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Serotype-Specific Immune Unresponsiveness to Pneumococcal Conjugate Vaccine following Invasive Pneumococcal Disease▽

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Following the introduction of the pneumococcal 7-valent conjugate vaccine (PCV7) into the routine infant immunization schedule in England, Wales, and Northern Ireland, pneumococcal serotype-specific immunoglobulin G (IgG) antibody testing was offered as a clinical service to all children within the program with invasive pneumococcal disease (IPD) to confirm an adequate antibody response to PCV7. As of March 2008, serum samples taken within 14 to 90 days of vaccination had been submitted from 107 children who had received one or more doses in the second year of life. Sera were assayed by a multiplexed microsphere assay incorporating both cell wall polysaccharide and serotype 22F adsorption. A protective serotype-specific antibody level was defined as a concentration of ≥0.35 μg/ml. Eight children failed to develop a response to their infecting serotype (6B [*n* = 4], 18C [*n* = 2], 4 [*n* = 1], and 14 [*n* = 1]), despite receiving at least three doses of PCV7 in the second year of life or two doses in the second and two or three in the first year of life. A further two children were nonresponsive to a serotype (6B) different than that causing disease. None of the 10 children had a clinical risk factor for IPD. Two had marginally low levels of total serum IgG but mounted adequate responses to the other six PCV serotypes. This serotype-specific unresponsiveness may reflect immune paralysis due to large pneumococcal polysaccharide antigen loads and/or a potential genetic basis for nonresponse to individual pneumococcal serotypes.

Streptococcus pneumoniae is a major cause of morbidity and mortality in children less than 5 years of age (1, 20). Pneumococcal polysaccharide vaccines (PPV) are efficacious against invasive pneumococcal disease (IPD) in older age groups (29) but are not beneficial in children under 2 years of age (8, 17). The immune response to most serotypes is poor in children up to 5 years of age but improves up to 15 years of age (2, 8, 17, 25). Moreover, repeated doses of PPV have been associated with hyporesponsiveness to certain serotypes (23), as has been shown with repeated doses of meningococcal group C polysaccharide vaccine (12). Hyporesponsiveness occurs when antibody levels following a second antigenic challenge are lower than those following the first.

The issue of hyporesponsiveness to repeated doses of PPV has been reviewed recently (23). This paper also mentioned, as a related phenomenon, two case reports in which children convalescing from IPD were unable to respond to their infecting serotype when vaccinated with PPV (23). However, the evidence of immune unresponsiveness in these two cases was weak and anecdotal. In one report, a 6-month-old infant with serotype 14 IPD responded with a 512-fold increase to vaccination with serotype 4 polysaccharide administered 2 weeks after the onset of infection but not to immunization with serotype 14 polysaccharide given 6 weeks after the onset (22). Since, even in children up to 5 years, serotype 14 polysaccharide is poorly immunogenic (8), a specific inability to respond to the infecting serotype cannot be inferred in this case. The second report was of a 9-month-old infant with IPD due to serotype 18C (26) (not 19F as quoted by O'Brien et al. [23]). At 27 months of age, the child was vaccinated with a 14-valent PPV (PPV14) and responded adequately to serotypes 3, 8, and 9, but the response to the other serotypes was poor. There was no antibody response to serotype 18C. At 4 years of age, the child was reimmunized with PPV14. Preimmunization levels for all evaluated serotypes were within normal limits for the child's age, with a twofold increase seen in serotype 18C-specific antibody after revaccination.

The availability of pneumococcal conjugate vaccines (PCV) allows proper investigation of the ability of children with IPD to respond to their infecting serotype. PCV, unlike PPV, induces a T-cell-dependent response that renders it highly immunogenic in infants and does not induce hyporesponsiveness to subsequent doses. The 7-valent PCV (PCV7) was introduced in England and Wales in September 2006 to be administered in a routine schedule at 2, 4, and 13 months to infants, with a single-dose catch-up for children aged 12 to 23 months (6, 7). Pneumococcal serotype-specific immunoglobulin G (IgG) antibody testing was offered by the Health Protection Agency (HPA) as a clinical service to all children with IPD in the birth cohort eligible for PCV7 to confirm an adequate antibody

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TABLE 1. Categorization of children by number of doses of PCV7 received in their first and second years of life

Category	No. of doses of PCV7 in:	
	1st year of life	2nd year of life
Immunized under a reduced schedule	0	1
	1	1
	2	1
Immunized under original licensed schedule	0	2
	1	2
	3	1
Overimmunized	2	2
	3	2
	0	3
	1	3
	0	4

response to the PCV7. This provided an opportunity to study the relationship between the infecting serotype and the ability to mount an antibody response to that capsular polysaccharide. We report the findings in children investigated from September 2006 to March 2008.

