Antibody Responses After Primary Immunization in Infants Born to Women Receiving a Pertussis-containing Vaccine During Pregnancy: Single Arm Observational Study With a Historical Comparator

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(See the Editorial Commentary by Cherry on pages 1645–7.)

Introduction. In England, antenatal pertussis immunization using a tetanus/low-dose diphtheria/5-component acellular-pertussis/inactivated-polio (TdaP$_5$/IPV) vaccine was introduced in October 2012. We assessed infant responses to antigens in the maternal vaccine and to those conjugated to tetanus (TT) or the diphtheria toxin variant, CRM.

Methods. Infants of 141 TdaP$_5$/IPV-vaccinated mothers in Southern England immunized with DTaP$_5$/IPV/*Haemophilus influenzae* b (Hib-TT) vaccine at 2-3-4 months, 13-valent pneumococcal vaccine (PCV13, CRM-conjugated) at 2–4 months and 1 or 2 meningococcal C vaccine (MCC-CRM- or MCC-TT) doses at 3–4 months had blood samples taken at 2 and/or 5 months of age.

Results. Antibody responses to pertussis toxin (PT), filamentous hemagglutinin (FHA), fimbriae 2 + 3 (FIMs), diphtheria, tetanus, Hib, MCC and PCV13 serotypes were compared to responses in a historical cohort of 246 infants born to mothers not vaccinated in pregnancy. Infants had high pertussis antibody concentrations pre-immunization but only PT antibodies increased post-immunization (fold-change, 2.64; 95% confidence interval [CI], 2.12–3.30; $P < .001$), whereas FHA antibodies fell (fold-change, 0.56; 95% CI, .48–.65; $P < .001$). Compared with infants of unvaccinated mothers, PT, FHA, and FIMs antibodies were lower post-vaccination, with fold-differences of 0.67 (0.58–0.77; $P < .001$), 0.62 (0.54–0.71; $P < .001$) and 0.51 (0.42–0.62; $P < .001$), respectively. Antibodies to diphtheria and some CRM-conjugated antigens were also lower, although most infants achieved protective thresholds; antibodies to tetanus and Hib were higher.

Conclusions. Antenatal pertussis immunization results in high infant pre-immunization antibody concentrations, but blunts subsequent responses to pertussis vaccine and some CRM-conjugated antigens. In countries with no pertussis booster until school age, continued monitoring of protection against pertussis is essential.

Keywords. antenatal immunization; maternal vaccination; pertussis; immune interference; conjugate vaccines.

The United Kingdom (UK) introduced a temporary immunization program against pertussis for pregnant women on 1 October 2012 [1], following a marked increase in pertussis cases across all age-groups, but particularly in young infants, who were at increased risk of severe disease, hospitalization, and death [2]. These infants were too young to be protected by the infant

immunization program, which, in the UK, is given at 2-3-4 months. Vaccinating pregnant women (ideally between 28 and 32 weeks gestation, but up to 38 weeks) offered the opportunity for early protection through transplacental transfer of maternal antibodies until active immunity could be achieved through infant immunization [3, 4]. Because this program was an emergency response, the vaccine offered to pregnant women was one that was readily available as a preschool booster—a combined tetanus, low-dose diphtheria, 5-component acellular pertussis, inactivated polio vaccine (TdaP/IPV; Repevax; Sanofi Pasteur). The UK antenatal immunization program rapidly achieved 60% vaccine coverage, with >90% vaccine effectiveness in preventing infant disease [5, 6].

Maternally derived antibodies are, however, known to interfere with infant responses to primary immunization with the same vaccine antigens [7], as has been observed following immunization with diphtheria-tetanus-acellular pertussis (DTaP) vaccines at birth [8]. Because the polysaccharide-based vaccines given in infancy (*Haemophilus influenzae* b [Hib], meningococcal C [MCC], and 13-valent pneumococcal [PCV13] vaccines) are conjugated to tetanus toxoid (TT) or a naturally occurring diphtheria toxin variant (CRM), high maternal tetanus and diphtheria antibody concentrations could potentially interfere with infant immune responses against these conjugate vaccines, particularly as reduced priming schedules for MCC (1 dose) and PCV13 (2 doses) are used in the UK.

