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

Running head: Sex-differences in immune responses.

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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.

Keywords: antibody, memory B cells, sex-differences, infant, vaccine, individual participant data, meta-analysis

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].

Women carry two X chromosomes which contain many genes involved in immune response mechanisms [13, 14], and sex-hormones are believed to influence protection [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.

Methods:

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-specific responses were measured.

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).

Results

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 to 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).

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 (figure 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) (figure 1, supplementary table 2).

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) (figure 2, supplementary table 2).

Tetanus toxoid and *Haemophilus influenzae* b vaccine

IgG or memory B cells 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 (figure 2, supplementary table 2).

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 booster vaccination (at ~10-13 months of age). Antibody persistence was measured pre-booster (at 9 or 12 months of age) and one year following the booster (at 24 months of age). Antibody persistence was greater in girls compared with boys for all serotypes, with statistically significant differences observed for eight serotypes prior to boosting and nine serotypes at one year following the booster. Significant differences were also observed for five serotypes at one month after the priming series. The antibody response to only one serotype (6B) was significantly higher in girls compared with boys one month post-booster (figure 3, supplementary table 3).

Fewer data were available for assessment of OPA thus confidence intervals for estimates were wide, however a similar consistent pattern of point estimates which were mostly higher in girls was observed (supplementary table 4, supplementary figure 1).

An analysis of the proportions of children with serotype-specific IgG ≥ 0.35 μg/mL showed that the persistence against serotypes 1, 6B, 19F and 23F was greater for females at 10-12 months (pre-boost), with differences of between 6% to 15%. Antibody persistence against serotype 18C was also significantly higher in females at one-year post booster (supplementary table 5). With the exception of serotypes 6B and 23F, proportions of children with IgG ≥ 0.35 μg/mL at one month after vaccination (either prime or boost) were consistently high and therefore differences in proportions were undetectable.

Discussion:

Biological sex has a pervasive influence on immune responses as documented by a large body of literature on infections and autoimmune diseases. The incidence of almost all autoimmune diseases is higher in women [30], with, for example, incidence rates of hyperthyroidism and multiple sclerosis approximately twice as high as for men [30, 31]. Conversely, higher rates of some childhood infections occur in males: for example, incidence of both bacterial and viral meningitis in children is higher in males than females [31, 32]. Furthermore, bacterial meningitis and septicaemia rates (especially Gram negative infection) were higher in male than in female newborns,[33] children,[34] and in boys under five years of age [35, 36]. A meta-analysis of serogroup-specific pneumococcal disease cases revealed that pneumococcal isolates were 1.8 times more frequently found in males across all serogroups [37].

To the extent that biological sex is not practically modifiable in the context of immunisation programs its contribution to variation in immune response has been relatively neglected. However, sex biases can reveal important insights into mechanisms of immunogenicity and have practical implications for vaccine licensing, efficacy and related adverse events. Previous literature reviews on vaccine responses have mainly summarised data from adults or older-children rather than infants receiving a primary course of immunisation and reveal a general pattern of higher humoral responses in females [3, 5, 38, 39]. Our analysis is the first individual participant data meta-analysis of infant vaccine studies undertaken with the specific aim of investigating whether vaccine immunogenicity is affected by biological sex. Overall, for all vaccines and all measures of immunogenicity, female responses were either higher than or equivalent to males and there were no instances where male responses were significantly higher than those in females.

The clinical relevance of such differences in immune response is unclear. Important factors to consider in the current analyses are i) the magnitude of the difference, ii) the relationship between immune response and correlates of protection, iii) the importance of herd immunity in addition to direct protection and iv) that the immune responses as measured by B-cell assays may only be surrogates of more important T-cell responses or responses at mucosal surfaces where infection occurs.

