Antibody Concentrations Against the Infecting Serotype in Vaccinated and Unvaccinated Children With Invasive Pneumococcal Disease in the United Kingdom, 2006–2013

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Background. This study aimed to estimate, following invasive pneumococcal disease (IPD), the proportion of children with protective immunoglobulin G (IgG) concentrations against the infecting serotype compared with other vaccine serotypes, and to assess risk of recurrent IPD.

Methods. Pneumococcal antibody concentrations were available for 413 children with vaccine-type IPD diagnosed during 2006–2013. We compared serotype-specific IgG concentrations against the infecting vs other vaccine serotypes, after adjusting for confounders such as age using multilevel analyses.

Results. After IPD, a higher proportion of vaccine-naive children had IgG concentrations ≥0.35 µg/mL against their infecting serotype than other vaccine serotypes (51% vs 36%; P < .001). In contrast, among children immunized with pneumococcal conjugate vaccine (PCV) both before and after IPD, the proportion with IgG concentrations ≥0.35 µg/mL against the infecting serotype was lower compared with other vaccine serotypes (71% vs 98%; P < .001). These children also had lower IgG geometric mean concentrations (GMCs) against the infecting serotype (2.22 µg/mL) vs other vaccine serotypes (15.64 µg/mL) in multilevel models (IgG GMC ratio, 0.24; 95% confidence interval, 0.18–0.32), although their IgG GMC was higher compared with vaccine-naive children. Vaccinated children with IgG concentrations <0.35 µg/mL against their infecting serotype generally remained unresponsive despite further vaccine doses. However, recurrent IPD with the same infecting serotype was rare (7/3030 children [0.2%]) and not associated with unresponsiveness.

Conclusions. Vaccination with PCV before and/or after IPD was associated with lower IgG concentrations against the infecting serotype compared with other vaccine serotypes, but recurrent IPD was rare. Further studies are needed to understand this phenomenon in immunized children.

Keywords. immunization; immunoglobulin G; invasive pneumococcal disease; pneumococcal conjugate vaccine; vaccination.

Pneumococcal conjugate vaccines (PCVs) are highly effective in preventing invasive pneumococcal disease (IPD) caused by vaccine serotypes in children [1]. The United Kingdom introduced the 7-valent PCV (PCV7) (Prevenar, Pfizer Ltd) in September 2006 at a reduced 2, 4, and 12/13-month infant schedule, alongside a catch-up program for children aged <2 years [2]. Beginning in April 2010, PCV7 was replaced with a 13-valent PCV (PCV13) (Prevenar13; Pfizer Ltd), which includes 6 additional serotypes. As part of enhanced national surveillance, Public Health England (PHE) provided complementary national serotype-specific pneumococcal antibody testing for vaccine-eligible children who...
developed IPD after PCV introduction, with the aim of providing individualized post-IPD pneumococcal immunization advice to ensure adequate long-term protection against vaccine-type IPD.

 Shortly after PCV7 introduction, we described 8 children who remained unresponsive to their infecting serotype despite repeated pneumococcal vaccination following IPD [3]. We also identified a fully vaccinated child with a cochlear implant who developed recurrent serotype 4 meningitis and continued to have nonprotective antibody concentrations against the infecting serotype despite repeated PCV vaccination [4]. As a related phenomenon, recent studies have reported an association between carriage of a pneumococcal serotype before or at the time of PCV and a lower antibody response to the homologous serotype [5–9]. We were, therefore, interested to know if unresponsiveness after IPD might be more common than previously thought and whether it was specifically associated with the infecting serotype. We also speculated that, although recurrent IPD is rare and occurs in <5% of cases [10, 11], unresponsive children might be at increased risk of recurrent IPD by the same serotype.

 In this study, we analyzed serotype-specific pneumococcal antibody concentrations in children who had a serum sample submitted to PHE after vaccine-type IPD since PCV7 introduction. Our main objective was to estimate the proportion of children with protective immunoglobulin G (IgG) concentrations against the infecting serotype following IPD compared with other noninfecting vaccine serotypes. We also explored factors associated with lower IgG concentrations against the infecting serotype, including pneumococcal vaccination status and trends over time since PCV introduction, as well as the risk of recurrent IPD.