Following the introduction of the antenatal pertussis program, therefore, we undertook a clinical service evaluation to assess responses to primary immunization in infants born to UK women who received Repevax in pregnancy and compared their responses to a historical cohort of infants born to women who did not receive Repevax during pregnancy.

METHODS

Infants born to women who received Repevax during pregnancy were identified from general practices (GP) in Hertfordshire, Gloucestershire, and South London, UK, prior to receipt of their first vaccinations. Any infant eligible for the national immunization program could be included. Recruitment commenced in December 2012 and the final blood sample was taken in July 2014. Following informed written consent, a blood sample was obtained by experienced pediatric nurses and doctors within 7 days before the first immunization visit and 3–6 weeks after the third immunization visit. Infants were immunized at their GP surgeries with the following vaccines obtained from the Department of Health, which holds a central national stock:

- Diphtheria, tetanus, 5-antigen pertussis, inactivated polio and Hib (TT-conjugated) (DTaP5-IPV-Hib; Pediacel; Sanofi Pasteur) at 2-3-4 months

- PCV13 (CRM-conjugated; Prevenar13; Pfizer Ltd) at 2–4 months
- Until 30 May 2013, 2 doses at 3 and 4 months of any 1 of 3 licensed MCC vaccines: NeisVac-C (Baxter Healthcare Ltd, UK), Menjugate (Novartis Vaccines and Diagnostics, Italy), or Meningitec (Pfizer Ltd, UK). NeisVac-C is conjugated to tetanus toxoid (MCC-TT), whereas the latter 2 are conjugated to CRM. From 1 June 2013, infants were to receive a single dose at 3 months of NeisVac-C or Menjugate [9]. The MCC vaccine administered was dependent on local vaccine stock.
- Oral rotavirus vaccine (Rotarix, GSK Biologicals) at 2–3 months from July 2013 onward.

Maternal and infant vaccination history were obtained at the second blood sampling visit and confirmed from infant immunization records, if required. Antibodies to pertussis toxin (PT), filamentous hemagglutinin (FHA) and fimbriae 2 and 3 combined (FIMs), diphtheria toxin, TT, and Hib polyribosylribitol phosphate IgG were quantified using in-house enzyme-linked immunosorbent assays (ELISAs) at Public Health England (PHE) Immunoassay Laboratory, Porton Down, based on published methods [10, 11], and validated in accordance with International Conference on Harmonisation guidelines [12]. MenC responses were measured at PHE Meningococcal Reference Unit using a serum bactericidal antibody (SBA) assay with rabbit complement as previously described [13]. Serotype-specific pneumococcal antibodies were measured at the Immunobiology Unit, Institute of Child Health, using the World Health Organization reference ELISA (http://www.vaccine.uab.edu/ELISA%20Protocol.pdf) as previously described [14]. We were unable to test vaccine responses against pertactin due to temporary unavailability of the antigen used in the assay.

To fulfill a duty of care, infants with antibodies below putative protective thresholds after primary immunization for MenC (SBA <8), Hib (<0.15 µg/mL), diphtheria (<0.1 IU/mL), tetanus (<0.1 IU/mL), or serotype-specific pneumococcal antibody (<0.35 µg/mL for ≥7 serotypes) were offered an extra dose of the relevant vaccine [15]. Although there is evidence that antibodies to PT, pertactin, and fimbriae are involved in protection, there are no threshold antibody levels for pertussis antigens that are accepted as indicative of individual protection [16]. Therefore, additional doses of pertussis-containing vaccine were not offered.