MATERIALS AND METHODS

Following the reporting (to the Health Protection Agency by any route) of a case of IPD in a child eligible for routine or catch-up PCV7, the HPA contacts the laboratory that referred the isolate for serotyping or electronically reported the case to obtain name and contact details of the child's general practitioner and pediatrician (and to request referral of the isolate if not already done). The HPA also contacts the child's general practitioner to obtain dates of PCV7 immunizations and clinical risk group information. The child's pediatrician is contacted to request an appropriate blood sample. Sera are submitted to the Health Protection Agency Vaccine Evaluation Unit in Manchester, United Kingdom, for pneumococcal serotype-specific IgG antibody assaying. This complementary service has been offered since 4 September 2006 to confirm an adequate antibody response to the PCV7 for all children within the program (i.e., born on or after 4 September 2004) with confirmed IPD together with clinical advice about further vaccinations. An adequate response was defined as the concentration of serotype-specific IgG to all seven serotypes contained within PCV7 being $\geq$0.35 μg/ml.

Serum samples were assayed by a multiplexed microsphere assay incorporating both cell wall polysaccharide and serotype 22F adsorption (16). A putative protective serotype-specific antibody level was defined as a concentration of $\geq$0.35 μg/ml (32). Children were included in this report only if they met all the following criteria: the infecting pneumococcal serotype has been identified, the child received one or more doses of PCV7 in the second year of life and was not in a clinical risk group for IPD (7), and at least one blood sample was collected 14 to 90 days after a dose of PCV7 in the second year of life.

In order to categorize the children by the number of doses of vaccine received, we have divided them into three categories (Table 1). The first category includes children who have received one dose in the second year of life and two or fewer doses in the first year of life. These children we term "immunized under a reduced schedule." The second category contains children who had received two doses in the second year of life and one dose or less in the first year of life or had received one dose in the second year of life and three doses in the first year of life. These children we term "immunized under original licensed schedule." The third category contains children who had received either three or four doses in the second year of life and none or one dose in the first year of life or had received two doses in the second year of life and two or three doses in the first year of life. These children we have termed "overimmunized." Some children from whom more than one serum sample was available appear in more than one category.

The application for the enhanced surveillance and postvaccination antibody testing was approved by the Thames Valley Research Ethics Committee (reference no. 06/MRE12/17).

RESULTS

As of March 2008, 362 serum samples had been submitted from 241 infants and young children. Of these 241 children, 107 had received one or more PCV7 doses in the second year of life and an appropriate blood sample(s) had been collected. Of these 107 children, 85 were categorized as "immunized under a reduced schedule." Sera were also received from 40 children in the category "immunized under original licensed schedule." The serotype-specific IgG geometric mean concentrations, together with 95% confidence intervals and proportions of children in these categories who had achieved serotype-specific IgG concentrations of $\geq$0.35 μg/ml, are given in Table 2. Significantly lower serotype-specific IgG geometric mean concentrations were shown for children in the "immunized under a reduced schedule" category then for children in the "immunized under original licensed schedule" category.

Sera were also received from a further 13 children who were in the "overimmunized" category. Of these 13 young children, 3 (2.8% [3/107]) had mounted putatively protective concentrations of antibody to all the PCV7 serotypes and 10 (9.3% [10/107]) had failed to respond adequately to one serotype.

Not all children in the "immunized under a reduced schedule" category who failed to respond moved into the "immunized under original schedule" category, due to some being lost to follow-up. Likewise, some children in the "immunized under original schedule" category were not in the "immunized under a reduced schedule" category, as they were followed up only after their second dose in the second year of life. Some children appear in more than one category, as serum samples were collected following different numbers of doses. The numbers of children in various categories are given in Table 3.