For most outcomes, responses were higher in females than in males. The largest differences were seen in pneumococcal serotype-specific OPA where 2- to 3- fold higher responses in girls were observed for some serotypes. Such differences could be considered clinically relevant; however,

greater responses to vaccination in female infants do not necessarily imply increased direct protection if responses for both sexes are higher than the required thresholds for protection against disease. For some vaccine-induced responses, thresholds have been determined whereby assay values above the threshold are generally thought to provide protection against disease [40, 41] Our analysis of pneumococcal antibodies revealed that there were some significant differences in GMRs that did translate into significant differences in the proportions with IgG ≥ 0.35 μg/mL. This provides some insight into differences between the sexes in the proportions with assumed protection against disease however immune correlates of protection tend to vary by serotype and assay, and for some assays there are no agreed thresholds [42].

With the exception of tetanus, all vaccines included in this analysis rely, to some extent, on herd protection rather than direct protection to guard against disease and thus male infants (and the unvaccinated population in general) still benefit from higher humoral responses in females. The relative differences reported here, for a mostly UK population, will have different clinical relevance when applied to other countries.

There is a strong biological basis for sex-based differences in the immune system in response to pathogen exposure, infection and vaccination [14, 15, 43]. In general biological sex is determined by the presence or absence of the Y-chromosome whose expression of the *sry* gene in early foetal development results in the formation of testes rather than the default program which is to produce ovaries. The mechanisms underlying any effect of sexual dimorphism are complex and may arise from i) Y-chromosome genes other than *sry* (around 200 genes are present), ii) the radically different hormonal environment of the male versus the female from foetal life through infancy and beyond, iii) behavioural and environmental differences between

the sexes which may stem from genetic, hormonal or social factors and iv) the potential advantage of a diploid versus haploid state for the X-chromosome in females. Mediators of these differences may operate through a large variety of pathways and on different time scales. For instance the influence of the genetic and hormonal environment *in utero* may leave epigenetic differences on autosomal chromosomes that have effects at more remote time-points postnatally[44].

One of the most well-established mechanisms for differences in immunity is the sex-hormone milieu. Oestrogen and androgen receptors are present in a wide-range of immune cells and the immunosuppressive nature of androgens are established [14, 15]. Due to a variable distribution of oestrogen receptor subtypes on the immune cells and the exposure to different concentrations of oestrogens, the effect of oestrogen on different aspects of immune function can be variable whereas the effect of progesterone on immune function is thought to be mainly suppressive [3]. The concentrations of both hormones increases during pregnancy with an associated shift towards a more T helper cell type 2 (Th2) phenotype by the third trimester and an associated increased susceptibility to viral infections including influenza and varicella.

Previous work has found that immune responses following vaccination are different between the sexes. Following yellow fever vaccination, the number of differentially expressed genes of the innate immune system was much greater in women than men with notable differences in induction of Toll-like receptor-interferon signalling [3]. Sex-dependent differences in the immune response to vaccination might also result from differences in expression of immune genes located on the X chromosome, and are associated with certain X-linked primary immunodeficiencies. Toll-like receptors (TLR) 7 and 8 are both located on the X chromosome

and recognise viral single-stranded RNA. Although it is unknown whether these genes have an effect on the responses to vaccines, it is possible that differential expression of TLR 7/8 through failure of X inactivation may enhance antiviral responses [45].

Whilst there appear to be a variety of mechanisms, there are clearly vaccine antigens for which there are no sex-differences. We observed no sex-differences in response to tetanus vaccines nor in response to Hib vaccines (which are often conjugated to a tetanus toxoid). The majority of meningococcal and pneumococcal vaccines administered in these studies were conjugated to a mutant diphtheria cross-reacting material (CRM_{197}). The consistent pattern for greater responses in females seen following immunisation with meningococcal, pneumococcal and diphtheria vaccines, but not seen for tetanus and Hib, may suggest a sex-differential effect of the carrier protein. There exists a complicated interplay of effects of different carrier proteins for different antigens in crowded immunisation schedules administering multiple vaccines in combination [46].

The findings in this report have important implications for future randomised trials. It is important that trials of new vaccines are designed to compare immune responses according to sex, and in situations where vaccine responses have been convincingly shown to be higher in females, demonstrate that sufficient protection is provided in males independently.

