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Differences by sex in IgG levels following infant and childhood vaccinations: An individual participant data meta-analysis of vaccination studies

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ABSTRACT

Background: If immune responses to vaccination differ between males and females, sex-specific vaccination schedules may be indicated. We systematically reanalysed childhood vaccination studies conducted in The Netherlands for sex-differences in IgG-responses. To assess the impact of potential sex-differences in IgG-responses, we explored sex-differences in vaccine failure/effectiveness and reactogenicity.
Methods: Six studies with IgG-measurements for 1577 children following infant pneumococcal (PCV7/PCV10/PCV13) and/or DTaP-IPV-Hib(-HepB) vaccinations, or the pre-school DTaP-IPV booster were included. We performed one-stage individual participant data meta-analyses per time-point of the effect of sex on IgG levels against pneumococcal serotypes, diphtheria toxoid, tetanus toxoid, pertussis Ptx/FHA/Prn and Hib-PRP using linear mixed models. Using existing study data, we compared reactogenicity after PCV7/PCV10 and DTaP-IPV-Hib(-HepB) vaccination in girls and boys. Vaccine failure/effectiveness was compared between girls and boys for invasive pneumococcal disease (IPD), invasive Hib disease and pertussis using notification data.
Results: For pneumococcal vaccination, the geometric mean concentration ratio of IgG levels in girls versus boys pooled across serotypes was 1.15 (95%CI 0.91–1.45) 1 month following the primary series, 1.16 (1.02–1.32) at age 8 months, 1.12 (1.02–1.23) pre-booster (age 11 months) and 0.99 (0.89–1.10) post-booster (age 12 months). Diphtheria toxoid, tetanus toxoid, pertussis Ptx/FHA/Prn and Hib-PRP IgG levels did not differ between girls and boys, except for Hib post-booster (1.24; 95%CI 1.01–1.52) and tetanus before pre-school booster (0.71; 0.53–0.95). We found no difference between boys and girls in reactogenicity at age 4 or 11 months or in vaccine failure/effectiveness for IPD, invasive Hib disease or pertussis.
Conclusion: For most vaccine antigens investigated, there were no consistent differences in vaccine-induced IgG levels. Vaccine-induced pneumococcal IgG levels were slightly higher in girls, but only between the primary series and the 11-month booster. These results, along with similar reactogenicity and vaccine failure/effectiveness, support the uniform infant vaccination schedule in the Dutch national immunisation programme.

1. Background

Childhood immunisation programmes are generally uniform programmes for all children, based on the assumption that vaccinating all children similarly ensures individual protective antibody levels and the necessary levels for herd immunity. However, susceptibility to numerous childhood infectious diseases differs between girls and boys. For example, boys are more susceptible to pneumococcal disease (both before and after introduction of infant pneumococcal vaccinations) [1], whereas girls are more susceptible to pertussis [2,3]. Furthermore, differences between males and females in both innate and adaptive immunity have been

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found to exist from infancy until old age [4]. These differences could be due to genetic and hormonal factors, as well as environmental factors such as nutritional status and infectious disease burden [4,5]. Underlying immunological differences between the sexes may also result in differential immune responses to vaccination. Should it become evident that substantial differences in the protection induced by vaccination exist, sex-specific vaccination schedules may need to be considered to achieve equal protection for girls and boys.

Until recently, the available evidence regarding possible sex-differences in IgG levels following vaccination consisted of sporadic reports of sex-specific IgG levels in vaccination studies and reviews thereof [6–8]. These reviews included some studies conducted in children/adolescents on vaccines commonly included in childhood vaccination programmes. However, they might be affected by selective reporting of results within the reviewed studies, and by publication bias. The first study which is not likely to be affected by these issues is a recent individual participant data meta-analysis performed using data from vaccine trials carried out by one UK research centre. It found higher levels of diphtheria toxoid IgG, higher meningococcal group A, W and Y serum bactericidal titers and higher pneumococcal serotype-specific IgG and opsonophagocytosis in girls than in boys at one or more measurement time points (5 months, 12 months, 13 months or 24 months) [9]. No differences were found in diphtheria toxoid memory B-cells, *Haemophilus influenzae* type b (Hib) anti-PRP IgG, tetanus toxoid IgG or memory B-cells, or meningococcal serogroup C (MenC) IgG, serum bactericidal MenC titer or MenC memory B-cells [9].