**METHODS**

**Ethical Considerations**

PHE has approval under Section 60 of the Health and Social Care Act 2001 to obtain patient identifying information to monitor the efficacy and safety of vaccination programs.

**Enhanced Surveillance of IPD**

Enhanced national surveillance of IPD in vaccine-eligible children (ie, born since 4 September 2004) up to 5 years of age began when PCV7 was introduced on 4 September 2006 [2]. Following laboratory confirmation of IPD, general practitioners and pediatricians were requested to complete a clinical questionnaire and advised about vaccination and testing for serotype-specific pneumococcal antibodies. Recommendations varied depending on the child’s age, pre-IPD immunization history, and infecting serotype. In general, unimmunized or partially immunized children were advised to complete the recommended schedule and provide a serum sample 1 month later for pneumococcal antibody testing, whereas fully immunized children were recommended to have an extra PCV dose and provide a serum sample 1 month later. Following this blood test, those with IgG concentrations below the putative protective threshold (<0.35 μg/mL) [12–14] against ≥2 vaccine serotypes or with IgG <1.00 μg/mL for all tested serotypes were advised to receive another PCV dose, followed by a blood test a month later. One more dose was recommended if the child remained unresponsive to ≥2 vaccine serotypes.

**Analysis of Serotype-Specific Antibody Concentrations**

Details of pneumococcal antibody testing are described elsewhere [3]. Samples were assayed by a multiplex microsphere assay incorporating both cell wall polysaccharide and serotype 22F adsorption [15]. Specific IgG concentrations against 12 of the PCV13 serotypes were measured; serotype 6A was not available from the American Type Culture Collection and, because of cross-reactivity with serotype 6B, could not be included in our multiplex immunoassay. Results below the lower limit of quantification (0.1 μg/mL) were assigned an arbitrary value of 0.05 μg/mL for analysis.

**Study Population**

All vaccine-eligible children in England, Wales, and Northern Ireland who developed laboratory-confirmed IPD between 4 September 2006 and 3 September 2013 were offered a blood test. For the main analyses, we included only children with IPD caused by the 12 assayed PCV13 serotypes. Two groups, differing by their immunization status, were included:

1. Children with serum sample 14–90 days after IPD and no vaccination in between.
2. Children with serum sample 14–90 days after first vaccination post-IPD. This second group included those who developed PCV7-type IPD and were subsequently immunized with PCV7 or PCV13, and those with additional PCV13-type IPD who were then immunized with PCV13. Most of these children were immunized to complete the primary series (<12 months old) or to boost their immune response post-IPD (≥12 months old). For children who had blood samples submitted after IPD as well as after vaccination post-IPD, only the first sample was considered and they were included in the first group.

The children in the 2 groups were further characterized by their immunization status prior to IPD, creating 4 vaccination status categories (vaccine-naive children, children only vaccinated before IPD, children only vaccinated after IPD, and children vaccinated before and after IPD). Some children who were not protected against their infecting serotype after first vaccination post-IPD received further vaccine doses, and response to vaccination was assessed on a case-by-case basis. Finally, all children with ≥2 IPD episodes were analyzed separately.
Statistical Analysis
We analyzed the proportion of children with IgG concentrations ≥0.35 µg/mL against their infecting serotype for each vaccination status category. We also compared antibody concentrations against the infecting serotype with antibody concentrations against other noninfecting vaccine serotypes. Comparison of proportions was performed using χ² or Fisher exact test, as appropriate. Children immunized with PCV7 were considered to be immunized against PCV7 serotypes and unimmunized against the extra PCV13 serotypes.

To compare IgG concentrations against the infecting serotype with other vaccine serotypes while allowing for differences between individual cases and serotype characteristics, we created a multilevel model with logged IgG concentrations for the 12 serotypes nested within individuals. Variables included at the serotype level were infecting serotype (yes/no), serotype evaluated (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), and delay for the blood sample (14–56 days, 57–90 days). Variables included at the individual level were age at blood sample (<1, 1–2, ≥3 years), clinical risk group (yes/no), and PCV era (before/after 1 April 2010). We repeated the model for each vaccination status category.