Data Analysis
The primary aim was to assess whether antenatal immunization adversely affected the proportion of infants achieving protective antibody concentrations to conjugate vaccines and to diphtheria and tetanus. Because there are no established thresholds for protection for pertussis antigens and because infants of vaccinated women would be expected to achieve high antibody

concentrations to the pertussis antigens, the secondary aims were to compare post-primary geometric mean concentrations (GMCs) to PT, FHA, and FIMs with those in a historical control group and to investigate the relationship between pre-immunization and post-immunization IgG antibody concentrations. Other analyses included investigating the timing of antenatal vaccination on pre-immunization antibody concentrations and assessing infant responses according to the MCC vaccine received.

A minimum target sample size of 100 was chosen to give acceptable precision for proportions above protective titers. For example, if 90% of infants achieved the threshold, the 95% confidence interval (CI) would be 82%–95%. This planned recruitment was increased to 140 when the infant MCC schedule was reduced to a single dose at 3 months so that sufficient data could be collected to confirm that this group remained adequately protected.

Geometric means were calculated with 95% CI and compared using the Student t-test. Proportions above cut-offs with exact 95% CI were compared using the χ^2 or Fisher exact test, as appropriate. MenC SBA titers <4 were assigned a value of 2 and, for other antigens, results below the detection limit were set at the detection limit. The effect of timing of antenatal vaccination (<10/≥10 weeks before birth and as a continuous variable) was assessed using normal errors regression on logged antibody concentrations/titers and logistic regression on proportions above thresholds. Normal errors regression was also used to assess the effect of prevaccination antibody levels on post-vaccination levels of the same antibody with factors included to allow for interval between last vaccination and blood sample and MCC schedule. The effect was measured as a fold-change on post-vaccination levels per 2-fold change in pre-level. When assessing MCC vaccination schedule, infants receiving Menjugate_Menjugate (n = 3), Menjugate_Meningitec (n = 1), or Meningitec_NeisVac-C (n = 3) at 3–4 months or Meningitec alone (n = 4) at 3 months were excluded because of small numbers. Normal errors regression was on logged titers and included interval to blood sample.

Post-vaccination responses were compared to a historical cohort of 246 infants whose mothers did not receive a pertussis-containing vaccine in pregnancy [17]. This was an open, non-randomized study conducted by the same investigators in 2 of the same geographical areas (Gloucestershire/Hertfordshire) in 2011–2012 that assessed antibody responses in infants 1 month after primary immunization with the same vaccines and schedule and with samples tested by the same laboratories and assays as in this evaluation. Data were adjusted for interval between last vaccination and blood sampling but not for MCC vaccination schedule because two-thirds of infants in the current evaluation were recruited after the national schedule was reduced to a single MCC dose.

RESULTS

A total of 141 children born to women who received TdaP/IPV (Repevax) in pregnancy and who were eligible for the nationally recommended primary immunization schedule were recruited. Of these, 127 had pre- and post-immunization antibody results against ≥1 vaccine antigen, whereas 9 had pre-immunization and 4 had post-immunization bloods only. Not every blood sample could be tested for all antigens because of insufficient sample or assay failure. The median interval (interquartile range [IQR]) between antenatal vaccination and infant birth was 9.9 (IQR, 8.0–11.1) weeks. The infants' median (IQR) ages at pre- and post-immunization blood samples were 55 (52–58) and 151 (144–161) days, respectively, and ages at each vaccination visit were 59 (57–61), 89 (86–95), 119 (115–128) days.

Infant Responses to Pertussis Antigens

At 2 months, prior to receiving their primary immunizations, antibody concentrations to the 3 tested pertussis antigens were high in most infants (Table 1, Figure 1). One month after completing primary immunizations, PT GMCs were higher than pre-immunization GMCs but FIMs and FHA GMCs were lower (Table 1). In the normal errors regression model, there was a significant inverse association within individuals between antibody concentrations before and after primary immunization to PT (0.89-fold per 2-fold increase in pre-vaccination concentration; 95% CI, .81–.98; $P = .023$) and FIMs (0.92-fold; 95% CI, .86–.98; $P = .011$), whereas for FHA there was a positive association (1.20-fold; 95% CI, 1.11–1.31; $P < .001$). Compared with the historical cohort of infants whose mothers did not receive Repevax in pregnancy, antibody concentrations after primary immunization were lower for all 3 pertussis antigens (Table 1, Figure 1).

