Pertussis Antibody Concentrations in Infants Born Prematurely to Mothers Vaccinated in Pregnancy

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abstract

BACKGROUND AND OBJECTIVES: Maternal antenatal pertussis-containing vaccination is recommended for the prevention of neonatal pertussis, but the ability of maternal vaccination to protect premature infants is unknown. We hypothesized that that infants born prematurely to antenatally vaccinated women would have higher pertussis antibody concentrations than those born to unvaccinated women.

METHODS: Mothers had been offered a combined tetanus, diphtheria, 5-component acellular pertussis, inactivated polio vaccine from 28 weeks' gestation as part of their routine antenatal care. Premature infants of vaccinated and unvaccinated mothers enrolled in a randomized controlled trial of pneumococcal conjugate vaccine schedules had antibody concentrations (pertussis toxin, filamentous hemoagglutinin [FHA], and fimbriae 2 and 3) measured at 2 months (before primary vaccination), 5 months (1 month after primary vaccination), and 12 months of age.

RESULTS: Mothers of 31 (19%) of 160 premature infants had received combined tetanus, diphtheria, 5-component acellular pertussis, inactivated polio vaccine in pregnancy. Compared with infants of unvaccinated mothers, those born to vaccinated mothers had significantly higher antibody concentrations at 2 months for all measured vaccine antigens ($P < .001$). The number of days between maternal vaccination and delivery and immunoglobulin G concentration at 2 months of age was positively correlated for pertussis toxin ($P = .011$) and FHA ($P = .001$). After primary immunization, infants of vaccinated mothers had significantly lower antibody concentrations for FHA ($P = .003$) compared with infants of unvaccinated mothers; these differences had resolved by 12 months of age.

CONCLUSIONS: Maternal vaccination administered early in the third trimester may provide protection for infants born prematurely.

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Dr Kent coordinated and supervised the study, carried out the statistical analysis, and prepared the manuscript; Dr Ladhani assisted with the study and reviewed and revised the manuscript; Dr Andrews carried out the statistical analysis and reviewed and revised the manuscript; Drs Matheson and England performed the sample analysis and reviewed and revised the manuscript; Dr Miller and Prof Heath developed and supervised the study and analysis and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

This work was previously presented at the annual meeting of the European Society of Paediatric Infectious Disease; May 15, 2015; Leipzig, Germany (abstract number 456).

The parent trial was registered with EudraCT (identifier 2007–007535–23).

WHAT'S KNOWN ON THIS SUBJECT: Antenatal pertussis vaccination is highly effective at preventing neonatal pertussis due to the transfer of maternal antibody. This transfer is limited by premature birth, and preterm infants, already at higher risk of disease, may not benefit from maternal vaccination.

WHAT THIS STUDY ADDS: Premature infants born to mothers vaccinated in pregnancy have higher antibody concentrations than infants of unvaccinated mothers at the time of their first vaccination but lower filamentous hemagglutinin antibodies after primary immunizations. These differences resolved by 12 months of age.

To cite: Kent A, Ladhani SN, Andrews NJ, et al. Pertussis Antibody Concentrations in Infants Born Prematurely to Mothers Vaccinated in Pregnancy. *Pediatrics.* 2016;138(1):e20153854

The United Kingdom introduced a temporary immunization program against pertussis for pregnant women in September 2012, after a significant increase in pertussis-related hospitalizations and deaths in young infants.[1] A combined tetanus, diphtheria, 5-component acellular pertussis, inactivated polio vaccine (Tdap/IPV; Repevax; Sanofi Pasteur, Lyon, France) was offered to all pregnant women from 28 weeks' gestation. The program achieved 64% vaccination coverage in the first year after its introduction, with an estimated 91% effectiveness in preventing confirmed pertussis infections in infants younger than 3 months of age.[2] Earlier administration within the recommended 28- to 34-week gestation window appears to result in higher infant antibody concentrations and affinity at birth and at 2 months of age.[3–5]

Premature infants have an increased risk of pertussis infection and are more likely to develop severe illness, resulting in prolonged hospitalization, intensive care admission, and death.[6,7] At the same time, because transplacental transfer of maternal antibodies to the fetus occurs predominantly in the last trimester of pregnancy,[8] premature infants may not benefit from maternal vaccination to the same extent as their term-born peers.