To assess whether antibody concentrations against the infecting serotype changed over time since PCV introduction, we developed a multivariable linear regression model using logged IgG concentrations against the infecting serotype for each individual. We included variables for calendar time (continuous variable from 2006 to 2013), age at blood sample, clinical risk group, delay for the blood sample, and serotype evaluated. We repeated the model for each vaccination status category. Results are given as IgG GMC ratios. The significance level was set at 5% and all tests were 2-sided. All analyzes were performed using Stata 13 software (StataCorp LP, College Station, Texas).

RESULTS

Study Population
During the 7-year period, 3030 vaccine-eligible children had ≥1 IPD episode and 1089 had a serum sample submitted for serotype-specific IgG concentrations (Figure 1). After excluding children with non-PCV13 IPD, with serotype 6A IPD, or with a serum sample submitted outside the 14- to 90-day window, 446 were included in the final analysis. In the first group, we assessed IgG concentrations against the infecting serotype in 183 children with a sample submitted post-IPD. Most children in this group developed IPD due to one of the extra PCV13 serotypes during the PCV7 era (Table 1). The second group, where we studied IgG concentrations after first vaccination post-IPD, comprised 230 children who developed vaccine-type IPD (PCV7-type during the PCV7 era and then mainly extra PCV13-type during the PCV13 era) and were subsequently vaccinated with the PCV recommended at the time. Finally, 33 children with ≥2 IPD episodes were analyzed separately.

Proportion of Children With IgG Concentrations ≥0.35 µg/mL Against the Infecting Serotype and Other Vaccine Serotypes
Among 164 vaccine-naïve children, 51% had IgG concentrations ≥0.35 µg/mL against their infecting serotype after IPD (Table 2). A lower proportion of infants aged <12 months had IgG concentrations ≥0.35 µg/mL compared with children aged ≥12 months (7/40 [17%] vs 77/124 [62%]; P < .001). Overall, vaccine-naïve children were more likely to have IgG concentrations ≥0.35 µg/mL against the infecting serotype than to the other vaccine serotypes (51% vs 36%; P < .001; Table 2).

A higher proportion of children immunized post-IPD had IgG concentrations ≥0.35 µg/mL against the infecting serotype than children tested directly after IPD, irrespective of their pre-IPD vaccination status (73% vs 52%; P < .001; Table 2). However, a lower proportion of these children had IgG concentrations ≥0.35 µg/mL against their infecting serotype than to other vaccine serotypes (73% vs 94%; P < .001; Table 2).

Children who were immunized pre-IPD were also less likely to have IgG concentrations ≥0.35 µg/mL against their infecting serotype after IPD than to other vaccine serotypes (63% vs 85%; P = .007; Table 2). In particular, the proportion of children with IgG concentrations ≥0.35 µg/mL against serotype 6B was much lower when serotype 6B was the infecting serotype than when it was not (29% vs 79%; P = .008; Table 3).

In children who were immunized before and after IPD, 71% (46/65) developed IgG concentrations ≥0.35 µg/mL against their infecting serotype compared with 98% (1505/1541) for other vaccine serotypes (Table 2). Serotype 6B was responsible for 9 of 19 (47%) cases with IgG concentrations <0.35 µg/mL against the infecting serotype despite vaccination before and after IPD (Table 4). Only 40% (6/15) of children with serotype 6B IPD had IgG concentrations ≥0.35 µg/mL against serotype 6B vs 93% (179/193) of children with IPD due to another serotype (P < .001; Table 3). Of the 19 children with IgG concentrations <0.35 µg/mL against their infecting serotype, 11 received further vaccine doses; 8 (73%) remained unresponsive, including 4 (36%) who remained unresponsive even when PCV was administered >1 year after IPD. Five of the 8 children had serotype 6B IPD.