The timing of antenatal vaccination prebirth was not associated with any of the infant pre-immunization antibody concentrations or proportions achieving protective thresholds for the antigens in the maternal vaccine, except for FHA, where a 1.08-fold increase (95% CI, 1.03–1.14) was observed per week prebirth ($P = .002$). The FHA GMC in infants whose mothers were vaccinated ≥10 weeks prebirth was 51.3 (95% CI, 41.2–63.9) IU/mL compared with 40.1 (32.9–48.9) IU/mL in those vaccinated <10 weeks ($P = .094$).

Infant Responses to Other Vaccine Antigens

Nearly all infants had protective antibody levels to diphtheria and tetanus prior to their first dose at 2 months and after primary immunization. Compared to the historical cohort, diphtheria antibody concentrations were significantly lower (0.55-fold, 95% CI, .46–.66; $P < .001$), whereas tetanus antibody concentrations were significantly higher (1.24-fold; 95% CI, 1.05–1.46; $P = .011$) (Table 2). There was an inverse association in the normal errors regression model between pre- and post-

Table 1. Geometric Mean Concentrations (GMCs) for the 3 Tested Pertussis Antigens Before and 1 Month After Primary Immunization in Infants Whose Mothers Were Given a Pertussis-containing Vaccine During Pregnancy Compared With GMCs at 1 Month After Primary Immunization in Infants in the Historical Cohort Whose Mothers Did Not Receive a Pertussis-containing Vaccine During Pregnancy

	N	Geometric Mean Concentration (95% CI)	Fold-ratio	P Value
Pre-1st dose				
Pertussis toxin (PT)	134	11.2 (9.6–13.1)	. . .	
Filamentous hemagglutinin (FHA)	135	46 (39.8–53.1)	. . .	
Fimbriae 2 + 3 (FIM)	133	123.2 (92.7–163.5)	. . .	
Post-3rd dose			(post vs pre)	
Pertussis toxin (PT)	129	28.8 (25.7–32.4)	2.64 (2.12–3.30)	<.001
Filamentous hemagglutinin (FHA)	131	25.5 (23.0–28.3)	0.56 (0.48–0.65)	<.001
Fimbriae 2 + 3 (FIM)	130	113.9 (99.0–131.1)	0.82 (0.59–1.13)	.22
Historical control			(post vs historical control)	
Pertussis toxin (PT)	203	43.2 (39.4–47.2)	0.67 (0.58–0.77)	<.001
Filamentous hemagglutinin (FHA)	199	41.1 (37.5–45.1)	0.62 (0.54–0.71)	<.001
Fimbriae 2 + 3 (FIM)	197	224.9 (196.1–258.0)	0.51 (0.42–0.62)	<.001

Abbreviation: CI, confidence interval.

vaccination levels for diphtheria antibodies (fold-change, 0.76; 95% CI, .71–.82; $P < .001$) but not for tetanus antibodies (fold-change, 1.08; 95% CI, .99–1.18; $P = .069$).

After primary immunization, 96.2% of infants achieved the short-term protective threshold for Hib (≥ 0.15 µg/mL) and the Hib IgG GMC (4.92 µg/mL) was 2.3-fold (95% CI, 1.6–3.3; $P < .001$) higher than in the historical cohort (Table 2). For PCV13 serotypes, most infants had protective antibody concentrations (≥ 0.35 µg/mL), although the proportion achieving the protective threshold for serotypes 3, 5, and 9V was lower when compared with the historical cohort (Table 2). Pneumococcal serotype-specific GMCs were also significantly lower for seven serotypes (1, 3, 4, 5, 6A, 7F, and 9V) when compared with the historical cohort (Table 2).

