A Randomized Trial assessing the immunogenicity and reactogenicity of two hexavalent infant vaccines concomitantly administered with group B meningococcal vaccine.

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**Abstract**

**Background**

Four hexavalent (DTaP-IPV-Hib-HepB) vaccines are licensed in Europe, only one of which (Vaxelis, Hex-V), uses a meningococcal outer membrane protein complex as a carrier protein for *Hemophilus influenza* type b (Hib), creating potential interactions with the meningococcal vaccine 4CMenB.

**Methods**

In this single-center open-label randomized trial, infants were randomized in a 1:1 ratio to receive Hex-V or an alternative hexavalent vaccine (Infanrix-Hexa, Hex-IH) at 2, 3 and 4 months with 4CMenB (2, 4, 12 months) in the UK routine immunization schedule. The primary outcome was non-inferiority of geometric mean concentrations (GMCs) of anti-PRP (Hib) IgG at 5 months of age. Secondary outcomes included safety, reactogenicity, and immunogenicity of other administered vaccines measured at 5 and 13 months of age.

**Results**

Of the 194 participants enrolled, 96 received Hex-V and 98 Hex-IH. Non-inferiority of anti-PRP IgG GMCs at 5 months of age in participants receiving Hex-V was established; GMCs were 23-times higher following 3 doses of Hex-V than 3 doses of Hex-IH (geometric mean ratio (GMR) 23.25; one-sided 95% CI 16.21, -). 78/85 (92%) of Hex-V recipients and 43/87 (49%) of Hex-IH recipients had anti-PRP antibodies ≥1.0 μg/ml. At 5 months of age serum bactericidal activity titers against MenB strain 5/99 were higher following Hex-V than Hex-IH (GMR 1.56; 95% CI 1.13-2.14),. The reactogenicity profile was similar in both groups.

**Conclusions**

These data support flexibility in the use of either Hex-IH or Hex-V in infant immunization schedules containing 4CMenB, with the possibility that Hex-V may enhance protection against Hib.

## Introduction

In 2017 the UK added immunization against Hepatitis B into the routine infant vaccine schedule by replacing the existing pentavalent vaccine (diphtheria, tetanus, acellular pertussis, polio and *Hemophilus influenza* type B; DTaP-IPV-Hib) with a hexavalent vaccine (DTaP-IPV-Hib-HepB). This vaccine is administered at 2, 3 and 4 months of age, in a schedule that also includes the capsular group B meningococcus vaccine 4CMenB (Bexsero, GlaxoSmithKline, Rixensart, Belgium).[1]

While co-administration of 4CMenB and one of the available hexavalent vaccines for use in the UK, Infanrix Hexa (Hex-IH, GlaxoSmithKline, Rixensart, Belgium) has been extensively studied,[2,3] no data are available on concomitant use of 4CMenB and the hexavalent vaccine, Vaxelis (Hex-V, MCM Vaccines, Leiden, Netherlands). Previous head-to-head studies of these vaccines conducted in the absence of 4CMenB suggested that a primary immunization course of Hex-V was more immunogenic than Hex-IH against *Hemophilus influenza* type b (Hib), while after a fourth (booster) dose the reverse was true [14–6].

Given the increasing use of 4CMenB globally,[7] comparing Hex-IH and Hex-V when used alongside 4CMenB is crucial to inform the design of immunization schedules that allow the flexible use of these vaccines while optimizing their immunogenicity and reactogenicity profiles.[4,5]

These vaccines differ in key aspects, with additional pertussis antigens (fimbriae types 2 and 3) in Hex-V compared with Hex-IH [8] and the use of different carrier proteins for conjugation to the Hib polysaccharide, i.e. tetanus-toxoid for Hex-IH and a meningococcal outer membrane complex (OMPC) for Hex-V. The latter difference is especially relevant to co-administration with 4CMenB as this vaccine also contains meningococcal outer membrane proteins. There is therefore a theoretical risk of carrier induced epitopic suppression of the immune response to the Hib component of Hex-V when given

concurrently with 4CMenB. This in turn could potentially lead to a cohort of infants with sub-optimal immune responses to the Hib antigen with a risk of a recurrence of a Hib outbreak similar to that seen in the UK from 1999-2003.[9] Increasing the total dose of meningococcal outer membrane proteins by concurrent administration of Hex-V with 4CMenB may also lead to an increase in adverse vaccine reactions both locally and systemically compared to Hex-IH.

Accordingly, we conducted a non-inferiority unblinded randomized trial comparing the immunogenicity and reactogenicity at 5 and 13 months of both licensed DTaP-Hib-IPV-HepB vaccines when administered at 2, 3 and 4 months of age alongside the current UK vaccination schedule (including 4CMenB).

## Methods

### Study design and participants

In this single center, open label, non-inferiority randomized clinical trial, we recruited healthy infants born at term gestation living in the UK aged between 8 and 13 weeks who had not yet received their primary immunizations. Exclusion criteria were confirmed or suspected immunodeficiency, allergy to any constituents or excipients of the vaccines used in the trial, latex hypersensitivity, contraindications to vaccination as defined by Department of Health guidelines[10] or participation in another interventional clinical trial. Following recruitment, maternal pertussis immunization status was determined by maternal recall or by request to primary care providers.

The study received ethical approval from the South Central – Oxford A Research Ethics Council (reference number: 19/SC/0052) and is registered on the ISRCTN clinical trials register (ISRCTN85819697).

**Randomization and masking**

Infants were randomly assigned in a 1:1 ratio using computer generated block randomization (random block sizes of 2 and 4), to receive either Hex-IH or Hex-V at 2, 3 and 4 months. Study visits were conducted in participants' homes with randomization occurring at the study center prior to the first study visit by study staff not involved in this visit, who placed the vaccines in a sealed envelope. This was opened by research nurses after parental consent and participant screening, and immediately prior to vaccine administration, thereby maintaining vaccine allocation concealment. Following vaccine administration the trial became open label.

**Procedures**

Hex-IH is produced as a lyophilized Hib powder and is reconstituted with a solution containing DTaP-IPV-HBV to a total volume of 0.5 ml. Hex-V is produced in a ready to use liquid form of 0.5 ml volume. Both vaccines are administered intramuscularly. The antigen composition of each vaccine is summarized in a supplementary table (Table S1).

Participants also received their other routine vaccinations as per the UK routine childhood immunization schedule: PCV 13 (Prevenar 13, Pfizer, New York, USA), oral rotavirus vaccine (Rotarix, GlaxoSmithKline, Rixensart, Belgium), 4CMenB, Hib-MenC (Menitorix, GlaxoSmithKline, Rixensart, Belgium) and MMR (Priorix, GlaxoSmithKline, Rixensart, Belgium) (Table S2). Vaccination visits occurred at 2, 3, 4 and 12 months of age. Blood (serum) samples were taken at 5 and 13 months of age.

**Outcomes**

Antigen-specific IgG concentrations were measured by ELISA at the ImmunoAssay Group PHE Porton Down laboratory (Salisbury, UK; assay methods published previously)[11] using serum samples collected at 5 and 13 months of age for Hib polysaccharide (polyribosylribitol phosphate [PRP]), pertussis antigens (pertussis toxin, pertactin, filamentous haemagglutinin) and tetanus and diphtheria toxoids. The samples were also analyzed for human complement serum bactericidal antibody (hSBA) against reference strains for three key 4CMenB vaccine antigens: factor H binding protein 1 (fHbp) by 44/76-SL, NadA by 5/99, and OMV (porin A [PorA]) by NZ98/254. These assays, as well as an assay for rabbit complement SBA (rSBA) titers for the recommended MenC reference strain C11 (C:16:P1.7-1,1) were done at the Vaccine Evaluation Unit, PHE, Manchester, UK, by means of a previously published methodology.[12,13] Analysis of IgG concentrations against Hepatitis B surface antigen was conducted at the Oxford University Hospitals NHS Foundation Trust Laboratories. Analysis of IgG concentrations against vaccine-serotype pneumococcal capsule antigens was conducted at the University College London laboratory.[14]

Participants' parents or legal guardian were asked to keep an electronic diary or paper diary card of reactions (both solicited and unsolicited) after each vaccination visit (at 2, 3, 4 and 12 months). This included measuring a temperature at 6 hours after vaccination or before the participant settled for their night-time sleep (whichever was earliest) and then daily for the next 5 days. Solicited events included local (erythema, induration, swelling and tenderness at the vaccination site) and systemic reactions (change in feeding, drowsiness, vomiting, diarrhea and irritability/fussiness). Severity of reactions were categorized as mild, moderate, and severe as outlined in the study protocol (supplementary file). Unsolicited adverse events in days 0 to 5 following vaccination were also recorded. Serious adverse events were recorded for the duration of the study.

**Statistical analysis**

The original sample size planned to give 85% power at a two-sided 5% significance level, incorporating a 10% attrition rate and further allowances for protocol violations and unexpected dropouts, was 240 (n=120 in each arm). Disruptions to clinical activities due to the COVID-19 pandemic from March 2020 led to a re-evaluation of the study size. Recruitment was stopped at 194 participants, of which 172 participants had blood samples available for primary endpoint evaluation in the mITT analysis. To retain a study power of 85%, the type I error was increased from two-sided 5% (one-sided 2.5%) to one-sided 5%.