There are limitations to the analyses detailed herein. Trials combined in these analyses tested different vaccines and there were variations in trial procedures. Although trials included in these analyses were designed to answer different questions and comparisons between trials would not

be valid, comparisons between sexes within trials can be combined in an unbiased manner. Heterogeneity between trials is more likely to introduce 'noise' into calculations and obscure detection of true differences rather than induce bias.

Multiple comparisons are an issue in meta-analyses as type 1 error rates become inflated and false positive findings can result. However, the findings of this analysis when viewed in their entirety, are generally consistent in direction and magnitude and point to underlying biological effects which result in higher immunological responses in females. Although this is the first meta-analysis designed to assess sex-differences in vaccine-specific responses, limited data were available for some vaccine antigens. This results in low statistical power and wide confidence intervals for some comparisons therefore meta-analyses of larger numbers of studies are still needed.

Reporting bias is an important consideration in this field as characterising differences between female and male responses is not usually an aim of any vaccine trial and the post-hoc investigation of subgroup differences is not good practice due to the lack of statistical power. Thus sex-differential results are either not assessed in most trials or not generally reported which, although appropriate, hampers the relevance of literature-based reviews. Although our policy is to publish all results from clinical trials, the publication of analyses according to subgroups which were not the original intent of the study is not undertaken. Here, we have systematically analysed individual participant data from all our available studies and publish results of significant and non-significant analyses concurrently.

While the possibilities of "personalised vaccination" [47] are currently remote, a detailed understanding of the influence of biological sex on immunogenicity could potentially allow the utilisation of these effects in order to optimise protection through routine immunisations. However, only with sufficient high-quality evidence will it be feasible to fully evaluate whether further improvements can be made to current routine infant vaccination schedules, which have well-established and significant public health benefits [48], preventing an estimated 2 million child deaths every year [49].

Footnotes:

Contributions

CISB wrote the initial draft. MV analysed the data, prepared the figures, and wrote the second draft which was reviewed and edited by MDS, DFK, JT and AJP. All authors reviewed and approved the final manuscript prior to submission.

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Declarations of interests

AJP has previously conducted studies on behalf of Oxford University funded by vaccine manufacturers, but currently does not undertake industry funded clinical trials. AJP chairs the UK Department of Health's (DH) Joint Committee on Vaccination and Immunisation (JCVI); the views expressed in this manuscript do not necessarily reflect the views of JCVI or DH.

MDS acts as chief or principal investigator for clinical trials conducted by the University of Oxford, sponsored by vaccine manufacturers, but receives no personal payments from them. MDS has participated in advisory boards and industry sponsored symposia for vaccine manufacturers, but receives no personal payments for this work. MDS, DFK and JT have received financial assistance from vaccine manufacturers to attend scientific conferences. The other authors have no conflicts of interest.

Role of the funding source

No specific funding was obtained for this work. Salary support for two authors (MDS, DFK) was provided by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, which had no role in the analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and was responsible for the decision to submit the paper for publication. CISB is grateful to the Oxford University Clinical Academic Graduate School for support and is now funded as a Clinical Research Fellow by the Global Research in Paediatrics Network of Excellence (GRiP), part of the European Union Seventh Framework Programme (FP7/2007–2013, Grant Agreement number 261060). MV is funded through a NIHR Doctoral Research Fellowship.

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Table 1: Details of included studies