A trend in serotype-specific IgG concentrations against the infecting serotype over time was observed in children immunized both before and after IPD. The proportion of children with IgG concentrations ≥0.35 µg/mL against the infecting serotype increased from 38% in 2006–2007 to 100% in 2012–2013 (P trend <.001; Supplementary Figure 1). This was also seen in the multivariable linear regression model, where the adjusted IgG GMC doubled each year (2.09 per year; 95% confidence interval [CI], 1.31–3.33; P = .003). Such a trend was not
observed among children who had only been immunized post-IDP (IgG GMC ratio, 1.18 per year; 95% CI, .80–1.75; \( P = .41 \)).

**Adjusted Serotype-Specific IgG GMCs After IPD According to Vaccination Status**

Multilevel models to compare IgG GMCs against the infecting serotype with other vaccine serotypes confirmed the trends observed when studying the proportion of children achieving the \( \geq 0.35 \mu g/mL \) putative protective threshold. In vaccine-naive children, the IgG GMC against the infecting serotype was significantly higher than the IgG GMC against the same serotype in children infected with other serotypes (IgG GMC ratio, 1.77; 95% CI, 1.46–2.15; Table 5). However, for vaccine-naive children immunized after IPD, the IgG GMC against the infecting serotype was 2-fold lower than the IgG GMC against the same serotype in children infected with other serotypes (IgG GMC ratio, 0.52; 95% CI, 0.42–0.65). Receiving PCV before IPD was also associated with a lower IgG GMC against the infecting serotype compared to the same serotype in children infected with other serotypes, and this was most significant in those who were vaccinated before and after IPD (IgG GMC ratio, 0.24; 95% CI, .18–.32). This association remained statistically significant even when serotype 6B was excluded (IgG GMC ratio, 0.32; 95% CI, .24–.43).
Risk of Further IPD Episodes

Only 33 of 3030 children (1.1%) had ≥2 IPD episodes, including 1 child with 3 episodes (0.03%). Sixteen (48%) children were in a clinical risk group and only 7 (21%) had the same infecting serotype for both episodes (3, 4, 6B, 10A, 10A, 17F, and 23F). Only 2 children had 2 IPD episodes caused by the same vaccine-preventable serotype despite age-appropriate immunization; 23F IPD in an asplenic child and the previously reported child with a cochlear implant (serotype 4 infection) [4]. We also identified 1 unresponsive case with serotype 18C IPD who subsequently developed serotype 18B IPD 13 months later.

DISCUSSION

The provision of a national pneumococcal antibody testing service as part of enhanced surveillance provided a unique opportunity to study serotype-specific antibody concentrations following IPD in vaccine-eligible children. Overall, vaccine-naïve children, especially infants, often had low IgG concentrations against their infecting serotype after IPD. A higher proportion of children vaccinated post-IPD had IgG concentrations ≥0.35 µg/mL against their infecting serotype, but to a lower extent compared with noninfecting vaccine serotypes. Children immunized prior to developing vaccine-type IPD were also less likely to have IgG concentrations ≥0.35 µg/mL against their infecting serotype compared with noninfecting vaccine serotypes. Children immunized prior to developing vaccine-type IPD were also less likely to have IgG concentrations ≥0.35 µg/mL against their infecting serotype compared with noninfecting vaccine serotypes, irrespective of their post-IPD vaccination status. Low IgG concentration against the infecting serotype was associated with serotype 6B, clustered around the period following PCV7 introduction, and often did not reverse despite multiple PCV doses post-IPD. The number and proportion of children with IgG concentrations <0.35 µg/mL against their infecting serotype declined with time since PCV introduction and, reassuringly, recurrent IPD was rare.

The finding that vaccine-naïve infants had low IgG concentrations against their infecting serotype is not surprising as they are unable to produce antibodies against bacterial capsular polysaccharides [16–20]. However, the observation that a lower proportion of children vaccinated before IPD developed

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1: Serum Sample After IPD (n = 183)</th>
<th>Group 2: Serum Sample After First Vaccination Post-IPD (n = 230)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 mo</td>
<td>43 (23.5)</td>
<td>33 (14.4)</td>
<td></td>
</tr>
<tr>
<td>12–35 mo</td>
<td>96 (52.5)</td>
<td>124 (53.9)</td>
<td></td>
</tr>
<tr>
<td>≥36 mo</td>
<td>44 (24.0)</td>
<td>73 (31.7)</td>
<td>0.033</td>
</tr>
<tr>
<td>Mean age, mo, at sample</td>
<td>25.0</td>
<td>27.9</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of Children in the Study—England, Wales, and Northern Ireland, September 2006–September 2013