Immune responses at 5 and 13 months of age are summarized as medians and IQRs, and geometric means (GMs) with 95% CIs for log-transformed data. Geometric mean ratios (GMRs; Hex-V/Hex-IH) with 95% CIs are presented to compare the GMs of each antigen between the arms; one-sided 95% CI for the primary outcome and two-sided 95% CIs for all secondary outcomes. GMRs produced for pertussis antigens were adjusted for receipt of pertussis vaccination during pregnancy (yes/no). Non-inferiority was claimed if the lower bound of the one-sided 95% CI of the GMR was >0.5 for the 5-month Hib antibody response. Where non-inferiority was confirmed, superiority of Hex-V over Hex-IH was tested using a Student's t-test and presented with a two-sided 95% CI.

Although the study was not powered based on specific thresholds of anti-PRP IgG concentrations, the difference between arms was reported with a one-sided 95% Yates' continuity corrected CI, and a non-inferiority margin of ≥-10%. Difference in proportions between arms and accompanying two-sided 95% CIs were presented for secondary outcomes for pathogens with accepted correlates of protection (Table S3). Values equal to half the lower limit of detection (LLOD) were imputed for immune responses reported as lower than the LLOD. For assays with an upper limit of detection (Hep B), the value of the upper limit was used for results higher than this value.

All safety analyses are descriptive, with solicited adverse reactions presented as frequencies with 95% binomial exact CIs. Safety was evaluated in all participants who received at least one 6-in-1 vaccination.

The primary outcome was assessed in the per-protocol cohort as a sensitivity analysis. The per-protocol cohort consisted of participants who received all three 6-in-1 vaccinations within pre-defined windows, slightly relaxed due to COVID-19 disruptions, and gave a blood sample at the 5-month timepoint, within the relaxed visit window.

### Role of the funding source

The funders (MCM Vaccine) had no role in study design, data collection, data analysis, data interpretation, write up of the report or the decision to submit the manuscript for publication. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

## Results

### Participants

Between July 2019 and April 2020, 204 infants were randomized to the 6-in-1 study, of whom 194 were eventually enrolled (96 randomized to Hex-V and 98 Hex-IH). (Figure 1). Baseline characteristics in the enrolled participants were similar between the arms: 54% and 51% of the Hex-V and Hex-IH arms, respectively, comprised of females; median age at enrolment was 60 days in both arms; median birth weights were 3.5kg (Hex-V) and 3.4kg (Hex-IH) (Table 1). Antenatal pertussis vaccination was

received by 89% of mothers on the trial. There were 4 (2%) withdrawals after enrolment before the primary endpoint. The primary modified intention-to-treat (mITT) cohort consisted of 85 and 89 participants in the Hex-V and Hex-IH arms, respectively; and the per-protocol cohort was comprised of 73 and 75 participants in the Hex-V and Hex-IH arms, respectively. Two participants in the Hex-IH arm had inadequate 5-month blood samples which were unable to be processed. The mITT cohort for analysis at the secondary endpoint, at 13 months of age, consisted of 84 participants from the Hex-IH arm, and 80 from the Hex-V arm.

**Immunogenicity**

Anti-PRP IgG geometric mean concentrations (GMCs) at 5 months of age in the Hex-V arm were 23-times higher than concentrations in the Hex-IH arm, demonstrating non-inferiority of Hex-V compared to Hex-IH (GMR 23.25; one-sided 95% CI 16.21, -) (Table 2). Results were similar within the per-protocol cohort (GMR 24.08; one-sided 95% CI 16.19, -), and superiority of Hex-V over Hex-IH in anti-PRP IgG GMCs at 5 months was also demonstrated ($p<0.0001$). Over 90% of infants in the Hex-V arm had anti-PRP IgG concentrations at the ≥1.0 μg/ml correlate of protection, with a between group difference of 42.3% (95% CI 29.1%-55.5%), meeting the non-inferiority criteria for this threshold (Figure 2, Table S4). More participants had anti-PRP IgG GMCs ≥1.0μg/ml at 5 months of age after vaccination with Hex-V than after receiving Hex-IH (difference of 42.34%; 95% CI 29.15-55.52%). At 13 months of age, GMCs were almost 6-times greater in the Hex-V arm than in the Hex-IH arm (GMR 5.79; 95% CI 3.75-8.94), with 100% of Hex-V recipients achieving anti-PRP IgG concentrations above the 0.15 and 1.0μg/ml correlates of protection.

At 5 months of age, hSBA geometric mean titers (GMTs) against the 5/99 strain of MenB in the Hex-V arm were statistically significantly higher in the Hex-V arm compared to the Hex-IH arm (GMR 1.56; 95% CI 1.13-2.14). The point estimates of hSBA GMTs against the NZ98/254 and 44/76-SL MenB

strains were also higher in participants receiving Hex-V *versus* Hex-IV at this timepoint, but this was statistical significance. IgG GMCs against pertussis fimbriae were over 63-times higher in the Hex-V arm than in the Hex-IH arm at 5 months (GMR 63.40; 95% CI 49.94-85.63), which remained high at 13 months (GMR 30.27; 95% CI 22.65-40.44). IgG GMCs against diphtheria and pertussis FHA were lower in Hex-V recipients than in those receiving Hex-IH, with upper bounds of the GMR 95% CIs below 1. IgG GMCs against pertussis FHA after Hex-V vaccination remained lower than those reported in the Hex-IH arm at 13 months of age, however GMCs against diphtheria were similar between arms by this timepoint (GMR 1.01; 95% CI 0.75-1.35).

At both 5 and 13 months of age, IgG GMCs against tetanus were statistically significantly higher in participants receiving Hex-V compared to those receiving Hex-IH (5 months: GMR 1.88; 1.50-2.36; 13 months: GMR2.46 (1.74, 3.48). IgG GMTs against MenC were similar between the Hex-V and Hex-IH arms at 5 months, but were statistically significantly higher in the Hex-V arm at 13 months (GMR 1.69; 95% 1.15-2.48). No evidence of a statistical difference in immune response to the 13 pneumococcal strains was observed between Hex-V and Hex-IH arms at either the 5 or 13 month timepoint. (Table S4)

**Reactogenicity and Safety**

No obvious differences in occurrence or severity of solicited adverse reactions between the two 6-in-1 vaccines was apparent. During the five days after the first dose of the study vaccines, the most commonly reported systemic symptoms were irritability/fussiness (81% Hex-V, 77% Hex-IH) and drowsiness (73% Hex-V, 79% Hex-IH) (Table S5). Similar reactogenicity was observed after each study visit at which a 6-in-1 vaccine was administered, with few reports of severe reactions (Figure 3, Figures S1-4). Local reactogenicity was mostly mild in both vaccine arms across all study visits (Figure 3). During the study period, 6/98 (6%) participants in the Hex-IH arm reported SAEs, compared to 8/96 (8%) receiving Hex-V (Table S6). One SAE in the Hex-IH arm was considered a SAR, where the

participant was admitted to hospital following their first immunization with a fever of 39°C, tachycardia and tachypnoea. This was felt to be an expected but uncommon post-vaccination event. No other SAEs were considered related to the study vaccinations.

**Discussion**

Here we present the first immunogenicity and reactogenicity data comparing two hexavalent vaccines administered in infancy alongside 4CMenB. These data demonstrate non-inferiority of Hex-V compared to Hex-IH for Hib immunogenicity, with anti-PRP IgG GMCs over 20-fold higher at 5 months after Hex-V than Hex-IH. No increase in reactogenicity was observed, supporting the introduction of Hex-V as an alternative to Hex-IH in the routine childhood immunization schedule of the UK and other countries deploying 4CMenB in infancy.

These data are important given the widespread use in infant schedules of hexavalent (DTaP-IPV-Hib-HepB) vaccines and, increasingly, 4CMenB, which is now licensed in over 40 countries and routinely recommended in ten European countries and South Australia. [7,15,1617] Of particular concern was the possibility of carrier-induced epitopic suppression, in which antibody responses against the target (polysaccharide) antigen of protein-polysaccharide conjugate vaccines are impacted by concomitant administration with vaccines containing the same protein.[17,18] For example, priming with Diphtheria toxoid can suppress responses to Diphtheria-Men A conjugates.[18] whereas priming with $CRM_{197}$ does not seem to suppress subsequent antibody responses to Meningitis A conjugate vaccines in which it, or Diphtheria Toxoid, is used. Although this study was not specifically designed to assess the immunogenicity of Hex-V with and without co-administered 4CMenB, the impressive anti-PRP IgG concentrations observed here suggests that the shared meningococcal outer membrane proteins between 4CMenB and Hex-V in no way impaired the immunogenicity of the latter vaccine.

Instead, immunization with Hex-V generated anti-PRP IgG GMC's more than 20-fold higher than Hex-IH after early infant immunization. This is consistent with previous studies comparing these two vaccines without concomitant 4CMenB[4,5], which demonstrated that this difference persisted to 12 months, a timepoint not evaluated in this study. This enhanced immunogenicity for Hib may take on particular relevance for the UK owing to the imminent withdrawal from this country's schedule of the Hib-MenC vaccine currently given at 12 months of age, with the potential for an additional dose of DtaP-IPV-Hib-HepB at 18 months of age.[19] Of note is that the previous studies suggest that following administration of the toddler booster dose the course of Hex-IH ultimately generates higher anti-PRP IgG GMC's than Hex-V, and the possibility of heterologous boosting with Hex-IH after Hex-V at 18 months warrants further study.[19]

With regard to 4CMenB immunogenicity, the results show higher bactericidal antibody titers against the 5/99 strain in Hex-V participants compared to the Hex-IH group at 5 months, although all participants in both groups had SBA titers ≥1:4. While the reason for this is unclear, one biologically plausible explanation is a contribution from the meningococcal OMPC in Hex-V to this immune response. No convincing additional immunogenicity was seen for the other MenB strains, however.