Study number	*Full study title*	*Sponsor*	*Ref*
1	A Phase II Randomised Comparison to Determine the Safety and Immunogenicity of a Conjugate Vaccine Combination containing Meningococcal Group C & Pneumococcal capsular Polysaccharide – CRM197 conjugate, given concurrently with DTP/Hib in healthy infants (D139-P502)	Chiron S.r.l. Via Fiorentina, 1 53100 Siena, Italy	[20]
2	A Phase IV, Single Centre, Open-label Study to Investigate the Kinetics of the B Cell Response to the C Saccharide Component of Chiron's Meningococcal C Conjugate Vaccine (Menjugate) Administered to Healthy Children at least 12 months of Age After Priming with Menjugate at 2, 3 and 4 Months of age. (2004-004962-33)	Chiron S.r.l. Via Fiorentina, 1 53100 Siena, Italy	[18]
3	A Phase II, Randomized, Open label, Controlled, Multicenter Study to Evaluate the Safety, Immunogenicity and Induction of Immunological Memory after Two or Three Doses of Chiron Meningococcal ACWY Conjugate Vaccine Administered to Healthy Infants at 2, 3, 4 or 2, 4, 6 Months of Age (NCT00262002)	Chiron S.r.l. Via Fiorentina, 1 53100 Siena, Italy	[24, 25]
4	A Phase II, Single Centre, Open-label, Randomized Study to Investigate Meningococcal Serogroup A, C, W-135 and Y Saccharide Specific B Cell Response to a Primary and a Booster Course of the Novartis Meningococcal ACWY Conjugate Vaccine in Healthy Infants (NCT00488683)	Novartis Vaccines and Diagnostics Srl Via Fiorentina, 1 53100 Siena, Italy	[19]
5	Double blind, randomised controlled trial of the immunogenicity and tolerability of a meningococcal group C conjugate vaccine (D110-500)	Wyeth – Lederle Vaccines	[21]
6	An open label randomised controlled study to evaluate the induction of immune memory following infant vaccination with a glyco-conjugate Neisseria meningitidis serogroup C vaccine and to assess the immune response to the concurrent infant routine immunisations administered in consistent versus alternating limbs (2009-016579-31)	University of Oxford	[22, 23]

7	A phase III randomised, open label clinical trial evaluating the immunogenicity of a 10-valent pneumococcal conjugate vaccine booster compared to the standard 13-valent pneumococcal conjugate vaccine booster given at 12 months of age to healthy children who have received the 13-valent pneumococcal conjugate vaccine at 2 and 4 months of age. (NCT01443416)	University of Oxford	[27]
8	Effect of needle size on serum antibody responses and incidence of local reactions following routine immunisation in infants - a randomised controlled trial.	University of Oxford	[28]
9	A randomised open-label immunogenicity study of a 10 Valent Pneumococcal vaccine. (PCV10) given as part of the routine infant immunisation schedule to children in Kathmandu, Nepal. (ISRCTN56766232)	University of Oxford	[26]