MenC SBA responses varied by MCC vaccination schedule (Supplementary Table 1). Post-immunization SBA GMTs were significantly lower for infants receiving a single MCC-CRM dose, compared to those receiving a single MCC-TT or 2 MCC-CRM doses. Overall, however, most infants (91.6%) achieved the protective threshold irrespective of MCC schedule, although the proportion was lowest (84.4%) in those receiving a single MCC-CRM dose at 3 months.

Pre-immunization Diphtheria and Tetanus Antibody Concentrations and Responses to Conjugate Vaccines

For Hib, there was no association in the normal errors regression model between post-immunization antibody levels and pre-vaccination levels of either tetanus or diphtheria. This was also the case for PCV13 serotypes, apart from serotype 14 for which an inverse association was found for both diphtheria (fold-change, 0.82; 95% CI, .72–.92; $P = .001$) and tetanus (0.78; 95% CI, .65–.93, $P = .005$).

Post-immunization MenC SBA titers, however, were inversely associated with pre-immunization diphtheria levels in infants receiving a MCC-CRM conjugate vaccine (fold-change, 0.74 per 2-fold increase in pre-vaccination titers; 95% CI, .60–.92, $P = .005$) but not in those receiving the MCC-TT vaccine (fold-change, 1.05; 95% CI, .83–1.32, $P = .71$). There was no association between pre-immunization tetanus antibody concentrations and MenC SBA titers overall or by any MCC vaccination schedule (eg, fold-change for single-dose MCC-TT, 1.15; 95% CI, .83–1.57, $P = .40$).

DISCUSSION

The UK antenatal immunization program against pertussis has been highly effective in preventing early infant disease and deaths [5, 6], but there was concern that high pre-immunization maternally derived antibody concentrations to pertussis, diphtheria, and tetanus might interfere with infants' response to the same vaccine antigens and those conjugated to CRM or TT [7]. We found that antibody responses to pertussis antigens were significantly attenuated compared to a historical cohort of infants whose mothers did not receive a pertussis-containing vaccine antenatally. For 2 pertussis antigens, GMCs were lower after the third dose than pre-immunization. In the UK, a pertussis booster is not given in the second year of life, and the only additional pertussis dose after priming is offered at school entry. Because there are no correlates of protection for pertussis, it will be important to monitor disease rates closely until school age among infants whose mothers were immunized antenatally.