Given the excellent control of tetanus and diphtheria achieved in countries deploying either Hex-IH or Hex-V[20,21] the observed differences in immunogenicity against these antigens is unlikely to be clinically significant. The differences in antibody concentrations against pertussis antigens observed are expected given a comparison between a vaccine containing three pertussis antigens (Hex-IH) and five antigens (Hex-V), however a World Health Organization review of acellular pertussis vaccines found no convincing evidence of a difference in the effectiveness of 3 versus 5 component vaccines.[22]

There were a number of limitations to our study. Recruitment to our study was affected by the COVID-19 pandemic, however the robust evidence of non-inferiority demonstrated suggests that this did not

affect the study integrity. A further result of the COVID-19 pandemic was that we were also unable to obtain results for Poliovirus neutralizing antibodies, as initially planned in the study protocol owing to laboratory constraints. An additional potential limitation was randomization occurring prior to formal enrolment in the study due to study visits being conducted in participant's homes. While this created a potential recruiting bias, this was minimized as both participants and study staff conducting the visit were unaware of group allocation until immediately prior to administration of the study intervention.

In conclusion, our study has shown that with regards to Hib immunogenicity, Hex-V is non-inferior to Hex-IH. Additionally, Hex-V is safe and well-tolerated and is therefore a potential candidate vaccine for use in the increasing number of countries deploying 4CMenB in their infant immunization schedule.

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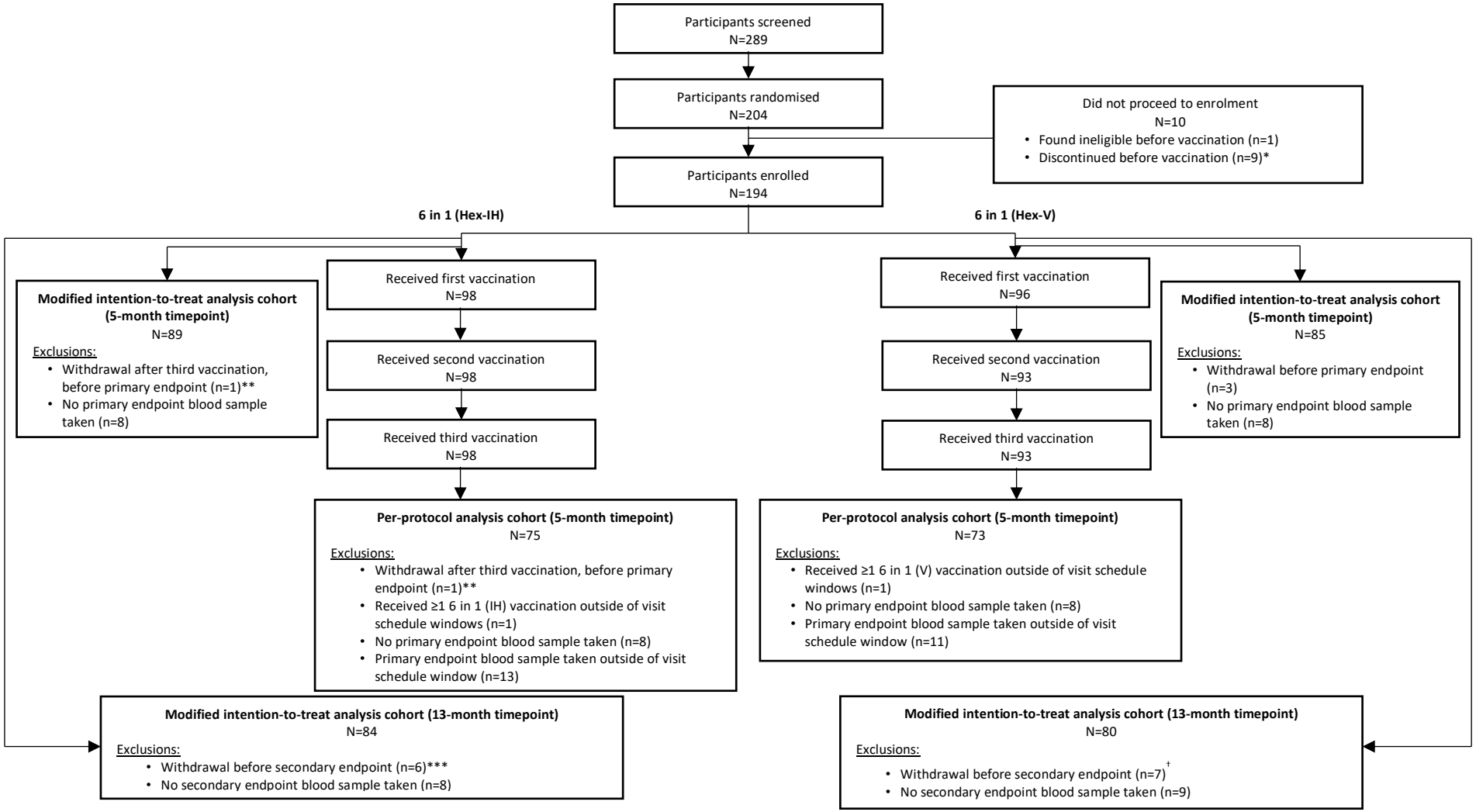
**Figure 1 – CONSORT**




Note that randomization took place prior to enrolment, with enrolment to the trial defined as infants receiving at least one dose of the study vaccinations.

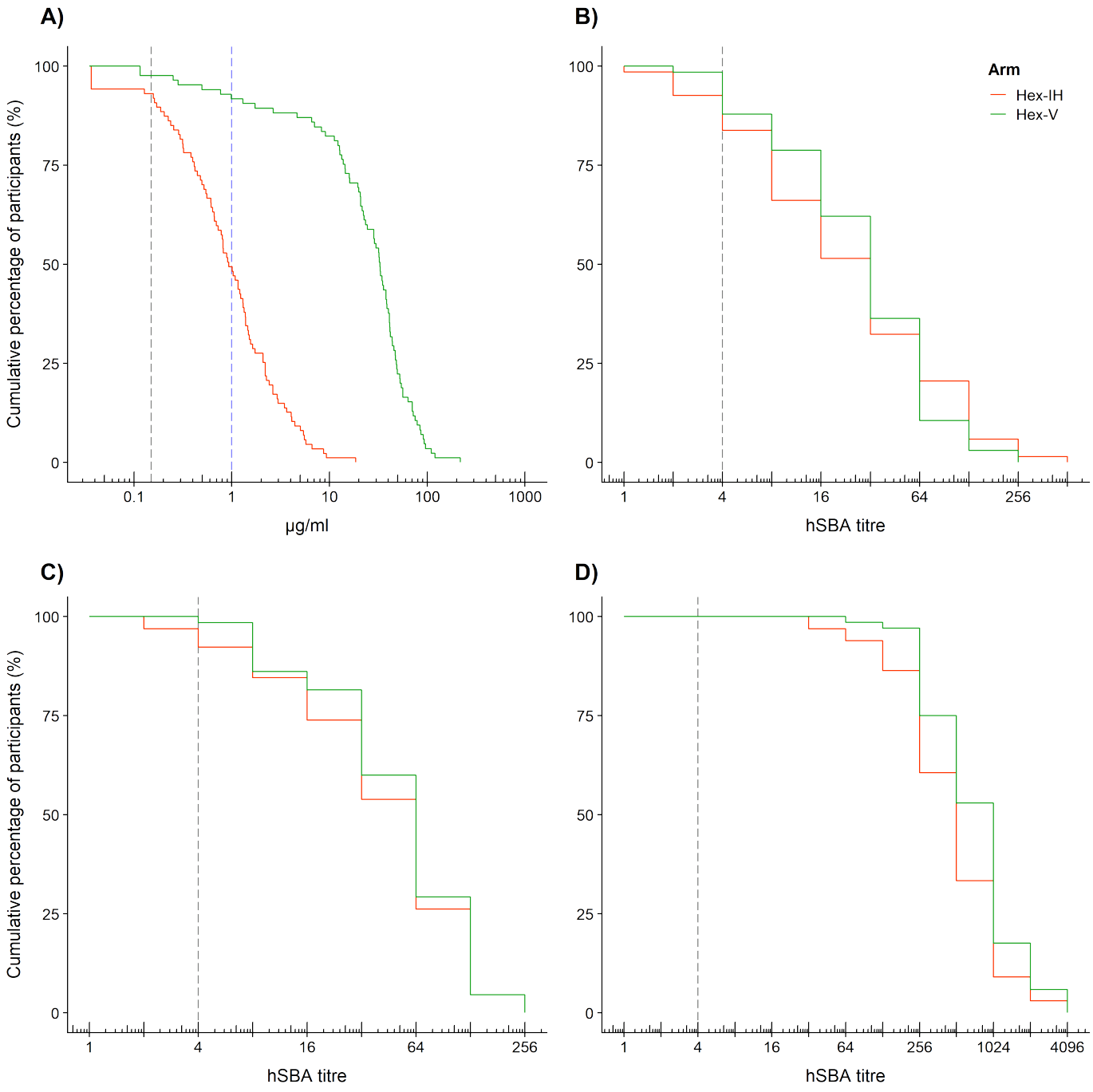
*Reasons for discontinuation included parents changing their minds, parents cancelling enrolment visits and unable to arrange a further suitable date, and participant already having first dose of vaccine. Neither team no parents were aware of allocation to randomization arm before their decision not to proceed with enrolment. N=4 participants were randomized to the Hex-IH arm, and n=6 to the Hex-V arm.

