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Immunogenicity of a hexavalent vaccine co-administered with 7-valent pneumococcal conjugate vaccine. Findings from the National Immunisation Programme in the Netherlands

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Abstract

The hexavalent vaccine Infanrix hexa™ was introduced into the national childhood vaccination schedule in the Netherlands in 2006. It is offered, concomitantly with pneumococcal vaccine (Prevenar™), to children at increased risk of hepatitis B, administered in a 4-dose schedule at 2, 3, 4 and 11 months of age. We assessed the immunogenicity of the HBV component of Infanrix hexa™ co-administered with Prevenar™, and compared pertussis and Hib components in Infanrix hexa™ with the standard Infanrix-IPV+Hib vaccine. Target thresholds for immune responses were achieved for all antigens studied. Over 99% (163/164) of children vaccinated with Infanrix hexa™ achieved an adequate immune response (≥10 mIU/ml) to the HBV component and peak anti-HBs geometric mean concentration (GMC) was 2264mIU/ml (95% CI:1850-2771mIU/ml). The GMC of a pertussis component, filamentous hemagglutinin (FHA), of Infanrix-hexa was significantly lower in children vaccinated with Infanrix hexa™ and Prevenar™ than in children vaccinated with Infanrix-IPV+Hib. Universal infant HBV vaccination using Infanrix hexa™ was introduced in the Netherlands in 2011. Despite very high rates of seroconversion for the HBV component of Infanrix hexa™, its long term immunogenicity and effectiveness should be monitored after concomitant vaccination.
Introduction

Combination vaccines are used in national immunisation programmes for children worldwide. Simultaneous administration with newer vaccines against meningococcal or pneumococcal infection is thought to be more convenient, cost-effective and efficient for health care workers, and more acceptable to parents.\(^1,4\) However, the composition of combination vaccines has become increasingly complex and concerns have been expressed that co-administration of multicomponent and mono/multivalent vaccines may lead to a suboptimal induced immune response.\(^7\) Reduced clinical efficacy was shown in the UK with the *Haemophilus influenzae* type b (Hib) component when given in a combined, acellular pertussis containing vaccine (DTaP-Hib)\(^4\) and detailed assessment of potential antigenic interaction is advocated as new vaccines are introduced into national immunisation programmes.\(^3,4\)

The hexavalent vaccine, Infanrix hexa™ (GSK), was introduced into the national childhood vaccination schedule in the Netherlands on 1 June 2006 for children born to hepatitis B infected mothers and children of whom either parent was born in middle- or high- endemic countries for hepatitis B (prevalence \(\geq\)2%). This corresponds to approximately 18% of the total birth cohort in the Netherlands. Infanrix hexa™ contains recombinant surface antigen of the hepatitis B virus (HBV) in addition to vaccine components against diphtheria (D), tetanus (T), pertussis (Pa), poliomyelitis (IPV) and *Haemophilus influenzae* type b (Hib).\(^5\) It is administered by a single injection given at the same time as the pneumococcal vaccine, Prevenar™ (Pfizer Pharmaceuticals), added to the schedule in 2006. This limits the number of injections to two at 2, 3, 4 and 11 months of age, respectively. For children who are not in the target group for HBV vaccination, the pentavalent Infanrix-IPV+Hib (DTPa IPV/Hib), was given in 2005–2006. An alternative vaccine, Pediacel Prevenar™, (Sanofi Pasteur, MSD) was used in 2007, while Infanrix–IPV+Hib was reintroduced from 2008 onwards and is given concomitantly with Prevenar™. Universal infant HBV vaccination using Infanrix hexa™ will be introduced in September 2011.