Blunting of infant responses to acellular pertussis antigens after antenatal immunization has been reported in 2 recent US studies that assessed responses after a 2-4-6 month priming schedule in 16 and 32 infants, respectively [18, 19].
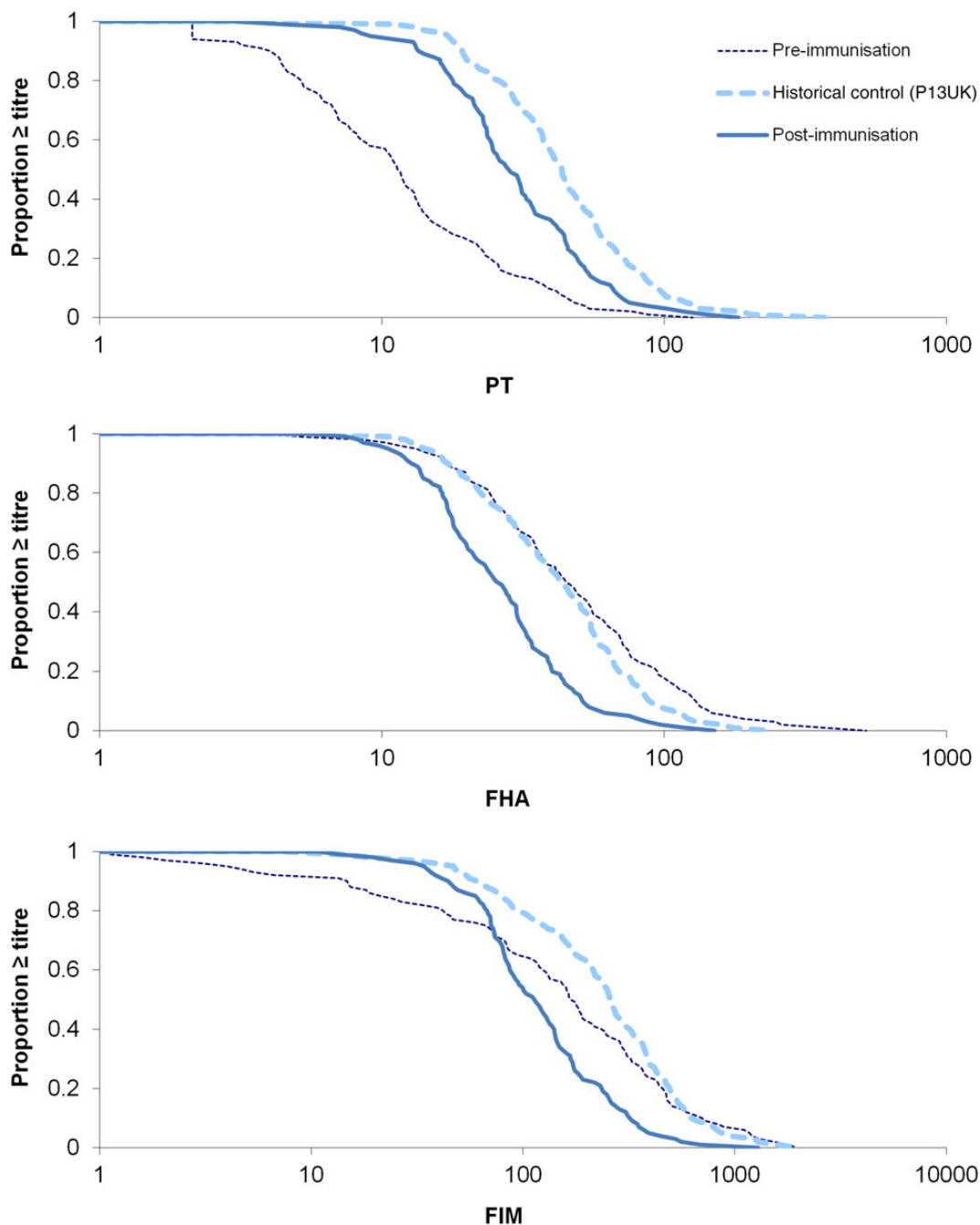
Figure 1. Proportion above the respective IgG antibody concentration for three pertussis antigens at 2 months (just before primary immunization, Pre-iMAP) and 5 months (1 month after primary immunization, Post-iMAP) in infants whose mothers received TDaP/IPV (Repevax; Sanofi Pasteur) during the late second or third trimester of pregnancy. P13UK refers to a historical cohort of infants whose mothers did not receive a pertussis-containing vaccine in pregnancy and who had vaccine responses tested 1 month after the nationally recommended primary immunization program. Abbreviations: FHA, filamentous hemagglutinin; FIM, fimbriae 2 + 3; IgG, immunoglobulin G; PT, pertussis toxin.

Although higher pertussis antibody concentrations were noted at birth and before primary immunization compared to infants whose mothers did not receive antenatal TdaP, these were lower after primary immunization and post-booster for most pertussis antigens. Neither study, however, had sufficient power to detect significant differences. It is postulated that passively acquired antibodies from the mother bind vaccine epitopes and mask them from infant B lymphocytes, thereby attenuating responses to those antigens in infants [20].