**Refers to the same participant

***Refers to all withdrawals in the Hex-IH arm before the secondary endpoint. Withdrawal reasons are: withdrawal of consent (n=2), moved out of area (n=3), and parent not wanting infant to undergo blood test (n=1).

†Refers to all withdrawals in the Hex-V arm before the secondary endpoint. Withdrawal reasons are: withdrawal of consent (n=4), moved out of area (n=3).

**Figure 2 – Reverse cumulative distribution curves of anti-PRP concentrations and hSBA titers at 5 months of age**



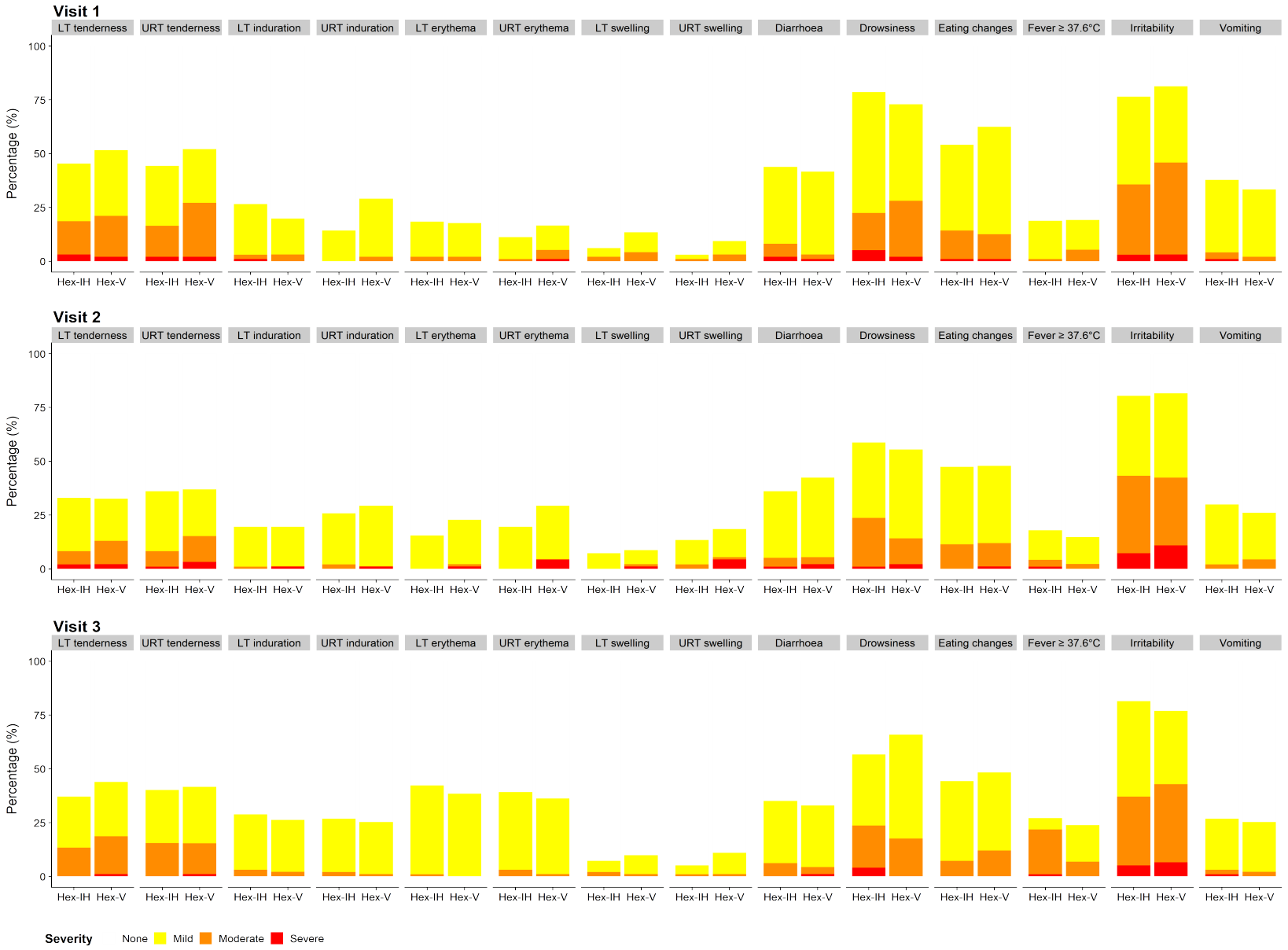

A) Hib. Dashed black line shows 0.15 µg/ml threshold, dashed blue line shows 1.0 µg/ml threshold.

B) MenB NZ98 254. Dashed black line shows 4 hSBA titer threshold.

C) MenB 44/76. Dashed black line shows 4 hSBA titer threshold.

D) MenB 5/99. Dashed black line shows 4 hSBA titer threshold.

**Figure 3 – Maximum severity of solicited local and systemic adverse events over days 0-5 following vaccinations with Hex-V or Hex-IH**




6 in 1 vaccine was given in the upper right thigh (URT) at all visits. MenB vaccine was given in the left anterolateral thigh (LT) at visits 1 and 3, and PCV13 vaccine was given in the LT at visit 2.

**Table 1 – Baseline demographics of the enrolled participants**

| | Hex-IH | Hex-V |
|---|---|---|
| Number enrolled | 98 | 96 |
| Sex (female) | 50 (51.0%) | 52 (54.2%) |
| Age at enrolment (days), median [IQR] | 60.0 [57.2-63.0] | 60.0 [57.0-63.0] |
| Age range (days) | 56-94 | 56-79 |
| Birth weight (kg), mean (SD) | 3.4 (0.5) | 3.5 (0.5) |
| Weight range (kg) | 2.5-4.5 | 2.2-4.5 |
| Mother received pertussis vaccine in pregnancy | 90 (91.8%) | 82 (85.4%) |

**Table 2 – Immunology results at 5 (primary outcome) and 13 (secondary outcome) months of age, following vaccination with Hex-V or Hex-IH**

