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Sex-dependent immune responses to infant vaccination: an individual participant data meta-analysis of antibody and memory B cells

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ABSTRACT

Background: Biological sex can be an important source of variation in infection and immunity and sex-dependent differences in immune response to vaccination have been reported in some studies.
Methods: We conducted an individual participant data meta-analysis of vaccine trials from one research centre, in which vaccines were administered to children under three years of age and immunological parameters measured. Log-transformed antigen-specific antibody and memory B cell results were meta-analysed and differences between girls and boys reported as geometric mean ratios.
Results: Antibody and memory B cell data were available from nine trials and 2378 children. Statistically significant differences between girls and boys were observed for diphtheria toxoid, capsular group A, W, and Y meningococcal, and pneumococcal vaccines. No sex-differences were observed for responses to *Haemophilus influenzae* type b, capsular group C meningococcal or tetanus toxoid vaccines.
Conclusions: In young children, immune responses to vaccines were consistently higher or equivalent in girls compared with boys. In no instance were responses in boys significantly higher than girls. While these data do not indicate differences in protection conferred by immunisation in boys and girls, they do support further consideration of biological sex in planning of clinical trials of vaccines.

1. Introduction

There is increasing evidence that biological sex influences the immune response to vaccination and infection, however the biological mechanisms underpinning such differences are not well understood [1–3]. Elucidating the precise hormonal, genetic, behavioural and environmental mechanisms which are involved in sex-differential responses is a focus of ongoing research.

In vaccinated adults, sex-differences in antibody response to vaccination have been observed to be greater for females after influenza [1], tetanus toxoid [4] and standard titre Schwarz measles vaccines [5] amongst others. Pneumococcal polysaccharide vaccine effectiveness has been reported to be greater in women than men [6] however other studies have shown pneumococcal antibody responses to be higher in men [7,8]. Persistence of antibody after diphtheria toxoid vaccination has been observed to be higher in men in cross-sectional studies however such findings may be influenced by widespread vaccination of military recruits [9].

There are few published estimates of sex-specific immune responses for vaccines administered in infancy or early childhood. Sex-specific estimates of immune responses to vaccination in children have been published in a small number of studies, which showed higher antibody titres to measles vaccine in female infants after vaccination with Edmonston-Zagreb measles vaccine but not after vaccination with Schwarz measles vaccine [10]. Additionally, higher anti-rubella titres have been reported in girls in studies of older children and adolescents [11,12].

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Women carry two X chromosomes which contain many genes involved in immune response mechanisms [13,14], and sex-hormones are believed to influence the immune response [15]. Oestrogens promote proliferation of B cells and their maturation into plasma cells and are associated with inflammation, whereas androgens are associated with decreased antibody production and increased production of anti-inflammatory cytokines [1,14].

In only a minority of vaccine studies are immunological responses to vaccination in males and females reported separately. Although attempts have been made to review the available evidence of sex-biases [3,6,15], the non-publication of sex-specific trial results, particularly non-significant findings, results in a form of publication bias which may distort conclusions drawn from systematic reviews. However, individual participant data from past vaccine studies can provide a source of information which is unaffected by publication bias. The aim of this meta-analysis was to collate all data from available vaccine studies from one research centre to characterise sex-differences in vaccine-specific humoral and cellular immune responses in children.

2. Methods

2.1. Data collection

Archives at a single study site in Oxford were surveyed to identify studies eligible for inclusion in the analysis. Studies were eligible in which licensed or unlicensed vaccines were administered to children less than three years of age, and vaccine antigen-specific responses were measured.

2.2. Statistical analysis

Immunological data were $\log_{10}$-transformed and analysed using separate linear mixed effects models for each parameter at each time point. Sex, randomised group (where applicable), type of priming vaccine received at two to four months, and type of booster vaccine (for post-booster time points) were included in models as fixed effects. A random intercept for each study was included to allow for variation between studies [16]. The anti-log of the parameter estimate for sex from the model was the estimate of interest presented herein as a geometric mean ratio (GMR) (female/male) with 95% confidence interval.