We describe the 10 cases of young children who were unable to respond to one of the serotypes in PCV7. Eight cases failed to respond to their infecting serotype following PCV7. A further two cases (cases 9 and 10) where nonresponse was to a different serotype than that causing disease were included. The serotype-specific IgG concentrations, together with the age at IPD, ages at which vaccinations were given, and infecting serotype, are given in Table 4. Eight children who had experienced IPD, due to serotype 6B ($n = 2$), 14 ($n = 2$), 18C ($n = 2$), 19F ($n = 1$), and 7F ($n = 1$), were not classified as vaccine failures, due to IPD occurring before PCV7 or not being caused by a serotype contained in PCV7, and two, with infections due to serotype 6B, were considered PCV7 failures. Total serum IgG was measured for these children, with age-normal levels being found for 8 of the 10 children. Cases 5 and 10 had levels of 3.73 g/liter and 4.31 g/liter (age-normal range, 4.9 to 15.6 g/liter). These borderline-low IgG levels are of rather doubtful significance as they did not impair the ability to respond to the noninfecting serotypes.

DISCUSSION

This is the first report of young children failing to respond adequately to immunization with PCV7, despite receiving more doses than the original licensed schedule, following IPD. Failure to respond adequately to their infecting serotype may potentially be explained by large pneumococcal polysaccharide loads interacting and then depressing the immune system's ability to respond by depleting the memory B-cell pool. This

TABLE 3. Numbers of children in various vaccination categories

Vaccination category(ies) of children from whom blood sample(s) were received	No. of children
Reduced schedule only	60
Original licensed schedule only	15
Reduced schedule and original licensed schedule	19
Overimmunized only	3
Original licensed schedule and overimmunized	4
Reduced schedule and overimmunized	4
Reduced schedule, original licensed schedule, and overimmunized	2
Total	107

interpretation is consistent with the results of animal studies reported by Felton and Ottinger, who demonstrated that large doses of pneumococcal polysaccharide can act as a paralyzing agent on the immune system of mice (9, 10). However, in two cases, nonresponse was to a different serotype than that which caused disease. Of the 10 cases, two were defined as vaccine failures according to the United Kingdom schedule: case 6 had received one dose of PCV7 in the second year of life as part of the catch-up, while case 7 had received two doses of PCV7 in the first year of life. Both of these cases were due to serotype 6B.

Infection with a specific pneumococcal serotype and subsequent failure to respond to the same serotype in the conjugate vaccine may be due to a genetic inability of the child's immune system or to high zone tolerance induced by the initial infection, with functional or apoptotic deletion of responsive B cells. The antigen processing of a soluble polysaccharide antigen and that of an intact organism or a conjugate vaccine are dissimilar. The human immune response to soluble pneumococcal capsular polysaccharides is a T-cell-independent event (19) that does not involve major histocompatibility complex restriction. Little is known about the human regulation of IgG anti-capsular polysaccharide responses to intact pneumococci following IPD, but murine studies of serotype 14 have demonstrated that, unlike with soluble polysaccharide, responses are T cell dependent and T-cell antigen receptor specific (15). However, the responses to the polysaccharide on the intact bacterium showed no apparent memory, accelerated kinetics of primary Ig induction, or more-rapid delivery of T-cell help. Therefore, the differing responses seen in the mouse models are not necessarily based on the ability to recruit T-cell help but may depend on the nature of the B-cell antigen receptor signaling and/or responding B-cell subpopulations. Whether this applies to the human response to infection with an encapsulated pneumococcus or to pneumococcal serotypes other than serotype 14, which is a neutral polysaccharide, is currently unknown.

During a randomized, double-blind, placebo-controlled trial of PPV23 or placebo in 50- to 85-year-olds, 14 subjects developed culture-confirmed pneumococcal pneumonia (24). Three subjects in the PPV23 arm had both pre- and postvaccination sera collected, together with a serotyped pneumococcus isolate (serotypes 6A, 7F, and 23F). These three vaccinated subjects who developed pneumococcal pneumonia had postvaccination concentrations of serotype-specific IgG of ≥0.35 μg/ml to all of the serotypes measured (9 serotypes were measured for the patient infected with 7F, and 13 serotypes for the patients with 6A and 23F infections) but not to their infecting strain's serotype (24). This suggests that these individuals may have been