| Antigen | Component/ serotype | 5 months | | | 13 months | | |
|---|---|---|---|---|---|---|---|
| | | Hex-V: GM (95% CI) [n] | Hex-IH: GM (95% CI) [n] | GMR* (95% CI) | Hex-V: GM (95% CI) [n] | Hex-IH: GM (95% CI) [n] | GMR* (95% CI) |
| Hib | | 20.34 (14.58, 28.37) [n=85] | 0.87 (0.66, 1.16) [n=87] | 23.25 (15.11, 35.78) | 88.07 (66.38, 116.85) [n=79] | 15.21 (10.89, 21.25) [n=84] | 5.79 (3.75, 8.94) |
| MenB | NZ98/254 | 27.34 (20.83, 35.88) [n=66] | 23.09 (16.42, 32.48) [n=68] | 1.18 (0.77, 1.82) | 23.22 (16.57, 32.53) [n=67] | 26.53 (18.32, 38.43) [n=74] | 0.88 (0.53, 1.44) |
| | 44/76-SL | 48.5 (37.91, 62.05) [n=65] | 40.03 (30.01, 53.4) [n=65] | 1.21 (0.83, 1.76) | 35.8 (28.11, 45.59) [n=68] | 39.72 (31.74, 49.71) [n=77] | 0.90 (0.65, 1.25) |
| | 5/99 | 709.47 (575.1, 875.23) [n=68] | 456.14 (356.77, 583.19) [n=66] | 1.56 (1.13, 2.14) | 2173.36 (1718.22, 2749.08) [n=70] | 1560.29 (1150.23, 2116.53) [n=79] | 1.39 (0.95, 2.04) |
| MenC | | 2.5 (2.12, 2.93) [n=72] | 2.42 (2.03, 2.88) [n=73] | 1.03 (0.82, 1.30) | 977.15 (772.31, 1236.32) [n=74] | 578.03 (425.1, 785.98) [n=80] | 1.69 (1.15, 2.48) |
| Diphtheria | | 0.24 (0.19, 0.29) [n=85] | 0.47 (0.39, 0.56) [n=87] | 0.51 (0.39, 0.67) | 0.86 (0.69, 1.08) [n=79] | 0.86 (0.7, 1.05) [n=84] | 1.01 (0.75, 1.35) |
| Tetanus | | 2.81 (2.38, 3.31) [n=85] | 1.49 (1.27, 1.75) [n=87] | 1.88 (1.50, 2.36) | 7.83 (6.25, 9.81) [n=79] | 3.19 (2.44, 4.17) [n=84] | 2.46 (1.74, 3.48) |
| HepB | | 244.96 (165.52, 362.52) [n=52] | 341.41 (263.35, 442.60) [n=53] | 0.72 (0.45, 1.14) | 75.00 (51.07, 110.14) [n=60] | 148.90 (102.07, 217.23) [n=62] | 0.50 (0.30, 0.86) |
| Pertussis | Fimbriae | 196.85 (160.29, 241.75) [n=83] | 3.11 (2.50, 3.87) [n=83] | 63.40 (46.94, 85.63) | 31.40 (25.05, 39.37) [n=79] | 1.07 (0.88, 1.29) [n=84] | 30.27 (22.65, 40.44) |
| | Pertactin | 37.42 (31.10, 45.03) [n=83] | 48.54 (40.35, 58.39) [n=85] | 0.77 (0.59, 1.00) | 8.68 (6.92, 10.89) [n=79] | 6.87 (5.49, 8.59) [n=84] | 1.28 (0.93, 1.76) |
| | Pertussis Toxin | 54.19 (45.73, 64.21) [n=85] | 35.69 (31.17, 40.86) [n=86] | 1.49 (1.20, 1.84) | 8.01 (6.56, 9.78) [n=79] | 9.10 (7.55, 10.97) [n=84] | 0.88 (0.67, 1.16) |
| | FHA | 31.76 (27.42, 36.78) [n=84] | 61.51 (53.91, 70.19) [n=86] | 0.51 (0.42, 0.62) | 5.65 (4.80, 6.64) [n=79] | 19.63 (16.56, 23.27) [n=84] | 0.28 (0.22, 0.36) |
| Pneumococcus | 1 | 0.42 (0.33, 0.54) [n=62] | 0.45 (0.36, 0.58) [n=68] | 0.93 (0.66, 1.32) | 8.47 (7.01, 10.23) [n=67] | 8.55 (6.87, 10.65) [n=69] | 0.99 (0.74, 1.32) |
| | 3 | 0.39 (0.32, 0.47) [n=60] | 0.49 (0.39, 0.61) [n=65] | 0.80 (0.60, 1.07) | 0.97 (0.81, 1.16) [n=65] | 0.94 (0.79, 1.11) [n=69] | 1.04 (0.81, 1.33) |
| | 4 | 0.35 (0.27, 0.45) [n=65] | 0.39 (0.32, 0.49) [n=70] | 0.88 (0.63, 1.23) | 3.99 (3.30, 4.81) [n=67] | 4.59 (3.79, 5.56) [n=69] | 0.87 (0.67, 1.13) |
| | 5 | 0.22 (0.17, 0.27) [n=60] | 0.20 (0.16, 0.25) [n=66] | 1.06 (0.76, 1.47) | 1.99 (1.70, 2.33) [n=66] | 1.89 (1.59, 2.24) [n=69] | 1.05 (0.84, 1.33) |
| | 6A | 0.11 (0.09, 0.13) [n=60] | 0.12 (0.10, 0.14) [n=66] | 0.91 (0.74, 1.13) | 7.18 (6.02, 8.56) [n=67] | 7.88 (6.39, 9.72) [n=69] | 0.91 (0.69, 1.20) |
| | 6B | 0.09 (0.08, 0.10) [n=69] | 0.08 (0.08, 0.09) [n=72] | 1.04 (0.92, 1.17) | 2.46 (1.93, 3.14) [n=69] | 2.93 (2.24, 3.84) [n=72] | 0.84 (0.58, 1.20) |
| | 7F | 0.65 (0.51, 0.84) [n=60] | 0.87 (0.68, 1.12) [n=67] | 0.75 (0.53, 1.06) | 3.64 (3.07, 4.33) [n=67] | 4.02 (3.51, 4.61) [n=69] | 0.91 (0.73, 1.13) |
| | 9V | 0.18 (0.14, 0.22) [n=62] | 0.20 (0.16, 0.25) [n=67] | 0.87 (0.65, 1.17) | 3.17 (2.59, 3.87) [n=66] | 3.71 (3.14, 4.38) [n=69] | 0.85 (0.66, 1.11) |
| | 14 | 1.04 (0.80, 1.35) [n=59] | 1.09 (0.84, 1.40) [n=66] | 0.95 (0.66, 1.37) | 14.61 (11.38, 18.78) [n=66] | 15.20 (12.20, 18.93) [n=69] | 0.96 (0.69, 1.34) |
| | 18C | 0.18 (0.14, 0.22) [n=60] | 0.24 (0.19, 0.30) [n=66] | 0.74 (0.54, 1.01) | 1.88 (1.57, 2.25) [n=67] | 2.06 (1.77, 2.41) [n=69] | 0.91 (0.72, 1.15) |
| | 19A | 0.36 (0.29, 0.46) [n=68] | 0.41 (0.34, 0.50) [n=72] | 0.88 (0.65, 1.18) | 10.05 (8.20, 12.31) [n=68] | 10.88 (9.10, 13.02) [n=72] | 0.92 (0.71, 1.21) |
| | 19F | 0.56 (0.46, 0.68) [n=60] | 0.58 (0.47, 0.71) [n=66] | 0.97 (0.73, 1.28) | 15.98 (12.73, 20.06) [n=67] | 17.92 (15.06, 21.32) [n=67] | 0.89 (0.67, 1.18) |
| | 23F | 0.09 (0.08, 0.10) [n=65] | 0.08 (0.07, 0.09) [n=70] | 1.14 (0.98, 1.33) | 2.00 (1.63, 2.45) [n=67] | 2.01 (1.65, 2.44) [n=69] | 1.00 (0.75, 1.32) |

*GMRs presented for pertussis are adjusted for maternal pertussis vaccination received during pregnancy (yes/no)

## Supplementary Tables

**Table S1 – Components of Hex-IH and Hex-V**

| Hex-IH | | | Hex-V | | |
|---|---|---|---|---|---|
| **Component** | **Dose** | **Additional information** | **Component** | **Dose** | **Additional Information** |
| *Diphtheria toxoid* | Not less than 20 international units (IU) | Absorbed onto aluminum hydroxide | *Diphtheria toxoid* | Not less than 20 international units (IU) | Absorbed onto aluminum phosphate |
| *Tetanus toxoid* | Not less than 40 international units (IU) | | *Tetanus toxoid* | Not less than 40 international units (IU) | |
| *Bordetella pertussis antigens* | | | *Bordetella pertussis antigens* | | |
| - Pertussis toxoid (PT) | 25 micrograms | Absorbed onto aluminum hydroxide | - Pertussis toxoid (PT) | 20 micrograms | Absorbed onto aluminum phosphate |
| - Filamentous Haemagglutinin (FHA) | 25 micrograms | | - Filamentous Haemagglutinin (FHA) | 20 micrograms | |
| - Pertactin (PRN) | 8 micrograms | | - Pertactin (PRN) | 3 micrograms | |
| | | | - Fimbriae Types 2 and 3 (FIM) | 5 micrograms | |
| *Hepatitis B surface antigen* | 10 micrograms | - Produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology - absorbed on aluminum phosphate ($AlPO_4$) | *Hepatitis B surface antigen* | 10 micrograms | - Produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology - Absorbed onto aluminum hydroxyphosphate sulfate |
| *Poliovirus (inactivated) IPV* | | | *Poliovirus (inactivated) IPV* | | |
| - Type 1 (Mahoney strain) | 40 D-antigen unit | Propagated in VERO cells | - Type 1 (Mahoney strain) | 40 D-antigen unit | Propagated in VERO cells |
| - Type 2 (MEF-1 strain) | 8 D-antigen unit | | - Type 2 (MEF-1 strain) | 8 D-antigen unit | |
| - Type 3 (Saukett strain) | 32 D-antigen unit | | - Type 3 (Saukett strain) | 32 D-antigen unit | |
| *Hemophilus influenza type b polysaccharide* | 10 micrograms | Absorbed on aluminum phosphate ($AlPO_4$) | *Hemophilus influenza type b polysaccharide*<br>- conjugated to meningococcal protein | 3 micrograms<br>50 micrograms | Absorbed onto aluminum hydroxyphosphate sulfate |

**Table S2 – Study visit schedule**

| Visit | | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 |
|---|---|---|---|---|---|---|---|
| **Age of participant** | | 2 months | 3 months | 4 months | 5 months | 12 months | 13 months |
| **Visit windows** | | 8 – 13 weeks of age | 28-42 days after visit 1 | 28-42 days after visit 2 | 28-42 days after visit 3 | 12 months of age (+28 days) | 28-42 days after visit 5 |
| **Relaxed visit windows** | | N/A | 21-49 days after visit 1 | 21-49 days after visit 2 | 21-49 days after visit 3 | 350-406 days of age | 21-49 days after visit 5 |
| **Group** | **Hex-IH** | 6 in 1(Hex-IH)<br>4CMenB<br>Rotavirus | 6 in 1(Hex-IH)<br>Rotavirus<br>PCV13 | 6 in 1(Hex-IH)<br>4CMenB | Blood sampling | Hib-MenC<br>PCV13 MMR<br>4CMenB | Blood sampling |
| | **Hex-V** | 6 in 1(Hex-V)<br>4CMenB<br>Rotavirus | 6 in 1(Hex-V)<br>Rotavirus<br>PCV13 | 6 in 1(Hex-V)<br>4CMenB | | | |