In order to ensure all estimates of sex-differences were solely comparing vaccine-induced responses, participants were only included if the vaccine received (experimental or routine) contained the antigen for analysis. Control groups receiving no vaccine or an alternative vaccine which did not contain the antigen of analysis were therefore excluded.

Due to the instability of models for binary data, particularly when the proportions of events are very high or very low, analyses of proportions were conducted as unadjusted two-stage random effects meta-analyses [17], with results presented as weighted risk differences.

Analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA). Two-stage meta-analyses of proportions were conducted using Stata version 13.0 (StataCorp, Texas, USA).

3. Results

3.1. Included studies

There were nine studies and 2378 children with data available for inclusion in the meta-analysis, of which 47% were female (Table 1). Information was available from six studies in which infants and children were randomised to receive different regimens of meningococcal vaccines [18–25], two studies in which pneumococcal vaccines were compared [26,27], and one study which was designed to assess the effect of different needle sizes in the delivery of routine vaccinations [28]. Seven studies were solely conducted in the UK, one study was conducted in the UK and Malta [22,23], and one study was conducted in Nepal [26]. Vaccines administered during the studies are detailed in supplementary Table 1. All trials which contributed to each analysis are listed in supplementary Tables 2–4.

The ratio of female to male infants in each study ranged from 0.69 to 1.03 with only one study having more females than males. For studies in which infants were enrolled at two months of age or younger, the ratio of female to male infants enrolled was 0.92, broadly reflecting the sex ratio at birth in the UK which is 0.95 [29] (Table 2).

3.2. Meningococcal vaccines

Seven trials were available in which capsular group C meningococcal vaccines were administered in prime-boost combinations either as the study vaccine of interest or as a routine vaccine given concomitantly (trials #1–6, 8) [18–25,28]. Immunological parameters (immunoglobulin (IgG), serum bactericidal assay (using rabbit or human complement) (rSBA, hSBA), and memory B cells) were measured post priming (at 5 months of age) and pre- and post-boost (12 and 13 months of age). The ratio of responses in girls compared with boys was close to 1.0 for most parameters and time points, and no significant sex-dependent differences were observed (Fig. 1, supplementary Table 2). Geometric mean ratios ranged from 0.91 to 1.18.

For capsular group A, W and Y meningococcal vaccines, two trials were available in which hSBA titres were measured (trials #3 and 4) [19,24,25]. Female/male response ratios ranged from 1.05 to 1.43 thus all point estimates favoured higher responses in girls. Significant differences were observed for responses to capsular groups A and Y at 5 months (1.33; 95% CI 1.00–1.77 and 1.43; 1.02–2.00 respectively); W and Y at 12 months (1.34; 1.02–1.78 and 1.43; 1.07–1.91 respectively); and capsular group A at 13 months of age (1.35; 1.00–1.83) (Fig. 1, supplementary Table 2).

3.3. Diphtheria toxoid vaccine

Seven trials were available in which IgG or memory B cell responses to diphtheria toxoid vaccination were measured (trials #1–3, 6–8) [18,20–28]. Antibody responses to diphtheria toxoid were significantly higher in girls compared with boys at 12 months (pre-boost) (1.28; 1.05–1.58) (Fig. 2, supplementary Table 2).

3.4. Tetanus toxoid and Haemophilus influenzae b vaccine

IgG or memory B cell responses to tetanus toxoid vaccination were available from six trials (#2, 3, 5–8) [18,21–25,27,28] and responses to *Haemophilus influenzae* type b (Hib) vaccination in four trials (#3, 5, 6, 8) [21–25,28]. There were no significant differences between girls and boys for these antigens at any time point (Fig. 2, supplementary Table 2).

3.5. Pneumococcal conjugate vaccines

Serotype-specific pneumococcal antibody concentrations were measured in three studies administering 10- or 13-valent pneumococcal conjugate vaccine as either the study vaccine or as a routine vaccine given concomitantly (#6, 7, 9) [22,23,26,27]. Opsonophagocytic activity (OPA) was measured in two of these studies (#7, 9). Response to vaccination was assessed one month following the priming series (at ~4–5 months of age) and at one month post