<table>
<thead>
<tr>
<th>Vaccination Status</th>
<th>Group 1: Serotype</th>
<th>Group 2: Other Vaccine Serotypes (n = 4288)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sample after vaccination post-IPD</td>
<td>12/19 (63)</td>
<td>775/907 (85)</td>
<td>.007</td>
</tr>
<tr>
<td>Total</td>
<td>96/193 (52)</td>
<td>1148/1940 (59)</td>
<td>.078</td>
</tr>
</tbody>
</table>

Table 2. Proportion of Children With Immunoglobulin G Concentrations ≥0.35 µg/mL by Vaccination Status—England, Wales, and Northern Ireland, September 2006–September 2013

Abbreviations: IgG, immunoglobulin G; IPD, invasive pneumococcal disease.

* Children immunized with 7-valent pneumococcal conjugate vaccine (PCV7) were considered to be immunized against PCV7 serotypes and unimmunized against the extra 13-valent PCV serotypes.

b Eleven serotypes per child (the 12 vaccine serotypes evaluated minus the infecting serotype). A child could have a different vaccination status according to the specific serotype evaluated and may contribute to >1 vaccination category. Values for 255 noninfecting serotypes (6.6%) were missing.
IgG concentrations ≥0.35 µg/mL against their infecting serotype (63% after IPD and 71% after vaccination post-IPD vs 85% and 98%, respectively, for noninfecting vaccine serotypes) was unexpected as PCV is highly immunogenic for all vaccine serotypes [21]. A generalized impairment in innate, antigen-presenting or T-cell immunity is unlikely because this phenomenon was specifically related to the infecting serotype. When assessing risk factors for low IgG concentrations, we observed a higher contribution of serotype 6B that clustered around the immediate period after PCV7 introduction. Nasopharyngeal carriage before or at the time of pneumococcal conjugate vaccination in infants and toddlers has been associated with lower responses to the carried serotype [5, 6, 8, 9]. When PCV7 was introduced in the United Kingdom, serotype 6B was the most frequently carried serotype (18%) in children aged <2 years [7, 22], and was also the main culprit in trials reporting carriage-associated lower immune responses following vaccination [6, 8, 9]. Soon after PCV7 introduction, carriage of vaccine-preventable serotypes decreased to <3% [23, 24], which may explain the progressive decline in number and proportion of immunized children with low IgG concentrations against their infecting serotype. The lower immunogenicity of serotypes such as 6B in PCV [25–27] may have played a role, but the fact that a significantly higher proportion of vaccine-naive than immunized children had IgG concentrations ≥0.35 µg/mL after serotype 6B IPD suggests that immunization prior to IPD is a contributing factor.

It is also possible that the infection itself contributed to the low IgG concentrations against the infecting serotype. Animal [28, 29] and human [30] studies suggest that large pneumococcal polysaccharide loads bind to immature, serotype-specific B cells which, in the absence of carrier-induced T-cell help, do not differentiate into antibody-producing plasma cells, therefore depleting the memory B-cell pool and resulting in serotype-specific immune paralysis [3, 19]. As a related phenomenon, children initially immunized with a pneumococcal polysaccharide vaccine develop significantly lower serotype-specific IgG antibodies following subsequent vaccination with PCV [31]. In our study, this may explain why a significant proportion of children had low IgG concentrations against their infecting serotype despite repeated vaccination with a highly immunogenic conjugate vaccine after IPD.