**Table S3 – Correlates of protection used**

| Vaccine antigen | | Assay | Level required for protection† |
|---|---|---|---|
| Hemophilus influenzae b (Hib) | | ELISA (anti-PRP IgG) | ≥0.15 µg/ml (short term)<br>≥1.0 µg/ml (long term) |
| Diphtheria | | ELISA (IgG to toxoid) | ≥0.1 IU/ml |
| Tetanus | | ELISA (IgG to toxoid) | ≥0.1 IU/ml |
| Hepatitis B | | ELISA (anti-HBs IgG) | ≥10 IU/ml |
| Group B meningococcus (MenB): | 44/76-SL<br>5/99<br>NZ98/254 | SBA (human complement) | ≥4 hSBA titer |
| Group C meningococcus (MenC) | | SBA (rabbit complement) | ≥8 rSBA titer |
| Polio | | Neutralization | ≥1/8 titer |
| Pneumococcus | | ELISA | ≥0.35 µg/ml |

**Table S4 – Proportion of participants achieving prespecified antibody concentrations/titers (defined correlates of protection) at 5 and 13 months of age, following vaccination with Hex-V or Hex-IH**

| Antigen | Component/ serotype | Threshold | 5 months | | | 13 months | | |
|---|---|---|---|---|---|---|---|---|
| | | | Hex-V, n (%) | Hex-IH, n (%) | Difference in proportions (95% CI) | Hex-V, n (%) | Hex-IH, n (%) | Difference in proportions (95% CI) |
| Hib | | ≥0.15 µg/ml | 83 (97.65%) | 81 (93.10%) | 4.54% (-2.84%, 11.93%) | 79 (100.00%) | 84 (100.00%) | 0.00% (-) |
| | | ≥1.0 µg/ml | 78 (91.76%) | 43 (49.43%) | 42.34% (29.15%, 55.52%) | 79 (100.00%) | 81 (96.43%) | 3.57% (-1.63%, 8.77%) |
| MenB | NZ98/254 | ≥4 hSBA titer | 65 (98.48%) | 63 (92.65%) | 5.84% (-2.52%, 14.20%) | 62 (92.54%) | 67 (90.54%) | 2.00% (-8.59%, 12.59%) |
| | 44/76-SL | ≥4 hSBA titer | 65 (100.00%) | 63 (96.92%) | 3.08% (-2.66%, 8.81%) | 68 (100.00%) | 77 (100.00%) | 0.00% (-) |
| | 5/99 | ≥4 hSBA titer | 68 (100.00%) | 66 (100.00%) | 0.00% (-) | 70 (100.00%) | 79 (100.00%) | 0.00% (-) |
| MenC | | ≥8 rSBA titer | 6 (8.33%) | 4 (5.48%) | 2.85% (-6.77%, 12.48%) | 74 (100.00%) | 78 (97.50%) | 2.50% (-2.22%, 7.22%) |
| Diphtheria | | ≥0.1 IU/ml | 67 (78.82%) | 83 (95.40%) | -16.58% (-27.48%, -5.68%) | 76 (96.20%) | 82 (97.62%) | -1.42% (-7.97%, 5.14%) |
| Tetanus | | ≥0.1 IU/ml | 85 (100.00%) | 87 (100.00%) | 0.00% (-) | 79 (100.00%) | 84 (100.00%) | 0.00% (-) |
| HepB | | ≥10 IU/ml | 50 (96.15%) | 53 (100.00%) | -3.85% (-10.98%, 3.29%) | 55 (91.67%) | 58 (93.55%) | -1.88% (-12.81%, 9.05%) |
| Pneumococcus | 1 | ≥0.35 µg/ml | 34 (54.84%) | 39 (57.35%) | -2.51% (-21.13%, 16.10%) | 67 (100.00%) | 69 (100.00%) | 0.00% (-) |
| | 3 | ≥0.35 µg/ml | 40 (66.67%) | 44 (67.69%) | -1.03% (-18.53%, 16.48%) | 62 (95.38%) | 63 (91.30%) | 4.08% (-5.79%, 13.95%) |
| | 4 | ≥0.35 µg/ml | 32 (49.23%) | 44 (62.86%) | -13.63% (-31.72%, 4.47%) | 67 (100.00%) | 69 (100.00%) | 0.00% (-) |
| | 5 | ≥0.35 µg/ml | 19 (31.67%) | 16 (24.24%) | 7.42% (-9.83%, 24.68%) | 66 (100.00%) | 69 (100.00%) | 0.00% (-) |
| | 6A | ≥0.35 µg/ml | 3 (5.00%) | 3 (4.55%) | 0.45% (-7.46%, 8.37%) | 67 (100.00%) | 69 (100.00%) | 0.00% (-) |
| | 6B | ≥0.35 µg/ml | 2 (2.90%) | 0 (0.00%) | 2.90% (-2.48%, 8.28%) | 68 (98.55%) | 70 (97.22%) | 1.33% (-4.73%, 7.39%) |
| | 7F | ≥0.35 µg/ml | 43 (71.67%) | 56 (83.58%) | -11.92% (-27.94%, 4.11%) | 67 (100.00%) | 69 (100.00%) | 0.00% (-) |
| | 9V | ≥0.35 µg/ml | 9 (14.52%) | 18 (26.87%) | -12.35% (-27.67%, 2.97%) | 64 (96.97%) | 69 (100.00%) | -3.03% (-8.65%, 2.59%) |
| | 14 | ≥0.35 µg/ml | 50 (84.75%) | 57 (86.36%) | -1.62% (-15.58%, 12.34%) | 66 (100.00%) | 69 (100.00%) | 0.00% (-) |
| | 18C | ≥0.35 µg/ml | 16 (26.67%) | 26 (39.39%) | -12.73% (-30.57%, 5.12%) | 65 (97.01%) | 69 (100.00%) | -2.99% (-8.53%, 2.56%) |
| | 19A | ≥0.35 µg/ml | 33 (48.53%) | 41 (56.94%) | -8.42% (-26.33%, 9.50%) | 68 (100.00%) | 72 (100.00%) | 0.00% (-) |
| | 19F | ≥0.35 µg/ml | 45 (75.00%) | 46 (69.70%) | 5.30% (-11.88%, 22.48%) | 67 (100.00%) | 67 (100.00%) | 0.00% (-) |
| | 23F | ≥0.35 µg/ml | 2 (3.08%) | 1 (1.43%) | 1.65% (-4.87%, 8.17%) | 66 (98.51%) | 67 (97.10%) | 1.41% (-4.91%, 7.72%) |

Note that pertussis has been omitted from this table due to no defined correlate of protection for this pathogen.

**Table S5 – Breakdown of maximum severity of solicited systemic adverse events over days 0-5 following each dose of study vaccination**