Hexavalent vaccines were first licensed by the European Medicines Agency (EMEA) in 2000. In September 2005, authorization of one such vaccine, Hexavac (Sanofi Pasteur, MSD), was suspended by the EMEA: this was due to concerns about long-term immunogenicity of the hepatitis B component when co-administered with meningococcal or pneumococcal vaccines, and reduced boostability post-priming with Hexavac in infants with a low initial immune response.\(^6\) The WHO target threshold of \(\geq 95\)% of vaccine recipients achieving a peak geometric mean concentration \(\geq 10\) IU/l has consistently been achieved in other research.\(^7-9\) However, reductions (albeit non-significant) have been observed in the seroconversion rate\(^8\) and geometric mean concentration (GMC)\(^8,9\) of HBV antibodies following vaccination with Infanrix.
hexa™ concomitantly with pneumococcal vaccine when compared to that of Infanrix hexa™ administered alone. Reduced Hib immunogenicity has similarly been reported in combination vaccines co-administered with meningococcal and pneumococcal vaccines conjugated to the CRM197 carrier protein. Long term immunogenicity of the HBV component and of all components (with the exception of PT) of Infanrix hexa™ administered alone have been shown. This is irrespective of peak GMCs post primary vaccination, because they were not determined in these studies. The effectiveness of Prevenar™ and the Hib component of Infanrix hexa™ have also been demonstrated. There is as yet however, no evidence/data regarding the long term immunogenicity or effectiveness of Infanrix hexa™ co-administered with Prevenar™.

In the context of the National Immunisation Programme (NIP) in the Netherlands, we assessed whether the immune response to HBV vaccination within the Dutch NIP was sufficient according to WHO standards. Our secondary objective was to compare the immunogenicity of the Hib and pertussis components between Infanrix hexa™ co-administered with Prevenar™ with that of the standard vaccine, Infanrix–IPV+Hib administered alone.

Materials & Methods

Study design
A sample of children vaccinated at 2, 3, 4 and 11 months of age who attended healthy baby clinics in 10 municipalities and who had an indication for hepatitis B vaccination, was invited to participate in the study. Children with chronic disease or Down’s syndrome, and children of HBsAg positive mothers were excluded. This group, Group 1, were children born after 1 June 2006 and were vaccinated with Infanrix hexa™ co-administered with Prevenar™. For children in group 1, information about the ethnicity of parents and their children, gestational age, birth weight, and gender was also recorded.

To meet the second objective, a second group of children not considered at risk of HBV, Group 2, born from 1 November 2004 through 31 March 2005 and vaccinated with Infanrix–IPV+Hib, were recruited. Parents with children aged 11 months in group 1 were invited in person to participate at the healthy baby clinic and those in group 2 received an information letter at home. Both groups were asked to return to the clinic 4 to 6 weeks after booster vaccination. Written informed consent was obtained from the parents and a blood sample was taken from the child. The study protocol was approved by the Medical Ethics Review Committee (METC) of UMC Utrecht (group 1) and by the Central Committee on Research in Human Subjects (CCMO) in the Hague (group 2).
Laboratory methods
Venous samples were collected from infants 4 to 6 weeks post-vaccination after the 4th vaccine dose. Serological testing was performed at the Dutch National Institute for Public Health and the Environment (RIVM). Hib, pertussis and pneumococcal specific antibodies were measured using an ELISA with a twofold dilution series of samples. On each plate an in-house reference serum and a control serum were included. The in-house reference sera were calibrated to international reference sera as follows: Hib IgG antibody concentrations (μg/ml) with reference serum of CBER, FDA (Lot 1983); pertussis IgG antibody concentrations in ELISA Units/ml (EU/ml) against pertussis antigens Ptx and FHA with lot 3 and PRN with lot 4 FDA; and pneumococcal IgG antibody concentrations (μg/ml) with 89S-reference serum. Hepatitis B markers included anti-HBs and HBsAg. Anti-HBs was determined using MIA (Axsym, Abbott). HBsAg was determined only in children with an anti-HBs titer of <1000 IU/ml. The proportion of respondents achieving seroprotection was estimated according to the relative frequency of vaccinees achieving antibody concentrations above the pathogen specific cut-off levels: 0.15 μg/ml for Hib-PRP, and 0.35 μg/ml for pneumococcus. There are no internationally accepted standards for pertussis. Field studies have shown however, that antibodies directed against virulence factors pertactin (prn), fimbriae 2/3 (Fim), and pertussis toxin (ptx) are protective. For filamentous hemagglutinin (FHA), this is more complex. We used the arbitrary industry standard of 25 EU/ml.

Power calculation
We determined the sample size by considering only the primary objective regarding HBV immunogenicity in group 1. The WHO standard for an adequate immune response requires ≥95% of the vaccinees to achieve an anti-HBs titre ≥ 10 IU/ml. We expected 98% of vaccines to achieve this. At a precision of 2.5%, with a confidence level of 95%, 120 children were required in group 1. Based on the response of 32% in a recent cross-sectional population-based Dutch national sero-survey, it was estimated that a minimum of 480 children should be invited in group 1.