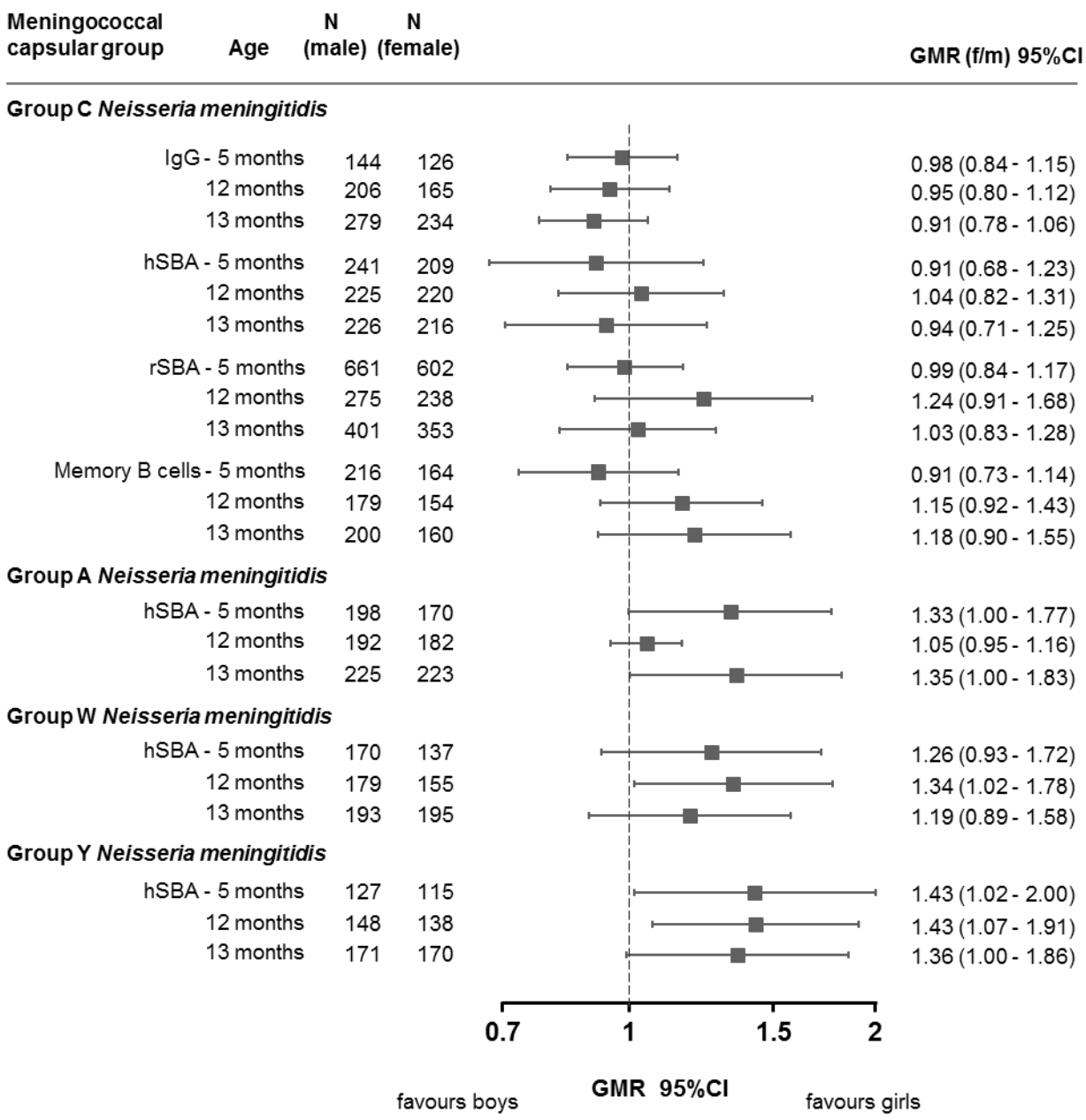
Table 2: Details of infants included the analysis

Study number	*Year enrolment commenced*	*Number girls/ number boys (ratio)*	*Age at enrolment*	*Ages at vaccination*
1	2000	51/74 (0.69)	12 months	12 months
2	2005	16/17 (0.94)	2 months	2,3,4 months
3	2004	157/152 (1.03)	2 months	2,3,4 months
4	2007	95/109 (0.87)	2 months	2,3,4 months
5	1997	108/123 (0.88)	2 months	2,3,4 months
6	2010	210/229 (0.92)	2 months	2,3,4 + 12 months
7	2012	50/75 (0.67)	12 months	12 months
8	2002	336/360 (0.93)	2 months	2,3,4 months

9	2010	98/118 (0.83)	6 weeks	6,14 weeks + 9 months, or 6,10,14 weeks
TOTAL		1121/1257 (0.89)		