| Visit | Symptom | Arm | None | Mild | Moderate | Severe | Any |
|---|---|---|---|---|---|---|---|
| 1 | Fever | Hex-IH | 78 (81%, 72%-88%) | 17 (18%, 11%-27%) | 1 (1%, 0%-6%) | 0 (0%, 0%-4%) | 18 (19%, 12%-28%) |
| | | Hex-V | 76 (81%, 71%-88%) | 13 (14%, 8%-22%) | 5 (5%, 2%-12%) | 0 (0%, 0%-4%) | 18 (19%, 12%-29%) |
| | Eating changes | Hex-IH | 45 (46%, 36%-56%) | 39 (40%, 30%-50%) | 13 (13%, 7%-22%) | 1 (1%, 0%-6%) | 53 (54%, 44%-64%) |
| | | Hex-V | 36 (38%, 28%-48%) | 48 (50%, 40%-60%) | 11 (11%, 6%-20%) | 1 (1%, 0%-6%) | 60 (62%, 52%-72%) |
| | Drowsiness | Hex-IH | 21 (21%, 14%-31%) | 55 (56%, 46%-66%) | 17 (17%, 10%-26%) | 5 (5%, 2%-12%) | 77 (79%, 69%-86%) |
| | | Hex-V | 26 (27%, 19%-37%) | 43 (45%, 35%-55%) | 25 (26%, 18%-36%) | 2 (2%, 0%-7%) | 70 (73%, 63%-81%) |
| | Vomiting | Hex-IH | 61 (62%, 52%-72%) | 33 (34%, 24%-44%) | 3 (3%, 1%-9%) | 1 (1%, 0%-6%) | 37 (38%, 28%-48%) |
| | | Hex-V | 64 (67%, 56%-76%) | 30 (31%, 22%-42%) | 2 (2%, 0%-7%) | 0 (0%, 0%-4%) | 32 (33%, 24%-44%) |
| | Diarrhea | Hex-IH | 55 (56%, 46%-66%) | 35 (36%, 26%-46%) | 6 (6%, 2%-13%) | 2 (2%, 0%-7%) | 43 (44%, 34%-54%) |
| | | Hex-V | 56 (58%, 48%-68%) | 37 (39%, 29%-49%) | 2 (2%, 0%-7%) | 1 (1%, 0%-6%) | 40 (42%, 32%-52%) |
| | Irritability | Hex-IH | 23 (23%, 15%-33%) | 40 (41%, 31%-51%) | 32 (33%, 24%-43%) | 3 (3%, 1%-9%) | 75 (77%, 67%-85%) |
| | | Hex-V | 18 (19%, 12%-28%) | 34 (35%, 26%-46%) | 41 (43%, 33%-53%) | 3 (3%, 1%-9%) | 78 (81%, 72%-88%) |
| 2 | Fever | Hex-IH | 78 (82%, 73%-89%) | 13 (14%, 7%-22%) | 3 (3%, 1%-9%) | 1 (1%, 0%-6%) | 17 (18%, 11%-27%) |
| | | Hex-V | 75 (85%, 76%-92%) | 11 (12%, 6%-21%) | 2 (2%, 0%-8%) | 0 (0%, 0%-4%) | 13 (15%, 8%-24%) |
| | Eating changes | Hex-IH | 51 (53%, 42%-63%) | 35 (36%, 27%-46%) | 11 (11%, 6%-19%) | 0 (0%, 0%-4%) | 46 (47%, 37%-58%) |
| | | Hex-V | 47 (52%, 41%-62%) | 33 (36%, 26%-47%) | 10 (11%, 5%-19%) | 1 (1%, 0%-6%) | 44 (48%, 38%-59%) |
| | Drowsiness | Hex-IH | 40 (41%, 31%-52%) | 34 (35%, 26%-45%) | 22 (23%, 15%-32%) | 1 (1%, 0%-6%) | 57 (59%, 48%-69%) |
| | | Hex-V | 40 (44%, 34%-55%) | 38 (42%, 32%-53%) | 11 (12%, 6%-21%) | 2 (2%, 0%-8%) | 51 (56%, 45%-66%) |
| | Vomiting | Hex-IH | 68 (70%, 60%-79%) | 27 (28%, 19%-38%) | 2 (2%, 0%-7%) | 0 (0%, 0%-4%) | 29 (30%, 21%-40%) |
| | | Hex-V | 67 (74%, 63%-82%) | 20 (22%, 14%-32%) | 4 (4%, 1%-11%) | 0 (0%, 0%-4%) | 24 (26%, 18%-37%) |
| | Diarrhea | Hex-IH | 62 (64%, 54%-73%) | 30 (31%, 22%-41%) | 4 (4%, 1%-10%) | 1 (1%, 0%-6%) | 35 (36%, 27%-46%) |
| | | Hex-V | 52 (57%, 46%-67%) | 34 (37%, 27%-48%) | 3 (3%, 1%-9%) | 2 (2%, 0%-8%) | 39 (43%, 33%-54%) |
| | Irritability | Hex-IH | 19 (20%, 12%-29%) | 36 (37%, 28%-48%) | 35 (36%, 27%-46%) | 7 (7%, 3%-14%) | 78 (80%, 71%-88%) |
| | | Hex-V | 16 (18%, 10%-27%) | 36 (40%, 29%-50%) | 29 (32%, 22%-42%) | 10 (11%, 5%-19%) | 75 (82%, 73%-90%) |
| 3 | Fever | Hex-IH | 70 (74%, 64%-82%) | 5 (5%, 2%-12%) | 19 (20%, 12%-29%) | 1 (1%, 0%-6%) | 25 (26%, 18%-36%) |
| | | Hex-V | 67 (76%, 66%-85%) | 15 (17%, 10%-27%) | 6 (7%, 3%-14%) | 0 (0%, 0%-4%) | 21 (24%, 15%-34%) |
| | Eating changes | Hex-IH | 53 (55%, 45%-65%) | 36 (38%, 28%-48%) | 7 (7%, 3%-14%) | 0 (0%, 0%-4%) | 43 (45%, 35%-55%) |
| | | Hex-V | 47 (52%, 41%-62%) | 33 (36%, 26%-47%) | 11 (12%, 6%-21%) | 0 (0%, 0%-4%) | 44 (48%, 38%-59%) |
| | Drowsiness | Hex-IH | 42 (44%, 34%-54%) | 31 (32%, 23%-43%) | 19 (20%, 12%-29%) | 4 (4%, 1%-10%) | 54 (56%, 46%-66%) |
| | | Hex-V | 31 (34%, 24%-45%) | 44 (48%, 38%-59%) | 16 (18%, 10%-27%) | 0 (0%, 0%-4%) | 60 (66%, 55%-76%) |
| | Vomiting | Hex-IH | 71 (74%, 64%-82%) | 22 (23%, 15%-33%) | 2 (2%, 0%-7%) | 1 (1%, 0%-6%) | 25 (26%, 18%-36%) |
| | | Hex-V | 68 (75%, 65%-83%) | 21 (23%, 15%-33%) | 2 (2%, 0%-8%) | 0 (0%, 0%-4%) | 23 (25%, 17%-35%) |
| | Diarrhea | Hex-IH | 62 (65%, 54%-74%) | 28 (29%, 20%-39%) | 6 (6%, 2%-13%) | 0 (0%, 0%-4%) | 34 (35%, 26%-46%) |
| | | Hex-V | 61 (67%, 56%-77%) | 26 (29%, 20%-39%) | 3 (3%, 1%-9%) | 1 (1%, 0%-6%) | 30 (33%, 23%-44%) |
| | Irritability | Hex-IH | 17 (18%, 11%-27%) | 43 (45%, 35%-55%) | 31 (32%, 23%-43%) | 5 (5%, 2%-12%) | 79 (82%, 73%-89%) |
| | | Hex-V | 21 (23%, 15%-33%) | 31 (34%, 24%-45%) | 33 (36%, 26%-47%) | 6 (7%, 2%-14%) | 70 (77%, 67%-85%) |

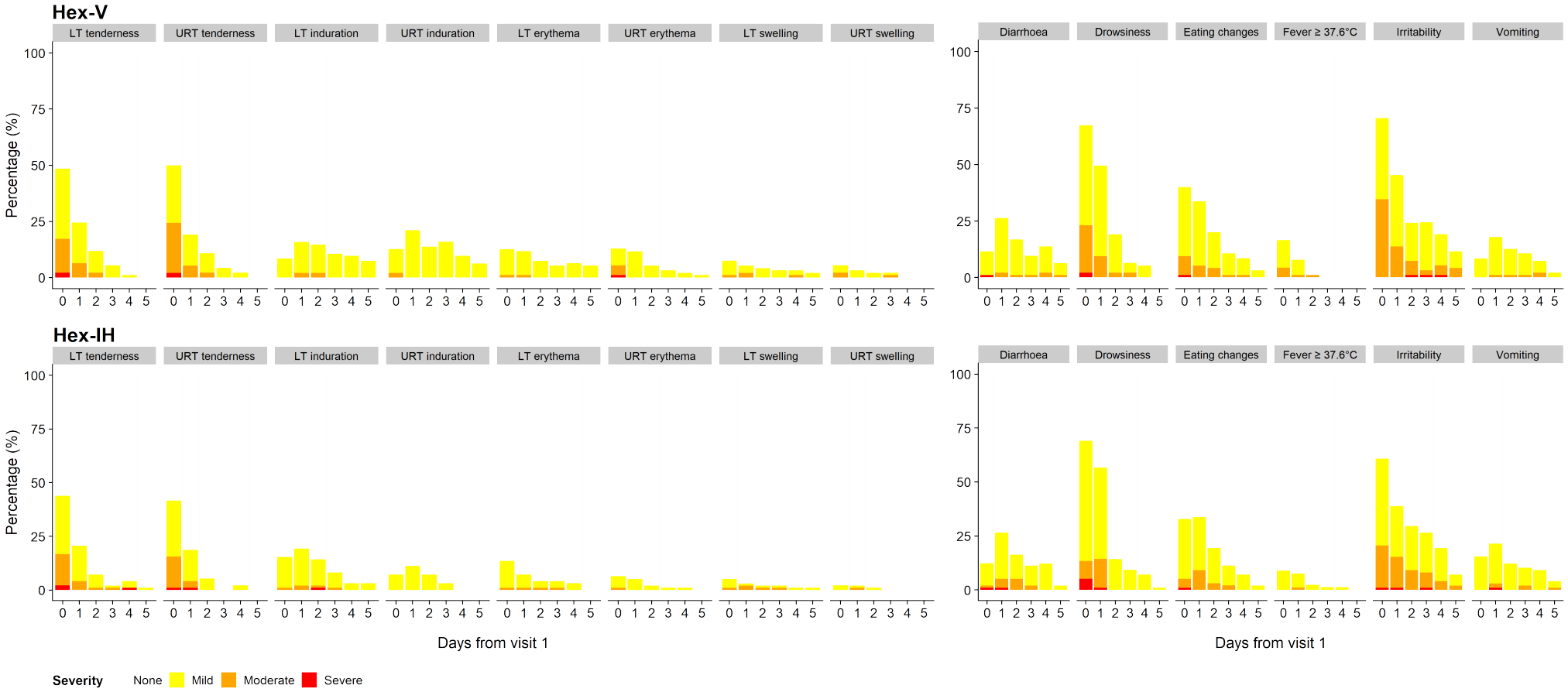
**Table S6 – SAE, SAR and SUSAR line listing**

| ID | Arm | Duration of event (days) | Description | Severity | Related to vaccine administration | Expected (if related) | Classification |
|---|---|---|---|---|---|---|---|
| 1 | Hex-IH | 3 | Bronchiolitis | Moderate | Unrelated | | SAE |
| 2 | Hex-IH | 3 | Bronchiolitis | Mild | Unrelated | | SAE |
| 2 | Hex-IH | 1 | Bronchiolitis | Mild | Unrelated | | SAE |
| 3 | Hex-V | 5 | Urinary tract infection with unilateral ureteric dilatation | Moderate | Unrelated | | SAE |
| 4 | Hex-IH | 2 | Viral infection | Moderate | Unrelated | | SAE |
| 5 | Hex-V | 9 | Bronchiolitis | Mild | Unrelated | | SAE |
| 5 | Hex-V | 1 | Head injury and respiratory tract infection | Moderate | Unrelated | | SAE |
| 6 | Hex-V | 17 | Respiratory tract infection | Mild | Unrelated | | SAE |
| 7 | Hex-IH | 1 | Post immunization pyrexia | Severe | Related | Yes | SAR |
| 8 | Hex-IH | - | Tonsillitis and gastro-esophageal reflux disease | Mild | Unrelated | | SAE |
| 9 | Hex-V | 4 | Bronchiolitis | Severe | Unrelated | | SAE |
| 10 | Hex-V | 7 | Bronchiolitis | Mild | Unrelated | | SAE |
| 11 | Hex-V | 3 | Croup | Moderate | Unrelated | | SAE |
| 12 | Hex-IH | 4 | Bronchiolitis | Moderate | Unrelated | | SAE |
| 13 | Hex-V | - | Bronchiolitis and laryngomalacia | Severe | Unrelated | | SAE |
| 14 | Hex-V | 32 | Respiratory tract infection | Mild | Unrelated | | SAE |