Statistical analysis
Data were entered and analysed using Microsoft Access and STATA 11. The proportion of respondents achieving seroprotection with its confidence limits was calculated using exact methods. The geometric mean concentration (GMC) was calculated using the antilog of the mean of the logarithmically transformed antibody concentrations. Given the non-normal distribution of the outcome variables, categorical associations were tested using the Kruskal-Wallis (KW) test. Based on Tukey’s ladder of powers, the square-root transformed outcome variable was used to conduct linear regression to determine how much of the variance in anti-
### Table 1. Proportion of samples achieving seroprotection (%), and peak antibody GMC levels of Infanrix hexa™ + Prevenar™ (Group 1) and Infanrix-IPV+Hib (Group 2) vaccines.

<table>
<thead>
<tr>
<th>Vaccine Component</th>
<th>Immunogen</th>
<th>Target concentration</th>
<th>% Achieving seroprotection</th>
<th>Geometric Mean Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 1 (n=164)</td>
<td>Group 2 (n=92)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infanrix hexa+ Prevenar</td>
<td>Infanrix IPV/Hib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% (n) [95%CI]</td>
<td>% (n) [95%CI]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GMC [95%CI]</td>
<td>GMC [95%CI]</td>
</tr>
<tr>
<td>Haemophilus</td>
<td>Anti-PRP</td>
<td>≥0.15μg/ml</td>
<td>98.7 (162) [95.9-99.9]</td>
<td>98.9 (88) [93.9-99.9]</td>
</tr>
<tr>
<td>Influenza B</td>
<td></td>
<td></td>
<td>7.3 [5.9-9.0]</td>
<td>9.8 [7.0-13.9]</td>
</tr>
<tr>
<td>Pertussis</td>
<td>PT</td>
<td>&gt;25EU/ml</td>
<td>98.2 (161) [95.0-99.6]</td>
<td>100.0 (92) [96.7-100]</td>
</tr>
<tr>
<td></td>
<td>FHA</td>
<td>&gt;25EU/ml</td>
<td>100.0 (164) [97.9-100.0]</td>
<td>100.0 (92) [96.7-100]</td>
</tr>
<tr>
<td></td>
<td>PRN</td>
<td>&gt;25EU/ml</td>
<td>99.4 (163) [96.8-99.9]</td>
<td>100.0 (92) [96.7-100]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>380.3 [331.1-436.8]</td>
<td>410.1 [343.7-489.2]</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Anti HBS</td>
<td>≥10 mIU/ml</td>
<td>99.4 (163) [96.8-99.9]</td>
<td>2264.1 [1849.7-2771.3]</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
<td>98.8 (161) [95.9-99.9]</td>
<td>3.7 [3.2-4.2]</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td></td>
<td>98.2 (160) [95.0-99.6]</td>
<td>5.2 [4.4-6.0]</td>
</tr>
<tr>
<td></td>
<td>9v</td>
<td></td>
<td>98.8 (161) [95.9-99.9]</td>
<td>3.4 [3.0-3.8]</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>14</td>
<td>≥0.35μg/ml for all subtypes</td>
<td>99.4 (162) [96.8-99.9]</td>
<td>N/A [9.6-12.8]</td>
</tr>
<tr>
<td>serotypes</td>
<td>18c</td>
<td></td>
<td>98.2 (160) [95.0-99.6]</td>
<td>2.7 [2.3-3.0]</td>
</tr>
<tr>
<td></td>
<td>19f</td>
<td></td>
<td>100.0 (163) [97.9-100.0]</td>
<td>3.7 [3.3-4.2]</td>
</tr>
<tr>
<td></td>
<td>23f</td>
<td></td>
<td>98.2 (160) [95.0-99.6]</td>
<td>4.0 [3.4-4.8]</td>
</tr>
</tbody>
</table>

* Prevenar, N_{total}=163; † Due to insufficient samples, results for Anti-PRP were available only for n=89 samples only; ‡ Exact confidence intervals for a proportion; † EU/ml: ELISA unit per milliliter; ‡ Difference between the geometric mean titres is statistically significant, p<0.001; ‡ IU/ml: International units per milliliter; • Not applicable.
HBs could be explained by predictor variables. To detect significant differences between the GMCs of groups 1 and 2, Student’s t-test was conducted (independent groups, two-tailed).