Figure Legends

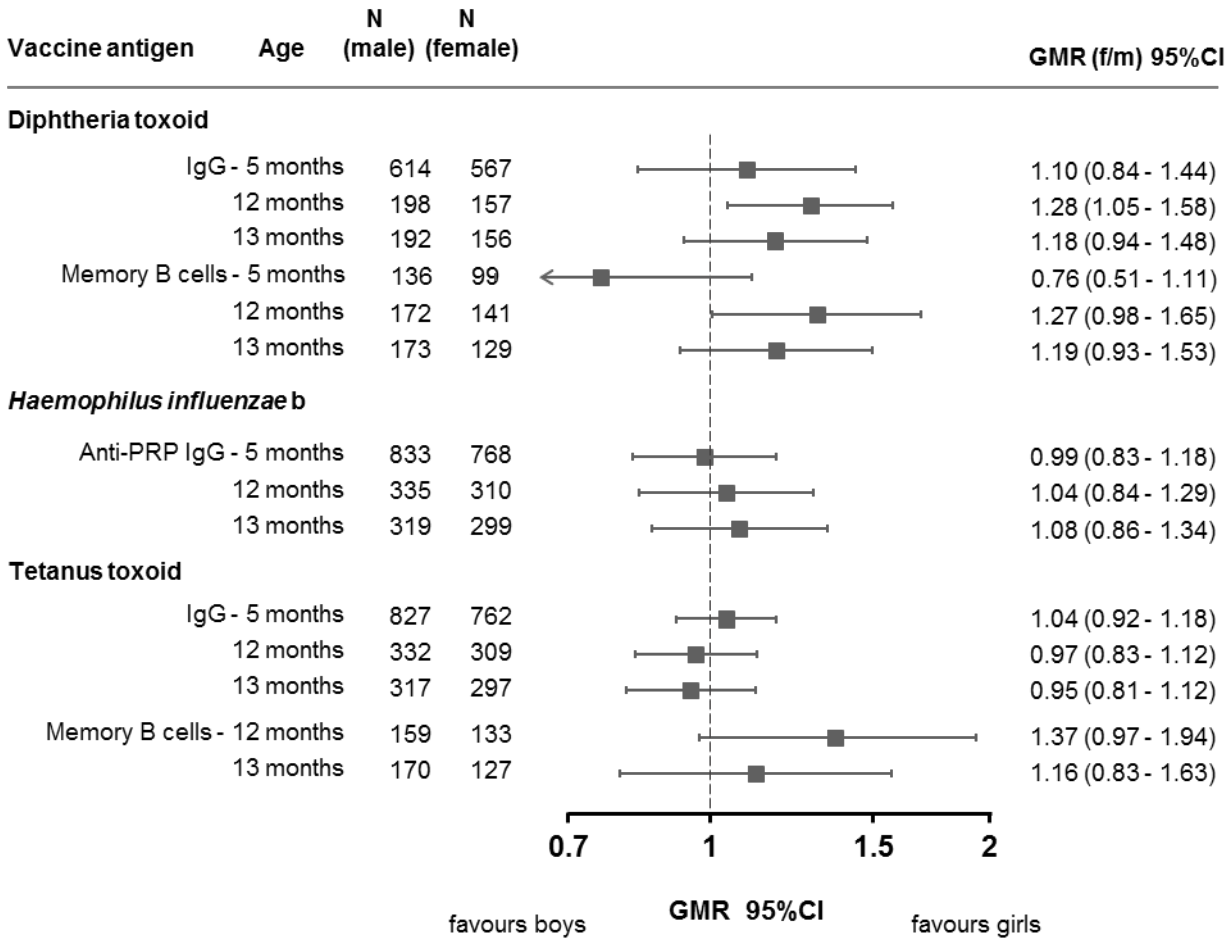
Figure 1 Female-male geometric mean ratios (95% CI) of serotype-specific immunogenicity from meta-analyses of meningococcal vaccines in infants.



Each point estimate represents the summary GMR from one meta-analysis. Lines indicate 95% confidence intervals. A GMR of 1.0 represents no difference in responses between females and males. 5 months = one-month post-prime, 12 months = pre-boost, 13 months=one-month post-boost, 24 months = persistence at one year post-boost.

hSBA: serum bactericidal assay (human complement), rSBA: serum bactericidal assay (rabbit complement), IgG: immunoglobulins, GMR: geometric mean ratio (female/male)