**Figure S1 – Maximum severity of solicited local and systemic adverse events over days 0-5 following vaccinations with Hex-V (V) or Hex-IH (IH) (severity scales for induration, erythema, and swelling according to trial protocol)**

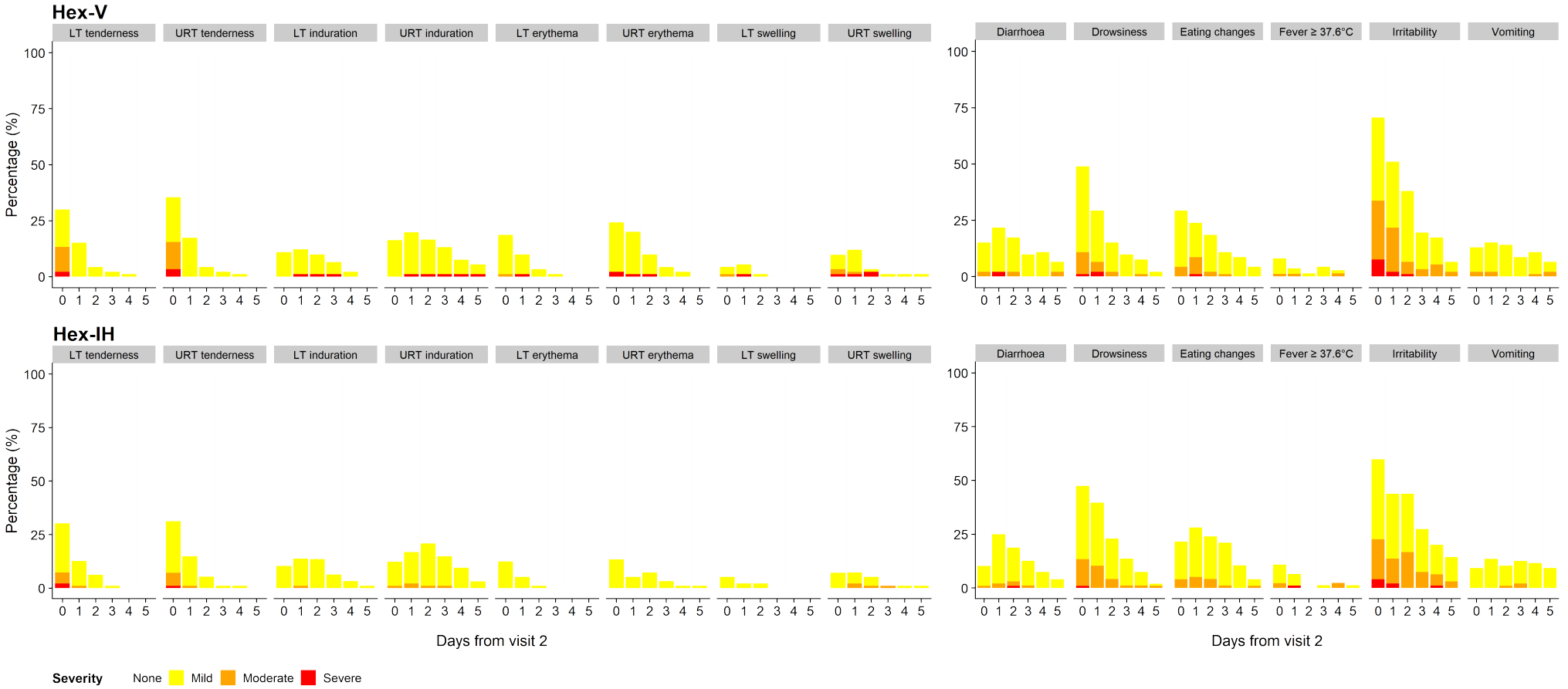

6 in 1 vaccine was given in the upper right thigh (URT) at all visits. MenB vaccine was given in the left anterolateral thigh (LT) at visits 1 and 3. PCV13 vaccine was given in the LT at visit 2.

**Figure S2 – Solicited local and systemic adverse events on days 0-5 following first vaccination with Hex-V or Hex-IH**



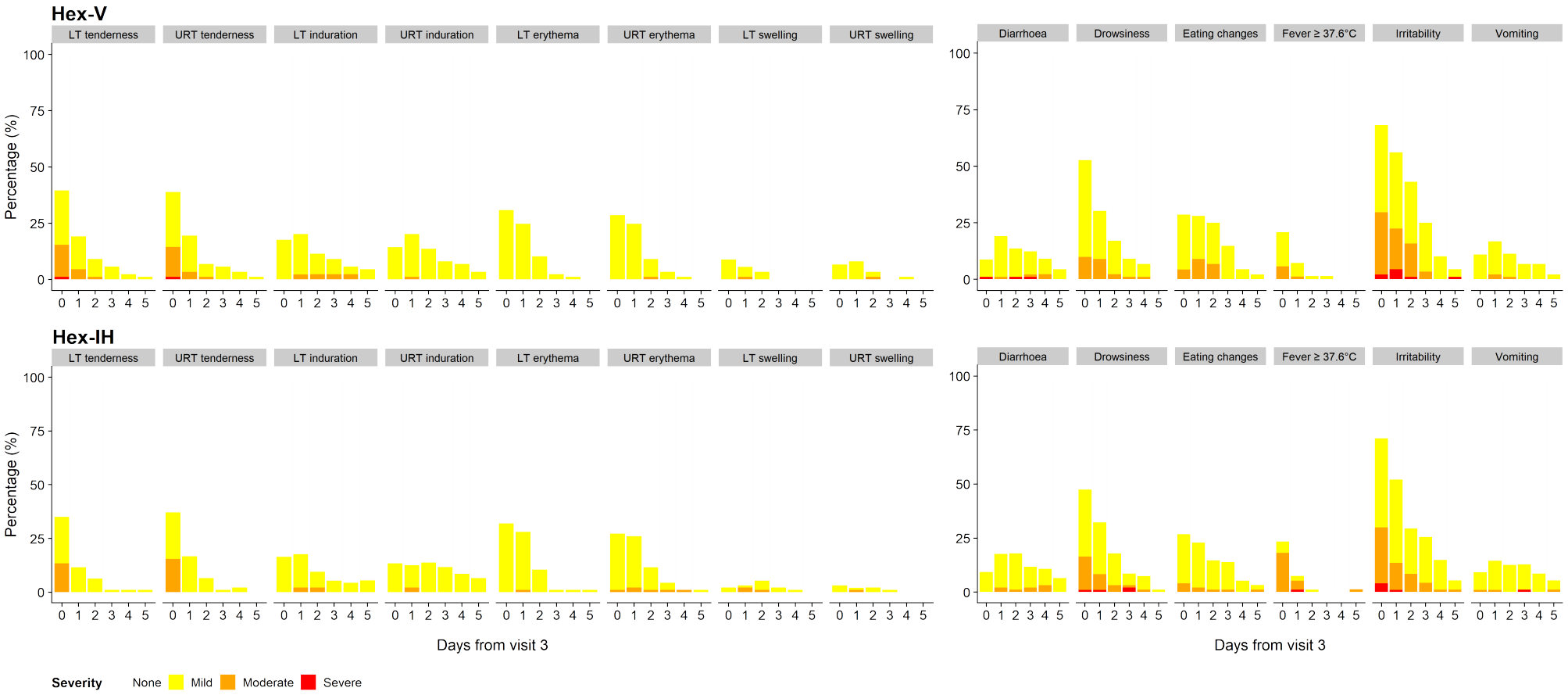

6 in 1 vaccine was given in the upper right thigh (URT) and Men B vaccine was given in the left anterolateral thigh (LT).

**Figure S3 – Solicited local and systemic adverse events on days 0-5 following second vaccination with Hex-V or Hex-IH**




6 in 1 vaccine was given in the upper right thigh (URT) and PCV13 vaccine was given in the left anterolateral thigh (LT).

**Figure S4 – Solicited local and systemic adverse events on days 0-5 following third vaccination with Hex-V or Hex-IH**




6 in 1 vaccine was given in the upper right thigh (URT) and Men B vaccine was given in the left anterolateral thigh (LT).