TABLE 2. Specific IgG concentration, protective antibody response, and infection characteristics of children in "reduced schedule" or "original licensed schedule" vaccination categories

Vaccination category	% of subjects with protective antibody response to all 7 serotypes in PCV7[a]	% of subjects with IPD due to serotype in PCV7	Serotype-specific IgG GMC [μg/ml (95% CI)][b]						
			4	6B	9V	14	18C	19F	23F
Reduced schedule	52.0 (39/75)	65.3 (49/75)	5.07 (3.66–7.02)	1.04 (0.65–1.67)	3.08 (2.23–4.26)	1.87 (1.25–2.81)	5.47 (4.05–7.40)	2.26 (1.51–3.38)	1.59 (0.97–2.60)
Original licensed schedule	77.8 (28/36)	52.8 (19/36)	17.73 (12.08–26.02)	3.34 (1.78–6.27)	8.87 (5.61–14.01)	9.10 (5.46–15.16)	11.29 (8.09–15.75)	8.57 (5.42–13.53)	8.02 (4.62–13.92)

[a] Protective antibody response was defined as a serotype-specific IgG concentration of ≥0.35 μg/ml.
[b] GMC, geometric mean concentration; CI, confidence interval.

TABLE 4. Vaccination, infection, and specific IgG characteristics of children who were immunologically unresponsive to a particular serotype

Case	Age (mo) when IPD occurred	Ages (mo) at which PCV7 administered	Time (days) from last dose of PCV7 to blood sample	Infecting serotype	Serotype-specific IgG concn (μg/ml) following last dose of PCV7[a]						
					4	6B	9V	14	18C	19F	23F
1	13.2	15, 17, and 19	78	18C	20.09	8.66	3.82	0.93	**0.02**	5.18	5.94
2	13.2	15, 19, and 25	28	18C	25.45	12.29	7.86	6.11	**0.03**	4.93	61.54
3	8.9	10, 14, 16, and 19	30	19F	6.64	6.27	1.63	6.47	5.65	**0.29**	6.85
4	7.0	8, 10, 12, and 14	28	6B	18.41	**0.34**	5.95	22.73	19.96	14.06	182.74
5	3.1	2, 5, 8, 14, and 17	60	6B	6.53	**0.05**	6.65	3.95	8.18	5.15	58.29
6	16.3	13, 20, and 23	45	6B	3.27	**0.01**	1.95	6.89	2.92	3.10	12.16
7	12.7	8, 11, 14, and 21	28	6B	100.24	**0.01**	56.24	115.36	83.37	31.29	39.14
8	12.5	14, 17, and 19	29	14	2.16	1.71	5.19	**0.25**	4.45	1.17	4.18
9	9.4	12, 14, and 17	36	14	19.41	**0.08**	6.17	7.35	20.15	9.18	15.84
10	13.7	13, 16, 20, and 26	49	7F	1.85	**0.08**	3.14	22.66	28.21	15.15	7.37

[a] The value for the serotype to which each child was immunologically unresponsive is in bold font.

nonresponsive to their infecting serotype before PPV23 administration and their infectious episode rather than that their nonresponsiveness was caused by disease.

In a study of 84 children with sickle cell disease who had received PPV23, 6 children went on to develop IPD in the period from 9 to 48 months following their last dose of PPV23 (3). Antibodies were measured in five of these patients. Four of these patients had either 6A or 6B infections and had not responded with a ≥2-fold rise in serotype-specific IgG to their last dose of PPV23 to these serotypes. Also, their serotype-specific IgG concentrations before IPD were low, at 0.97, 0.03, 0.13, and 0.25 μg/ml. The fifth case was due to serotype 23F, and this patient had responded with a ≥2-fold rise in serotype-specific IgG to all serotypes from before to after the last dose of PPV23, but before IPD, this subject had a low serotype 23F-specific IgG concentration of 0.08 μg/ml. The results of this study again suggest the nonresponsiveness of these individuals prior to IPD.