**Results**

In total, 478 children were eligible to participate in group 1 and 1181 in group 2. The proportion of respondents was 34% (n=164) and 8% (n=92) respectively. In group 1, 100% of children were born in the Netherlands, with only 26% of fathers and 23% of mothers themselves born in the Netherlands. Parents were of mixed ethnicities and the most commonly reported were: Turkish (15%), Moroccan (12%), Antillian (4%) and Surinamese (3%). The mean gestational age in group 1 was 39 weeks (range 33–42 weeks) and the mean birth weight was 3275g (range:1870g–4760g); 49% (n=72/146) were male.

At the time of booster vaccination, children were a median age of 11.1 months in group 1 (range: 9.6 to 13.4) and 11.7 months in group 2 (range: 10.1 to 13.5), p<0.001. The median time between last vaccination and blood sampling was 5.3 weeks in group 1 (range: 1.6 to 19.8) and 4.0 weeks in group 2 (range: 3.3 to 9.3 weeks), p<0.001. Proportions achieving seroprotection and geometric mean concentrations (GMCs) are presented in the table.

Of children in group 1, 99.4% (163/164) achieved an adequate immune response (≥10 mIU/ml) to the HBV component of Infanrix hexa™. The geometric mean concentration was 2264 mIU/ml (95% CI: 1850–2771 mIU/ml). Male infants had a lower anti-HBs concentration (1830 mIU/ml, 95% CI: 1357–2469 mIU/ml) than females (2898 mIU/ml, 95% CI: 2110–3980 mIU/ml, t=(-2.1), p=0.03). This difference persisted after controlling for ethnicity of parents (dichotomised as one-Dutch versus no-Dutch parent), birth weight and gestational age and explained 5% of the variance in anti-HBs (adjusted r-squared=0.05, p=0.002).

For both groups 1 and 2, no statistically significant differences in the proportions achieving seroprotection were seen between Infanrix hexa™ and Infanrix–IPV+Hib for Hib or pertussis. An adequate immune response was consistently achieved in over 98% of samples to all antigens tested. Five different children did not reach the seroprotective level in one component only, but each child responded satisfactorily to all the other components in the vaccines. In relation to Prevenar™, seven children did not achieve the seroprotective threshold of one or more components. In 2 cases, children did not respond to several subtypes (case 1 to subtypes 4, 9, 18c and 23f, and case 2 to subtypes 4 6b 9v 18c and 23f); five children showed an inadequate response to one component only (subtypes 6b (n=2), 14, 18c and 23f (n=1 for each). The proportion achieving pneumococcal antibody concentrations of ≥0.35 μg/ml ranged from 98.2% (subtypes 6B, 18C and
23F) to 100.0% (subtype 19F). The pneumococcal antibody GMCs ranged from 2.6μg/ml (subtype 18C) to 11.0μg/ml (subtype 14) (Table).

When comparing GMCs between groups 1 and 2, the titers against the pertussis FHA component of Infanrix hexa™ was significantly lower than in Infanrix–IPV+Hib (302EU/ml versus 422EU/ml; mean difference, 120EU/ml; \( p = 0.001 \)) There were no other statistically significant differences between antibody GMCs of other analysed vaccine components (Figure).