Table 2. Geometric Mean Concentrations and Proportions Above the Protective Thresholds for Diphtheria, Tetanus, Hib, and 13 Pneumococcal Serotypes After Primary Immunization in Infants Whose Mothers Were Given a Pertussis-containing Vaccine in the Third Trimester Compared With Infants in the Historical Cohort Whose Mothers Did Not Receive a Pertussis-containing Vaccine During Pregnancy

Vaccine Antigen	iMAP N	Geometric Mean (95% CI)	% >Threshold[a] (95% CI)	Historic Control N	Geometric Mean (95% CI)	% >Threshold[a] (95% CI)	Geometric Mean Fold Ratio[b] (iMap/control)	P Value for Fold Ratio
Diphtheria toxin	131	0.55 (.47–.63)	97.7 (93.5–99.5)	204	1.00 (.89–1.12)	100 (98.2–199)	0.55 (0.46–0.66)	<.001
Tetanus toxin	131	1.36 (1.24–1.50)	100 (97.2–100)	204	1.11 (.99–1.25)	100 (98.2–100)	1.24 (1.05–1.46)	.011
Hib	131	4.92 (3.71–6.51)	96.2 (91.3–98.7)	205	2.17 (1.71–2.77)	90.7 (85/9–94.3)	2.30 (1.59–3.34)	<.001
Pneumococcal serotype								
1	127	1.35 (1.18–1.54)	95.3 (90.0–98.2)	234	1.84 (1.63–2.07)	96.2 (92.8–98.2)	0.74 (0.61–0.89)	.001
3	124	0.56 (.51–.63)	76.6 (68.2–83.7)	231	1.65 (1.49–1.82)	97.4 (94.4–99.0)	0.34 (0.29–0.40)	<.001
4	127	1.08 (.96–1.22)	96.1 (91.1–98.7)	235	1.55 (1.41–1.70)	97.0 (94.0–98.9)	0.70 (0.60–0.82)	<.001
5	126	0.57 (.50–.65)	73.8 (65.2–81.2)	235	0.96 (.87–1.08)	88.5 (83.7–92.3)	0.59 (0.50–0.70)	<.001
6A	126	0.90 (.75–1.07)	81.0 (73.0–87.4)	234	1.56 (1.35–1.80)	89.3 (84.6–93.0)	0.58 (0.46–0.73)	<.001
6B	126	0.36 (.31–.42)	45.2 (36.4–54.3)	232	0.32 (.29–.36)	38.7 (32.4–45.4)	1.11 (0.92–1.33)	.28
7F	126	2.04 (1.80–2.32)	97.6 (93.2–99.5)	235	2.63 (2.37–2.93)	98.3 (95.7–99.5)	0.78 (0.65–0.93)	.005
9V	125	0.72 (.61–.85)	75.2 (66.7–82.5)	234	0.93 (.83–1.04)	87.6 (82.7–91.5)	0.78 (0.64–0.95)	.014
14	127	4.76 (3.94–5.76)	98.4 (94.4–99.8)	233	5.28 (4.54–6.13)	97.9 (95.1–99.3)	0.90 (0.71–1.15)	.41
18C	126	1.08 (.92–1.26)	90.5 (84.0–95.0)	235	1.19 (1.06–1.34)	89.4 (84.7–93.0)	0.91 (0.74–1.11)	.35
19A	126	1.27 (1.06–1.51)	87.3 (80.2–92.6)	234	1.56 (1.38–1.77)	94.9 (91.2–97.3)	0.81 (0.66–1.01)	.058
19F	126	4.01 (3.48–4.64)	100 (97.1–100)	234	4.57 (4.04–5.16)	99.6 (97.6–100)	0.88 (0.73–1.07)	.21
23F	124	0.64 (.54–.78)	64.5 (55.4–72.9)	234	0.69 (.60–.79)	68.8 (62.4–74.7)	0.94 (0.74–1.19)	.61

Abbreviations: CI, confidence interval; DT, diphtheria toxin; Hib, *Haemophilus influenzae* b; SBA, serum bactericidal antibody; TT, tetanus toxin.

[a] The protective threshold was ≥0.1 IU/mL for DT and TT, ≥0.15 µg/mL for Hib, ≥0.35 µg/mL for pneumococcal serotypes, and >8 for MenC SBA.

[b] Adjusting for interval to blood.

