRACT

Recent research links nutritional exposures early in life with alterations in functional immunity that persist beyond childhood. Here we investigate predictors of antibody response to polysaccharide vaccines in a cohort of Gambian adults with detailed records from birth and early infancy available. 320 adults were given a single dose of a Vi polysaccharide vaccine for *Salmonella typhi* and a 23-valent capsular polysaccharide pneumococcal vaccine. Anti-Vi antibody levels and antibodies against 4 pneumococcal serotypes (1, 5, 14 and 23F) were measured in serum samples collected at baseline and then 14 days following vaccination and compared to data available from birth and early infancy. Post-vaccination antibody titres to serotype 14 of the pneumococcal vaccine were negatively associated with rate of growth from birth to three months of age, infant weight at 12 months of age and season of birth, but no other associations were observed with early-life exposures. The strongest predictor of antibody levels was pre-vaccination antibody titres, with adult height and serum neopterin levels at time of vaccination also implicated. The current study does not support the hypothesis that nutritional exposures early in life consistently compromise antibody response to polysaccharide vaccines administered in young adulthood.

1. Introduction

The inter-relationship between nutritional status and immune function continues to be the focus of research and debate [1,2]. It is well documented that acute and chronic deficiency of both macro- and micro-nutrients results in an impairment to a number of components of the immune system [3] and supplementation with individual micronutrients has proven efficacious as therapy for certain infectious morbidities; for instance vitamin A and measles infection [4], and zinc and diarrhoeal disease [5]. More recent research also suggests that supplementation with specific micronutrients may have non-specific deleterious effects on immune function, with iron [6] and vitamin A [7] specifically implicated. Further work to understand the mechanisms of these effects is required.

In addition to the effects of contemporaneous nutritional status on human immune function, recent evidence from our group and others suggests that nutritional status during fetal life and early infancy may be critical for immune development, with effects persisting into adulthood. Using antibody response to vaccination as a functional indicator of immunity, we have previously shown that adults born of a lower birth weight have a reduced antibody response to a polysaccharide vaccine (Typhim Vi) [8]. This deficit persisted following a second 'booster' dose of the vaccine [9] but no such association with size at birth was observed with either a protein (rabies) vaccine [8] or a polysaccharide-conjugate (Hib) vaccine [9]. This differential response suggests an early-life programming effect on the generation of antibodies during a B-cell-dependent immune response.

Much of the programming literature has focused on poor maternal nutrition as the most likely candidate for these early-life effects, and uses low birth weight as a proxy indicator for poor nutrition *in utero*. However, low birth weight may also be predictive of a number of post-natal factors that could also be implicated in defining later disease risk. Recent attention has focused on the association between an infant's rate of growth during early-infancy and later disease risk, with faster rates of post-natal 'catch-up' growth implicated as a possible causative factor for certain chronic

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disease outcomes [10]. The current study was therefore designed to investigate in more detail the relationship between nutritional status early in life and response to vaccination in young adults. Here, we investigate antibody response to two polysaccharide vaccines in a cohort of Gambian adults with detailed anthropometric data available from birth and from early infancy.

2. Materials and methods

2.1. Study population

Since 1949, the UK Medical Research Council (MRC) has been collecting health and demographic data on the populations of three villages (Keneba, Kantong Kunda and Manduar) in the rural West Kiang region of The Gambia. From 1976, and with the establishment of a permanent field station in Keneba, this data collection has incorporated detailed information on maternal and infant health, including birth anthropometry and infant growth. In the current study, our recruitment pool consisted of all adults, born in the three study villages since 1976 and who were aged 18 years or older on 1st January 2006. Subjects were excluded if they could not be traced or were not accessible for follow up, if they were already enrolled in another MRC study or if they were known to be pregnant at the time of recruitment. Ethical approval for the study was given by the Ethics Committee at the London School of Hygiene and Tropical Medicine and by the joint Gambian Government/MRC The Gambia Ethics Committee. Informed written consent was obtained from each individual participant.

The study took place between February and May 2006. Subjects were seen on two occasions, 14 days apart. At visit 1 (Day 0) weight, height, waist and hip circumferences were measured using standard equipment. A single sample of fasted venous blood was collected for measurement of plasma leptin and serum neopterin: leptin was measured as a proxy marker of adiposity and neopterin as a marker of immune activation. This blood sample was additionally used for the assessment of pre-vaccination serum antibody titres and for the preparation of a thick film for detection of malaria parasites by microscopy. Following blood collection, each subject was given a single dose of a Vi polysaccharide vaccine for *Salmonella typhi* (Sanofi-Pasteur, Lyon, France) and a single dose of a 23-valent capsular polysaccharide vaccine (Pneumo, Sanofi-Pasteur, Lyon, France). Fourteen days later (Visit 2), a further venous blood sample was collected for post-vaccination serum antibody titres.