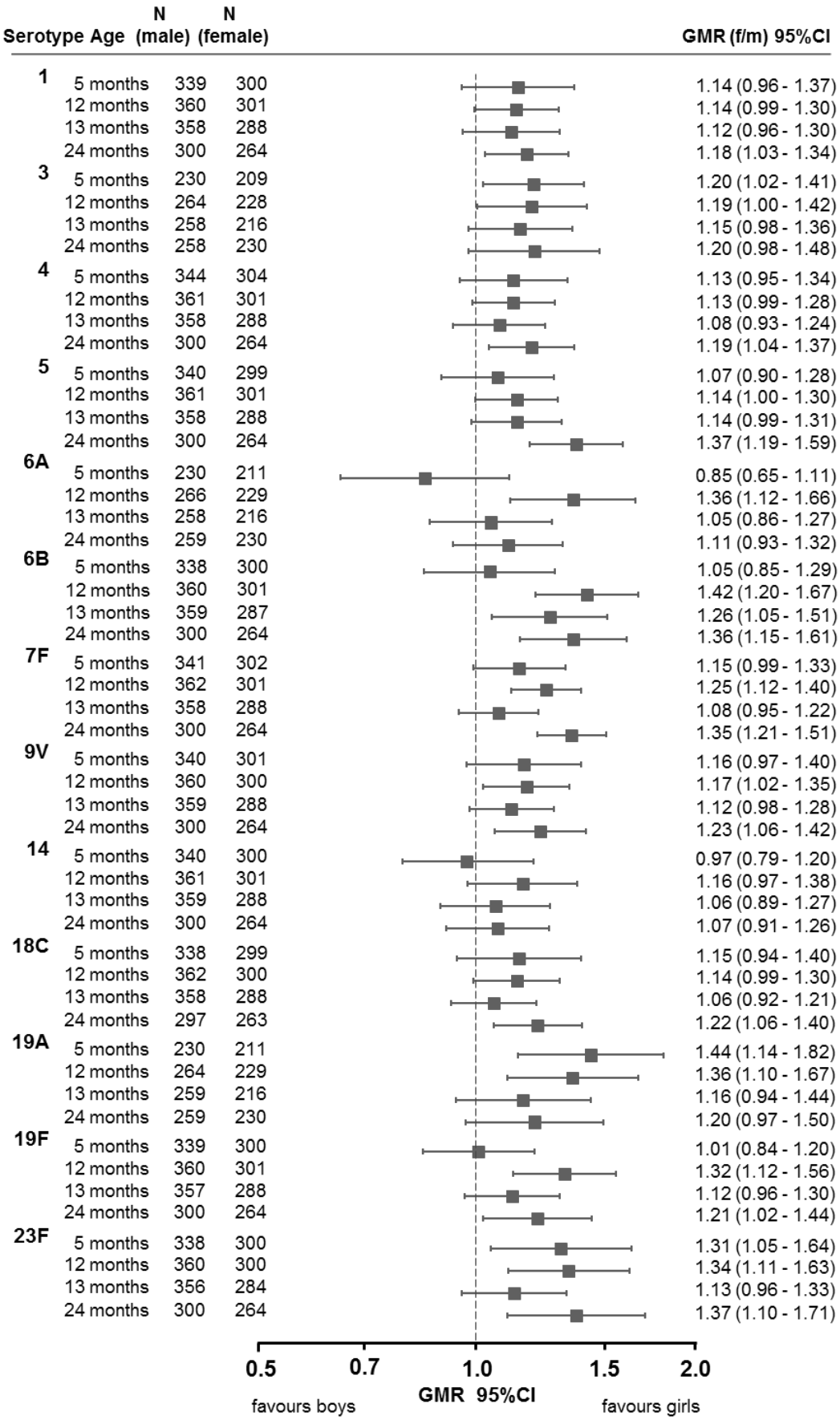
Figure 2 Female-male geometric mean ratios (95% CI) of serotype-specific immunogenicity from meta-analyses of diphtheria toxoid, tetanus toxoid and *Haemophilus influenzae* type B vaccine-induced responses in infants.



Each point estimate represents the summary GMR from one meta-analysis. Lines indicate 95% confidence intervals. A GMR of 1.0 represents no difference in responses between females and males. 5 months = one-month post-prime, 12 months = pre-boost, 13 months= one-month post-boost, 24 months = persistence at one year post-boost.