This observational substudy of a larger multicenter, randomized controlled vaccination trial in premature infants (Prems Under New Schedule [PUNS]) aimed to compare pertussis antibody concentrations before and after primary immunization in premature infants whose mothers received Tdap/IPV in pregnancy with those born to unvaccinated mothers.

METHODS

The PUNS trial was conducted at 8 neonatal units in England between May 2012 and May 2014. The maternal immunization program was introduced on September 1, 2012. Because infants were recruited into the clinical trial after birth, the study investigators had no influence on whether mothers were offered Tdap/IPV as part of their routine antenatal care, whether they accepted or declined vaccination, or on the timing of vaccination in pregnancy. This information was collected only after informed parental consent was obtained for the infant to be included in the PUNS study. Although any infant with a gestational age <35 weeks was potentially eligible for the randomized controlled trial, only those whose mothers would have been eligible for pertussis vaccination in pregnancy (>28 weeks' gestation) are included in this substudy. In addition, infants had to be medically fit for vaccination, between 7 and 12 weeks of age, and with written parental consent obtained.

All infants received a combined diphtheria, tetanus, and acellular pertussis–IPV–*Haemophilus influenzae* type b vaccine (Pediacel; Sanofi Pasteur MSD, Lyon, France) at 2, 3, and 4 months old and meningococcal C-CRM_{197} vaccine (Menjugate; Novartis Vaccines, Sienna, Italy) at 3 and 4 months of age. In addition, they were randomly assigned (1:1:1) to receive pneumococcal conjugate vaccine (Prevenar13; Pfizer, New York) at 2 and 4; or 2, 3, and 4; or 2, 4, and 6 months of age.

Mothers who were vaccinated received Repevax containing pertussis toxoid (2.5 μg), filamentous hemagglutinin (FHA) (5 μg), pertactin (3 μg), Fimbriae (Fim) types 2 and 3 (5 μg), diphtheria toxoid (≥2 IU), tetanus toxoid (≥20 IU), and inactivated poliovirus from 28 weeks of pregnancy. These pertussis antigen concentrations are equivalent to those in Adcel (Sanofi Pasteur).

Infant immunoglobulin (Ig)G concentrations against pertussis toxin (PT), FHA, Fim 2 and 3, diphtheria, and tetanus were measured by enzyme-linked immunosorbent assay at the Public Health England Immunoassay Laboratory at Porton Down, UK, before (~2 months of age) and 1 month after their primary immunizations (~5 months of age), and at 12 months of age. An antibody concentration of 0.1 IU/mL was accepted as a serological correlate of protection for diphtheria and tetanus, but there is no established correlate for pertussis.[9]

For statistical analysis, IgG concentrations were log transformed to normality. Statistical significance was testing by using Kruskal-Wallis test or Fisher's exact test (proportions) as appropriate and a $P < .05$ was classed as statistically significant. The main clinical trial was registered (EudraCT number 2007-007535-23) and East of England–Essex research ethics committee (Research Ethics Committee reference 07/HO301.11).

RESULTS

In this substudy, mothers of 31 (19%) of 160 premature infants born at 28 to 35 weeks' gestation had received Tdap/IPV in pregnancy (mTdap). The median gestation at mTdap administration was 28.5 weeks (interquartile range 28.0–29.6) and the median interval between vaccination and delivery was 24 days (interquartile range 9–35). The median birth gestation was slightly older in infants of vaccinated mothers compared with unvaccinated mothers (32.6 vs 31.0 weeks), although this difference was not statistically significant ($P = .057$).