In this study we aimed to investigate whether we could confirm the results of the UK meta-analysis on antibody levels/responses in a different population and for other pathogens. To this aim, we systematically reanalysed clinical childhood vaccination studies conducted by the National Institute for Public Health and the Environment (RIVM) in The Netherlands [10–15]. We assessed whether antigen-specific IgG levels between girls and boys differ following infant pneumococcal (PCV7/PCV10/PCV13) and DTaP-IPV-Hib(-HepB) vaccinations and pre-school DTaP-IPV booster vaccination. Furthermore, we broadened the scope of the study by studying sex-differences in vaccine failure/effectiveness and reactogenicity of the same vaccines.

2. Methods

2.1. Study data

2.1.1. Vaccine studies (IgG data)

Clinical vaccination studies conducted by the RIVM in The Netherlands from 2005 onwards were eligible for inclusion. Further inclusion criteria were availability of information on gender and availability of measurements of IgG levels specific for antigens currently included in the Dutch National Immunisation Programme. For each included study, information on the study design, time of enrolment, numbers of girls and boys, vaccinations received, available IgG measurements and measurement time-points and technique per study was collected (Supplementary Table 1). For infant vaccination studies, only children vaccinated with acellular pertussis vaccines were included. In a study investigating the 4-year booster vaccination including acellular pertussis, children primed with whole-cell pertussis during their first year of life were also included.

2.1.2. Surveillance data

From data collected by The Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM, Amsterdam, The Netherlands) we extracted cases of invasive pneumococcal disease (IPD) up to May 2016 for vaccine-eligible cohorts (PCV7: born from 01-04-2006 onwards; PCV10: born from 01-03-2011 onwards). We also extracted cases of invasive Hib disease from 2003 up to May 2016 for vaccine-eligible cohorts (born 1993 onwards).

From the Dutch registration system for notifiable diseases we extracted cases of pertussis among cohorts eligible for vaccination with acellular pertussis only (born from 01-11-2004 onwards; notifications from 2006 until May 2016).

2.1.3. Reactogenicity study

The study population has been described in detail elsewhere (Kemmeren et al, submitted). Briefly, children were vaccinated at 2, 3, 4 and 11 months with PCV7 and DTaP-IPV-Hib (cohort 1), PCV10 and DTaP-IPV-Hib (cohort 2), or PCV10 and DTaP-IPV-Hib-HepB (cohort 3). For the current analysis, we used data of the 3rd and 4 th vaccination (age 4 and 11 months respectively, corresponding to IgG measurements in the included vaccination studies) on local reactions (swelling, redness and/or pain) and fever (temperature $\geq$38 °C) measured the week after vaccination. We did not use data on other (less objectively measurable) systemic adverse events. PCV7 or PCV10 vaccinations were administered in the right leg, and DTaP-IPV-Hib or DTaP-IPV-Hib-HepB was administered in the left leg, allowing local reactions to these vaccinations to be distinguished.

2.2. Statistical analyses

2.2.1. IgG data

One-stage individual participant data meta-analyses were performed per antigen, per measurement time-point. Time-points were: post primary series (age 5–7 months), age 8 months, before 11 month booster, after 11 month booster (age +/- 12 months), before pre-school booster (age 3-4yrs: diphtheria and tetanus) and after pre-school booster (age 4 years: pertussis, diphtheria and tetanus). Analyses were performed using linear-mixed models with log-transformed IgG levels as the outcome variable with sex as a fixed effect. A fixed effect for group within a study (henceforth to be referred to as study-group) was included to account for differences between these study-groups in vaccination type and schedule and in IgG measurement technique. A random slope for sex per study-group was included to allow for heterogeneity.

The coefficient for sex with the corresponding 95% CI bounds was back-transformed to obtain geometric mean concentration ratios (GMC ratios) with 95% CI of the IgG levels in girls compared to boys. The GMC ratios for girls versus boys should be interpreted as the average ratios across study-groups (due to the random slope) [16].

Measurements 1 week and 1 month after the 11-month booster were combined, measurements at age 3 years and age 4 years before the pre-school booster were combined, and measurements 10 days and 28 days after the pre-school booster were combined to reduce the number of subgroups. A small group of individuals had a measurements 1 week and 1 month post-booster: a random intercept for individual and a fixed effect for time since booster were therefore included for this time-point.

For pneumococcal vaccination, serotype-specific analyses were performed for all PCV13-serotypes, excluding subjects vaccinated with PCV7 or PCV10 for the serotypes not included in their vaccinations. Further, an analysis pooled across serotypes was performed as a summary measure. In this analysis, a fixed effect for serotype and a random intercept for individual were added to the model.

For the post-4y-booster time-point, children for whom there was no record for the 4y booster vaccination were excluded. Although measurements of IgG against pertussis antigens were also performed in the children aged 3/4y (before booster), we did

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