PRP: Polyribosylribitol phosphate, IgG: immunoglobulins, GMR: geometric mean ratio (female/male)

Figure 3 Female-male geometric mean ratios (95% CI) of serotype-specific immunoglobulins from meta-analyses of pneumococcal vaccines in infants.


Serotype
Age
N (male)
N (female)
GMR (f/m) 95%CI
1
5 months 339 300 1.14 (0.96 - 1.37)
12 months 360 301 1.14 (0.99 - 1.30)
13 months 358 288 1.12 (0.96 - 1.30)
24 months 300 264 1.18 (1.03 - 1.34)
3
5 months 230 209 1.20 (1.02 - 1.41)
12 months 264 228 1.19 (1.00 - 1.42)
13 months 258 216 1.15 (0.98 - 1.36)
24 months 258 230 1.20 (0.98 - 1.48)
4
5 months 344 304 1.13 (0.95 - 1.34)
12 months 361 301 1.13 (0.99 - 1.28)
13 months 358 288 1.08 (0.93 - 1.24)
24 months 300 264 1.19 (1.04 - 1.37)
5
5 months 340 299 1.07 (0.90 - 1.28)
12 months 361 301 1.14 (1.00 - 1.30)
13 months 358 288 1.14 (0.99 - 1.31)
24 months 300 264 1.37 (1.19 - 1.59)
6A
5 months 230 211 0.85 (0.65 - 1.11)
12 months 266 229 1.36 (1.12 - 1.66)
13 months 258 216 1.05 (0.86 - 1.27)
24 months 259 230 1.11 (0.93 - 1.32)
6B
5 months 338 300 1.05 (0.85 - 1.29)
12 months 360 301 1.42 (1.20 - 1.67)
13 months 359 287 1.26 (1.05 - 1.51)
24 months 300 264 1.36 (1.15 - 1.61)
7F
5 months 341 302 1.15 (0.99 - 1.33)
12 months 362 301 1.25 (1.12 - 1.40)
13 months 358 288 1.08 (0.95 - 1.22)
24 months 300 264 1.35 (1.21 - 1.51)
9V
5 months 340 301 1.16 (0.97 - 1.40)
12 months 360 300 1.17 (1.02 - 1.35)
13 months 359 288 1.12 (0.98 - 1.28)
24 months 300 264 1.23 (1.06 - 1.42)
14
5 months 340 300 0.97 (0.79 - 1.20)
12 months 361 301 1.16 (0.97 - 1.38)
13 months 359 288 1.06 (0.89 - 1.27)
24 months 300 264 1.07 (0.91 - 1.26)
18C
5 months 338 299 1.15 (0.94 - 1.40)
12 months 362 300 1.14 (0.99 - 1.30)
13 months 358 288 1.06 (0.92 - 1.21)
24 months 297 263 1.22 (1.06 - 1.40)
19A
5 months 230 211 1.44 (1.14 - 1.82)
12 months 264 229 1.36 (1.10 - 1.67)
13 months 259 216 1.16 (0.94 - 1.44)
24 months 259 230 1.20 (0.97 - 1.50)
19F
5 months 339 300 1.01 (0.84 - 1.20)
12 months 360 301 1.32 (1.12 - 1.56)
13 months 357 288 1.12 (0.96 - 1.30)
24 months 300 264 1.21 (1.02 - 1.44)
23F
5 months 338 300 1.31 (1.05 - 1.64)
12 months 360 300 1.34 (1.11 - 1.63)
13 months 356 284 1.13 (0.96 - 1.33)
24 months 300 264 1.37 (1.10 - 1.71)
0.5
0.7
1.0
1.5
2.0
GMR 95%CI
favours boys
favours girls

Each point estimate represents the summary GMR from one meta-analysis. Lines indicate 95% confidence intervals. A GMR of 1.0 represents no difference in responses between females and males. 5 months = one-month post-prime, 12 months = pre-boost, 13 months = one-month post-boost, 24 months = persistence at one year post-boost.

IgG: immunoglobulins, GMR: geometric mean ratio (female/male)

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