A clinical implication of our findings is that children with IgG concentrations <0.35 µg/mL against their infecting serotype may be at increased risk of recurrent IPD. Such children also demonstrate poor functional opsonophagocytic activity against the same serotype, thus confirming the critical role of anticapsular polysaccharide antibodies in protecting against serotype-specific IPD [5, 6]. Additionally, the child who was unresponsive after serotype 18C IPD and subsequently developed serotype 18B IPD suggested that such children might also be at increased risk of IPD with vaccine-related serotypes. Our enhanced national surveillance over 7 years, however, indicates that recurrent IPD, especially with the same serotype, is rare, irrespective of vaccination status or IgG concentrations against the infecting serotype [10]. Moreover, the reduction in carriage of vaccine serotypes following routine pneumococcal vaccination [24] means that infants are less likely to carry a vaccine serotype at the time of vaccination, whereas those who are nonprotected against their infecting serotype should not be reexposed to the same vaccine-preventable serotype. Both these factors emphasize the importance of maintaining high vaccine coverage at a population level to ensure maximal herd protection.

A limitation of our study is that our findings are based on opportunistic analysis of serum samples following IPD rather than a carefully controlled trial and, as such, the results must be interpreted with caution. Although standardized national recommendations for vaccination and blood sampling were in place, these were not always followed and we had no control over which children had the recommended vaccines or blood samples taken. For example, children who died (6% of IPD cases) were not included. Of the submitted serum samples, too, we had to develop strict analytical criteria to interpret these data in a meaningful way. Additionally, categorization by immunization history meant that some subgroups included few cases for detailed analysis. Only serotype 6B IPD could be studied.

### Table 3. Proportion of Children With Immunoglobulin G Concentrations ≥0.35 µg/mL Against Serotype 6B—England, Wales, and Northern Ireland, September 2006–September 2013

<table>
<thead>
<tr>
<th>Vaccination Status</th>
<th>Children With Serotype 6B IPD (n = 40)</th>
<th>Children Infected by Other Vaccine Serotypes (n = 363)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sample directly after IPD</td>
<td>1/1 (100)</td>
<td>1/10 (10)</td>
<td>.182</td>
</tr>
<tr>
<td>Vaccine-naive children</td>
<td>2/7 (29)</td>
<td>96/121 (79)</td>
<td>.008</td>
</tr>
<tr>
<td>Children only vaccinated before IPD</td>
<td>13/17 (76)</td>
<td>18/39 (46)</td>
<td>.045</td>
</tr>
<tr>
<td>Children vaccinated before and after IPD</td>
<td>6/15 (40)</td>
<td>179/193 (93)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total</td>
<td>19/32 (59)</td>
<td>197/232 (85)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Values for 2.8% (10/413) of IgG concentrations against serotype 6B were missing.

Abbreviations: IgG, immunoglobulin G; IPD, invasive pneumococcal disease.
individually. Nevertheless, the use of multilevel regression models and adjustments for potential confounders improved statistical power and allowed a valid comparison of infecting serotypes with other vaccine serotypes at an individual level. Another limitation is the use of a universal putative protective threshold of 0.35 µg/mL despite evidence of serotype-specific

| Table 4. Number and Proportion of Children With Immunoglobulin G Concentrations ≥0.35 µg/mL—England, Wales, and Northern Ireland, September 2006–September 2013 |
|--------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | Aged <12 mo | | Aged ≥12 mo | | Total | | | |
| Infecting Serotype | No PCV Against Infecting Serotype Pre-IPD | ≥1 PCV Against Infecting Serotype Pre-IPD | No PCV Against Infecting Serotype Pre-IPD | ≥1 PCV Against Infecting Serotype Pre-IPD | No PCV Against Infecting Serotype Pre-IPD | ≥1 PCV Against Infecting Serotype Pre-IPD |
| PCV7 serotypes | | | | | | | |
| 4 | ... | ... | 2/2 (100) | ... | 2/2 (100) | ... |
| 6B | 6/8 (75) | 2/9 (22) | 7/9 (78) | 4/6 (67) | 13/17 (76) | 6/15 (40) |
| 9V | ... | ... | 1/1 (100) | 3/3 (100) | 1/1 (100) | 3/3 (100) |
| 14 | 6/6 (100) | 1/2 (50) | 10/16 (63) | 1/1 (100) | 16/22 (73) | 2/3 (67) |
| 18C | 1/1 (100) | 1/3 (33) | 2/3 (67) | ... | 3/4 (75) | 1/3 (33) |
| 19F | 1/2 (50) | 4/6 (67) | 1/2 (50) | 3/3 (100) | 2/4 (50) | 7/9 (78) |
| 23F | ... | ... | 0/1 (0) | 0/1 (0) | 2/3 (67) | 0/1 (0) | 2/4 (50) |
| Extra PCV13 serotypes | | | | | | | |
| 1 | 1/2 (50) | ... | 20/32 (63) | 5/5 (100) | 21/34 (62) | 5/5 (100) |
| 3 | 0/1 (0) | 2/2 (100) | 13/14 (93) | 8/9 (89) | 13/15 (87) | 10/11 (91) |
| 5 | ... | ... | ... | ... | ... | ... |
| 7F | 6/10 (60) | 4/4 (100) | 18/22 (82) | 1/1 (100) | 24/32 (75) | 5/5 (100) |
| 19A | 8/11 (73) | 2/3 (67) | 20/22 (91) | 3/4 (75) | 28/33 (85) | 5/7 (71) |
| Total | 29/41 (71) | 16/30 (53) | 94/124 (76) | 30/35 (86) | 123/165 (75) | 46/65 (71) |