For the other tested antigens, antibodies to diphtheria and some of the CRM-based conjugates were significantly lower when compared with the historical controls. An inverse association between pre-immunization diphtheria antibody and post-immunization responses was evident for MCC-CRM but not PCV13 serotypes, suggesting potentially different mechanisms for interference. For PCV13 serotypes, the proportion of infants achieving the protective threshold was similar to the historical controls except for serotypes 3, 5, and 9V. The first two serotypes, however, do not cause significant disease in children, whereas serotype 9V is rare since routine pneumococcal conjugate vaccination was introduced.

For MCC, nearly all infants (91.6%) achieved protective SBA thresholds. Those receiving a single MCC-CRM (Menjugate) dose, however, were less likely to be protected (84.4%). This compares with 95.5% in an earlier study by our group where infants of unvaccinated mothers received a single Menjugate dose at 3 months in the same study population [21]. However, as boosters for all conjugate vaccines are given at 12 months in the UK, individual protection and disease control in the population are unlikely to be adversely affected.

Interestingly, responses to tetanus, MCC-TT and Hib-TT were enhanced in infants whose mothers received Repevax compared with the historical cohort. This has previously been reported with tetanus vaccination [22]. Because there was no association between pre-vaccination tetanus antibody concentrations and Hib-TT responses, the immunological mechanism for the higher responses remains unclear.

We also found that the timing of antenatal pertussis immunization in the third trimester did not affect infant antibody concentrations at 2 months. In a US study, when TdaP was given to mothers at preconception or in early pregnancy, infants had low pertussis antibody concentrations at birth [23]. As a result of that study, revaccination in subsequent pregnancies if more than 1 year apart is currently recommended in the UK and elsewhere [24].

Our study included a 2-3-4 month priming schedule with no pertussis booster in the second year of life, in contrast to the US studies that used a 2-4-6 month schedule with a second year booster. Our results therefore have relevance for countries using the Expanded Program on Immunization (EPI) schedule of 6-10-14 weeks without a pertussis booster. We also assessed primary immunization responses to three conjugate vaccines and, for the first time, the impact of antenatal immunization with tetanus and diphtheria on PCV13 and MCC responses. Our results suggest that development of a combination vaccine

containing acellular pertussis antigens with tetanus would be preferable to the available TdaP products because of the interference observed with high levels of maternally derived diphtheria antibodies.

Because the antenatal immunization program against pertussis was introduced as a national outbreak control measure, there was insufficient time to set up a randomized controlled trial. Instead, we undertook a service evaluation that allowed us to assess infant vaccine responses rapidly and collect data from a real-life cohort with variable timing of vaccinations, different infant MCC vaccines as supplied from national stock and no significant exclusion criteria. This variability allowed us to assess the timing of antenatal vaccination and to compare vaccine responses in infants receiving different MCC vaccine products. Although we did not have a contemporary control group, PHE-led clinical trials have been conducted by the same team in the same geographical regions over many years with samples tested in the same accredited laboratories using standard operating procedures. Historical controls, however, do have limitations. Lack of randomization may result in bias due to differences in characteristics of participating subjects and noncontemporary comparisons may be affected by temporal changes that could influence antibody responses; for example, reduction in carriage exposure to PCV13 serotypes between 2011 and 2012 when the historical cohort was recruited and 2013–2014 when the current cohort was recruited. Despite these limitations, our findings with respect to pertussis antigens were similar to other studies and consistent effects in different directions were observed for diphtheria and CRM-based vaccines compared with tetanus and TT-based conjugates.

In conclusion, we observed high concentrations of maternally derived antibodies in infants before primary immunization. There was, however, significant attenuation of pertussis antibody responses and lower responses to some of the CRM-conjugate vaccines in infants whose mothers received Repevax antenatally. Despite this, the majority of infants achieved protective thresholds after primary immunization. The differences in MenC antibody responses after primary immunization favor the use of TT-conjugated vaccines in the infant program while the maternal pertussis immunization program is in place. Without correlates of protection, the modulation of infants' responses to pertussis antigens will necessitate longer-term follow-up of infants of vaccinated mothers.

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.

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