2.2. Laboratory methods

Plasma leptin and serum neopterin were measured at MRC Human Nutrition Research, Cambridge UK. Leptin was measured by ELISA (R&D Systems, Abingdon, UK) and neopterin by a competitive enzyme immunoassay principle (BRAHMS Atiengesellschaft, Berlin, Germany). Both analytes were measured in duplicate and following manufacturers' guidelines.

Anti-Vi immunoglobulin G (IgG) analysis was conducted at the Laboratory of Developmental and Molecular Immunity, National Institutes of Child Health and Human Development, Bethesda, USA. Briefly, microtitre plates were coated with Vi (0.2 μg/well) purified from *Citrobactor freundii* and goat anti-human IgG (Jackson Immuno Research Laboratories Inc., West Grove, PA) conjugated to alkaline phosphatase were used for ELISA. The anti-Vi IgG standard was a plasma sample from an adult vaccinated with Vi polysaccharide typhoid vaccine (provided by Wendy Keitel, Baylor University, Houston, TX). The Vi antibody content of this serum was also assayed by a radioimmunoassay (RIA) by Pasteur Merieux Connaught. The antibody levels were expressed in ELISA units (EU) and the reference sera were assigned a value of 75 EU. All samples were run in duplicate. Antibody levels were calculated using Program ELISA, version 12 (Center for Disease Control and Prevention, Atlanta, GA). The lowest detectable level of the assay for anti-Vi IgG was 0.1 EU. Prior to analysis, all data were log transformed, and results are presented as geometric means. For anti-Vi antibody levels, data are expressed as ELISA units (EU).

Pneumococcal capsular polysaccharide specific IgG levels were measured at the WHO Pneumococcal Serology Reference Lab at the UCL Institute of Child Health, London, UK. Standard enzyme linked immunosorbent assay methods [11] were used to quantify anti-capsular IgG antibodies to four specific pneumococcal serotypes (1, 5, 14 and 23F). These serotypes were selected on the basis of frequency of carriage within this population setting, 14 and 23F being amongst the most common [12], and their importance in causing invasive disease (1 and 5 account for >40% in a recent series of pneumococci causing bacteraemia [13]).

2.3. Statistical analyses

Comparisons amongst group means were made using two-sample *t*-tests. Vaccine data are presented as geometric means and 95% confidence intervals (CIs). Sex specific *z*-scores were calculated using UK reference data [14]. Associations between contemporary measures and antibody response to vaccination were compared by linear (for continuous variables) or logistic (for binary variables) regression analysis. Response to vaccination was assessed in relation to six early-life exposures (separate models); birth weight, low birth weight (<2.5 kg) *vs*. normal birth weight (as a binary variable), small for gestational age *vs*. appropriate for gestational age (as a binary variable), rate of infant growth from birth to three months of age, infant weight at 12 months of age and season of birth (harvest/wet season January–June; hungry/dry season July–December). Rate of change in weight from birth to three months was calculated as the difference between sex-specific birth weight standard deviation score and sex-specific weight at three months standard deviation score. We also looked at weight for age standard deviation differences between three and six months of age and six and 12 months of age. Associations between these early-life exposures and antibody responses were tested by multiple linear regression analysis. Probability values <0.05 were considered to be statistically significant for all tests. All statistical analyses were performed using DataDesk, version 6 for Windows, Data Description Inc., Ithaca, NY.

3. Results

3.1. Subject characteristics

A total of 858 individuals met the criteria for recruitment into the current study. Of these, 78 were known to have died prior to follow up, leaving a cohort of 781 to be traced. Of this number, 145 were excluded on the basis they were currently participating in another ongoing study and three because they were confirmed to be pregnant by an MRC midwife prior to the start of the study. Of the remaining 633 individuals who were eligible to participate, 241 were not available [dead (4), self-confirmed as pregnant (45), overseas (24), outside designated study area (58), not traceable (50), traceable but unavailable for study (60)] and 72 did not consent to participate. A total of 320 subjects (41% of 781 followed up) consented and participated in the current study. Compared to non-participants, participants were younger (22.2 y *vs*. 23.0 y; $p < 0.0001$) and there were significantly more males than females (51.9% *vs*. 45.3%). No differences were observed between the participants and non-participants in available early-life information (data not presented). Table 1 details the early-life characteristics of the subjects recruited. A total of 41 (12.8%) of subjects were born