Compared with infants of unvaccinated mothers, those born to vaccinated mothers had significantly higher antibody concentrations at 2 months for all measured vaccine antigens ($P < .001$) (Table 1), resulting in increased

TABLE 1 IgG GMCs (μg/mL) at 2 and 5 Months of Age

Antibody	2 mo GMC (95% CI)			5 mo GMC (95% CI)		
	mTdaP, *n* = 30	No mTdaP, *n* = 121	P	mTdaP, *n* = 15	No mTdaP, *n* = 73	*P*
PT	3.53 (2.18 to 5.71)	1.49 (1.28 to 1.74)	<.001	37.15 (26.08 to 52.93)	44.07 (37.89 to 51.26)	.35
FHA	17.50 (10.63 to 28.95)	3.36 (2.79 to 4.05)	<.001	23.04 (16.17 to 32.85)	45.55 (37.64 to 55.12)	.003
Fim 2&3	33.58 (17.04 to 66.17)	4.13 (3.15 to 5.41)	<.001	119.55 (66.90 to 213.63)	135.14 (100.86 to 181.08)	.72
Tetanus	1.06 (0.55 to 2.04)	0.15 (0.12 to 0.19)	<.001	1.76 (1.14 to 2.72)	1.44 (1.20 to 1.74)	.37
Diphtheria	0.16 (0.09 to 0.29)	0.03 (0.02 to 0.03)	<.001	0.55 (0.30 to 1.00)	1.08 (0.91 to 1.27)	.003

Due to the design of the vaccination study, fewer infants were sampled at 5 months of age.

TABLE 2 IgG GMCs (μg/mL) and Percentage of Infants With Seroprotective Antibody Concentrations at 12 Months of Age

Antibody	mTdaP, *n* = 28		No mTdaP, *n* = 115	
	GMC (95% CI)	Seroprotection % (95% CI)	GMC (95% CI)	Seroprotection % (95% CI)
PT	8.49 (5.92 to 12.17)	—	10.75 (9.37 to 12.34)	—
FHA	16.44 (12.29 to 21.99)	—	19.07 (16.33 to 22.27)	—
Fim 2&3	25.78 (16.90 to 39.36)	—	37.24 (30.00 to 46.23)	—
Tetanus	0.43 (0.28 to 0.68)	92.6 (76.5 to 99.1)	0.26 (0.22 to 0.31)	83.5 (75.4 to 89.7)
Diphtheria	0.17 (0.11 to 0.24)	78.6 (59.0 to 91.7)	0.18 (0.16 to 0.22)	76.5 (67.7 to 83.9)

—, no correlate of protection for these antibodies.

seroprotection rates for diphtheria (mTdap: 66.7% [20/30] vs no mTdap: 15.7% [19/121], $P < .001$) and tetanus (mTdap: 90.0% [27/30] vs no mTdap: 66.1% [80/121], $P = .012$). The number of days between maternal vaccination and delivery and IgG concentration at 2 months of age was positively correlated for PT (4% increase in PT concentration per day [95% confidence interval (CI) 1 to 6]; $P = .011$), FHA (7% [95% CI 3 to 10]; $P = .001$), tetanus (10% [95% CI 5 to 14]; $P < .001$), and diphtheria (6% [95% CI 1 to 11]; $P = .008$) but not significantly so for Fim 2 and 3 (5% [95% CI −1 to 11]; $P = .061$).

After primary immunization, both groups had significantly higher antibody concentrations for all measured vaccine antigens compared with preimmunization concentrations. However, infants of vaccinated mothers had significantly lower antibody concentrations for FHA ($P = .003$) and diphtheria ($P = .003$), compared with infants of unvaccinated mothers (Table 1). All infants had seroprotective antibody concentrations for tetanus and only 1 infant (in the "no mTdap" group) did not have protective antibody concentrations against diphtheria.

Table 2 shows the antibody concentrations and seroprotection rates at 12 months of age; there were significantly higher tetanus antibody concentrations in the mTdap group ($P = .015$) but no other significant differences between groups were found.

DISCUSSION

The emergency introduction of a maternal immunization program to control a national pertussis outbreak serendipitously provided an opportunity to assess antibody concentrations to maternal vaccine antigens in premature infants. We found significantly higher antibody concentrations at 2 months of age for all measured antigens in premature infants of vaccinated mothers compared with those born to unvaccinated mothers. Moreover, antibody concentrations at 2 months of age increased with the interval between maternal vaccination and birth for all but 1 measured vaccine antigen.