In immunogenicity studies, it is often reported that a minority (1 to 2%) of children are unresponsive to conjugate vaccination. One of these studies, of a PCV9, was of toddlers of 12 months of age to whom two doses were administered 2 months apart, followed by a dose of PPV23 at 18 months of age (11). One month following the two doses of PCV9, 2 of 37 (5%), 1 of 39 (3%), and 1 of 40 (2%) of the toddlers had serotype-specific IgG concentrations of ≤0.35 μg/ml for serotypes 6B, 9V, and 23F, respectively. Thus, 10% of healthy toddlers were nonresponsive to a particular serotype following two doses of PCV9. Following the dose of PPV23, only one toddler (2.7%) was not putatively protected with a concentration of ≤0.35 μg/ml. This percentage is similar to the 2.8% of the 107 young children who had had IPD and made an adequate immune response to all the PCV7 serotypes only when receiving immunization as defined in the "overimmunized" category. In contrast, the 9.3% of young children in this category who failed to respond to a specific serotype is three times higher.

In the present study, the inability of two children to respond to serotype 6B infection following IPD with serotype 7F or 14 cannot be explained by immune overload with polysaccharide, as serotype 7F and 14 polysaccharides do not share any cross-reactive determinants with serotype 6B (30). In this case it is assumed that these children's inability to mount an IgG response to this serotype was genetically determined.

It is known that significant variation occurs in the serotype-specific immune response to PCV, though the mechanisms behind this are poorly understood, with suggestions that the B-cell characteristics specific for a certain serotype may be different from those of B cells specific for other serotypes of pneumococci (14). In a murine model, it has been demonstrated that CRM197 conjugates of serotype 14 and 19F induce different patterns of cytokine response and, thus, different T-cell responses to the carrier protein, leading to different IgG subclasses to the polysaccharide and carrier protein (18). Studies of genetic influences on vaccine responses have mainly focused on human leukocyte antigen (HLA) alleles and Ig allotype genes (27). Serotype-specific IgG, Ig allotypes, and HLA types were determined in a study of the administration of PPV23 to unrelated white adults and Ashkenazi Jews (21). Selected individuals later received one or more doses of the vaccine and/or a single dose of a PCV5. The HLA type was not associated with antibody responses, but an association between serotype-specific IgG concentration and $Gm(23)^+$ allotype was demonstrated in unrelated, white, non-Jewish adults but not in Ashkenazi Jews (21). Repeated vaccination or the administration of PCV5 did not elicit measurable IgG responses in nonresponders. Persons who did not make IgG to an individual serotype also failed to make IgM or IgA to that serotype antigen (21).

Associations between host genetic factors, such as single-nucleotide polymorphisms in the interleukin-4 pathway (T-helper 2 cytokines), have been demonstrated to be linked to lower antibody responses following pneumococcal conjugate and polysaccharide vaccination but not to a complete nonresponse to a particular serotype (31).

In a murine model, in vivo humoral immune responses to pneumococcal polysaccharides have been demonstrated to be dependent on the presence of associated Toll-like receptor (TLR) ligands, and the presence of a TLR2 ligand(s) in PCV7 upregulates the induced serotype-specific IgG response (28). Thus, subtle polymorphisms affecting TLR structure or function may lead to an inability to seroconvert to a particular serotype following vaccination with PCV7.

Recently, a suggestion has been made that nasopharyngeal

carriage at the time of administration of PCV7 is associated with serotype-specific unresponsiveness to the carried pneumococcal capsular polysaccharide (5). Hyporesponsiveness caused by carriage could be induced by high polysaccharide loads depleting the serotype-specific B-cell pool. It is known that the polysaccharide antigen can be found in the urine of persons carrying pneumococci (13), as well as those with IPD (4), but it is not detectable in adults following immunization with PPV23, which contains 575 μg of polysaccharide (personal communication from Robert George). However, the reported hyporesponsiveness due to carriage at the time of administration of PCV7 did not persist following a booster of PCV7 (5). All 10 of the children in this report had received two or more doses of PCV7 in their second year of life; thus, it is unlikely that carriage has resulted in the inability of these children to respond.

The observations from these nine cases illustrate the complexity of the human immune response to a particular pneumococcal serotype following IPD, and future work should focus on these issues to enable understanding of the human immune response to large pneumococcal polysaccharide antigen loads, as well as potential genetic bases for nonresponse to individual pneumococcal serotypes. A practical implication of these findings may be that, in individuals who have had an episode of IPD, pneumococcal vaccination strategies should not be assumed to confer 100% protection. Monitoring of antibody levels postvaccination may be useful.

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