**Figure 1.** GMC ratio of group 1 to group 2 for vaccine components Hib, PT, FHA and PRN.

**Discussion**

The HBV component of Infanrix hexa™ co-administered with Prevenar™ adhered to the WHO guideline for an adequate immune response (≥95%), achieving seropositivity in >99% of cases. We found an anti-HBs GMC of 2264mIU/ml (95% CI:1850–2771), higher in girls than in boys. The anti-HBs GMC reported here is lower than has been reported elsewhere one month post-booster dose (given at 12–15 months) after the same primary vaccination schedule and using the same standard immune assays. Anti-HBs levels 2.6 to 3.4 times higher than those observed here are also reported where Infanrix hexa™ was administered alone (5754 mIU/ml, 6539 mIU/ml and 7517 mIU/ml respectively, though in the latter study, the vaccination schedule differed: 2, 4, 6 months with a booster at 12–19 months). Peak GMCs achieved post-vaccination are thought to be important because they are associated with the duration that concentrations remain above accepted protective thresholds. Although these studies are not directly comparable, such differences might be explained by the fact that children were boosted at 11 months here rather than at 12–19 months in the studies referenced. Second, there was a slightly longer period between the last vaccination and serum collection here (5.3 weeks), versus 4 weeks in Tichmann-Schumann et al. Third, children in our study who received HBV vaccination (group 1) all had parents of mixed
ethnicities whereas the reference studies\textsuperscript{8,9} included samples of the general population. Ethnic differences have been implicated in reduced serological response in other research.\textsuperscript{39} Fourth, it is possible that the maternal anti-HBs concentrations at the time of immunisation and sampling influenced infant anti-HBs, though the effect of this on the immune response to the vaccination series is uncertain. We could not study the effect of maternal antibody concentration. Finally, gender-linked differences in vaccine immune response are not uncommon;\textsuperscript{26} females have been reported to develop a more robust immune response to rubella and mumps vaccines for example.\textsuperscript{33,34} Although there are still uncertainties about the duration of long-term protection after vaccination against hepatitis B,\textsuperscript{35,36} it is clear that immunological memory with anamnestic response continues to protect children for many years against acute disease despite undetectable antibodies.\textsuperscript{13,37,38} Infanrix hexa\textsuperscript{™} was introduced into the universal childhood vaccine schedule in the Netherlands in September 2011 and protection against Hepatitis B will therefore be necessary for decades.\textsuperscript{39}

In relation to the antibody response to Prevenar when co-administered with Infanrix hexa\textsuperscript{™}, seroprotective thresholds for all seven serotypes included in the vaccine were achieved. GMCs for all components of Prevenar\textsuperscript{™} were similar to those reported in previous studies.\textsuperscript{8,9} On comparing Infanrix hexa\textsuperscript{™} (co-administered with Prevenar\textsuperscript{™}) and Infanrix−IPV+Hib (administered alone), there was no difference in the proportions seroprotected for Hib and pertussis. These findings are broadly similar to those in other research.\textsuperscript{8,9,40} Co-administration of Infanrix hexa\textsuperscript{™} with Prevenar\textsuperscript{™} did not affect GMCs for Hib, PRN or PT – but the FHA component in Infanrix hexa\textsuperscript{™} was significantly lower. Though speculative, it is hypothesized that FHA could play a role in modulating the protective immune response in combination vaccine formulations.\textsuperscript{41}

There were a number of study limitations. We studied a non-randomized sample of two groups of healthy infants recruited in 2006 and 2009. Different clinics participated in 2009 (group 1) and in 2006 (group 2) but regional variation in the delivery of the vaccination programme over time, including vaccine storage and administration is unlikely. National immunisation coverage in the Netherlands has consistently exceeded 94\% for DTPa−IPV/Hib in the general population since 2006. In 2009, uptake of Infanrix hexa\textsuperscript{™} in the risk group was 92.9\%.\textsuperscript{42} The time of the 4\textsuperscript{th} vaccination and sampling of children was statistically different between the groups (persisting when outliers were excluded i.e. those beyond +/- 2\textsuperscript{o} standard deviations of the mean). In absolute terms the difference was small and both vaccination and sampling were timely. Finally, the proportion of respondents from each clinic varied significantly by study group. This is probably explained by greater staff vigilance and a higher intensity of recruitment in the minority group who were administered a new vaccine. Other differences such as socioeconomic
background were not recorded, although, given that only healthy babies were included, it is unlikely that there were systematic differences between respondents and non-respondents that would influence the immunogenicity of the vaccines.

In conclusion, more than 99% of Infanrix hexa™ recipients vaccinated at 2, 3, 4 and 11 months of age and measured one month after booster vaccination, achieved an adequate immune response to the HBV component. For all components of both vaccines, standard seroprotective thresholds were achieved. The GMC for the anti-HBs component of Infanrix hexa™ co-administered with Prevenar™ reported here was robust, though it was lower than has been reported elsewhere. When compared to Infanrix–IPV+Hib vaccine, a significant reduction in peak GMC was observed for the FHA component of Infanrix-hexa. Antibodies to other components (Hib, PRN, PT) were similar. Despite very high rates of seroconversion, there is a lack of long term immunogenicity and effectiveness data for Infanrix hexa™ simultaneously administered with Prevenar™. Long term monitoring of children by immuno- and disease surveillance is indicated.

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