Children infected with serotype 6A were excluded.

Abbreviations: IgG, immunoglobulin G; IPD, invasive pneumococcal disease; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

| Table 5. Adjusted Immunoglobulin G Geometric Mean Concentration Ratios Following Invasive Pneumococcal Disease—England, Wales, and Northern Ireland, September 2006–September 2013 |
|--------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Vaccination Status | No. of Observations (No. of Children) | IgG GMC, Infecting Serotype, µg/mL | IgG GMC, Other Vaccine Serotypes, µg/mL | Adjustedf IgG GMC Ratio (Infecting Serotype/Other Vaccine Serotypes) | 95% CI | P Value |
|________________________________|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Vaccine-naive children | 1162 (217) | 0.44 | 0.23 | 1.77 | 1.46–2.15 | <.001 |
| Only vaccinated before IPD | 893 (124) | 2.63d | 1.62 | 0.66 | .37–1.18 | .161 |
| Only vaccinated after IPD | 920 (161) | 1.02 | 2.16 | 0.52 | .42–.65 | <.001 |
| Vaccinated before and after IPD | 1491 (193) | 2.22 | 15.64 | 0.24 | .18–.32 | <.001 |

Information on clinical risk group was missing for 21 children, and these observations were not considered in the models.

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G; IPD, invasive pneumococcal disease.

* Children immunized with 7-valent pneumococcal conjugate vaccine (PCV7) were considered to be immunized against PCV7 serotypes and unimmunized against the extra 13-valent PCV serotypes.

Serotype-specific IgG concentrations against 12 serotypes were assessed for each child. A child could have a different vaccination status according to the specific serotype evaluated and may contribute to ≥1 vaccination category.

At the individual level, results were adjusted for age at blood sample, clinical risk group, and PCV era. At the serotype level, results were adjusted for the serotype evaluated and delay for the blood sample.

d In crude analyses, the IgG GMC for infecting serotypes was higher than the IgG GMC for other vaccine serotypes. This is due to 5 elevated responses to serotype 3 IPD (GMC, 84.5 µg/mL).
correlates of protection [32]. The correlate of 0.35 µg/mL, however, is still a good approximation, and more data are needed before using serotype-specific correlates [33]. Finally, we did not have carriage data or sera before or at the time of IPD and, therefore, can only speculate on the timing and underlying mechanisms for the lower antibody concentrations against the infecting serotype. Additional studies are needed to fully understand the mechanisms underlying the lower antibody concentrations against the infecting serotypes in vaccinated children.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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**Author contributions.** N. B., R. B., and S. N. L. participated in research design. P. W., E. S., E. N., R. A., M. P. E. S., E. M., R. B., and S. N. L. participated in the acquisition of the data. N. B., S. N. L., and N. A. participated in data analysis. N. B. wrote the first draft of the manuscript, and all authors participated in the interpretation of data and reviewed the article.

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