However, the preimmunization geometric mean concentrations (GMCs) were substantially lower than those of term infants born to vaccinated mothers in a separate evaluation by using the same laboratory tests: PT (3.5 vs 11.2), FHA (17.5 vs 46.0), and Fim (33.6 vs 123.0).[1] This is likely due to a shortened period for maternal immunologic response and transfer of antibody to the fetus.[8] After primary immunization, antibodies to PT (37.2 vs 28.8), FHA (23.0 vs 25.5), and Fim (119 vs 114) were generally comparable between premature and term infants born to vaccinated mothers, but lower than in the sera of the infants of unvaccinated mothers.[1] Given that the UK schedule does not include any further pertussis immunization until children are 3 years old, it is reassuring that the observed differences between the groups had resolved by 12 months of age, a finding also previously reported in term infants.[10]

Although post hoc analysis of clinical trial data should be interpreted with caution, these results are biologically plausible and the observed trends are consistent with the recent studies in term infants.[1,3,5,10,11] Our findings, therefore, suggest that maternal vaccination early in the third trimester (ie, closer to 28 weeks' gestation, or even earlier, as administered in some settings[12]) may

also protect infants born prematurely against pertussis in early life. There are some limitations with these data; as an observational substudy of a larger clinical trial, the trial design did not permit measurement of antibody concentrations (either maternal or infant) at birth. By assessing antibody at 2 months, we have therefore estimated the nadir of maternal antibody concentrations before immunization of the infant. In addition, we have limited information on maternal vaccination history outside of pregnancy. It is, however, unlikely that women (in either group) would have been recently vaccinated, as there is no routine pertussis vaccination program after childhood in the United Kingdom and the maternal vaccination program that was introduced during the study.

CONCLUSIONS

Maternal vaccination delivered early in the third trimester may provide protection for infants born prematurely and any potential negative impact on the infant's immunologic response to primary immunization appears to resolve by 12 months of age.

ACKNOWLEDGMENTS

The following are members of the PUNS study group: Tim Scorrer, Neonatal Unit, Queen Alexandra Hospital, Portsmouth, UK; Matthew D. Snape, Oxford Vaccine Group, University of Oxford, and the National Institute for Health Research Oxford Biomedical Research Centre, Oxford UK; Andrew Pollard, Neonatal Unit, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK; Stephen Hughes, Department of Immunology, Royal Manchester Children's Hospital, Manchester, UK; Parkash Satodia, Neonatal Unit, University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK; John Chang, Neonatal Unit, Croydon University Hospital, London, UK; Esse Menson, Department of Paediatric Infectious Diseases, Evelina London Children's Hospital, London, UK; Carrie Heal, Neonatal Unit, Stepping Hill Hospital, Stockport, UK; Nicola Pritchard, Neonatal Unit, Royal Berkshire Hospital, Reading, UK; Andrew Collinson, Neonatal Unit, Royal Cornwall Hospital, Truro, UK; and Saul Faust, National Institute for Health Research Welcome Trust Clinical Research Facility, University of Southampton and University Hospital Southampton NHS Foundation Trust, UK.

We thank all children who took part in the study as well as their parents/guardians, the study staff at all the research centers, Pauline Kaye, Deborah Cohen, Teresa Gibbs, and all other members of the team at Public Health England for their invaluable help and support and Pfizer for financially supporting this investigator-led study.

ABBREVIATIONS

CI: confidence interval
FHA: filamentous hemagglutinin
Fim 2 and 3: Fimbriae types 2 and 3
GMC: geometric mean concentration
IgG: immunoglobulin G
IPV: inactivated polio vaccination
mTdap: maternal tetanus, diphtheria, and acellular pertussis (Tdap-IPV) vaccination
PT: pertussis toxin
PUNS: Prems Under New Schedule

DOI: 10.1542/peds.2015-3854

Accepted for publication Apr 4, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Prof Heath and Dr Ladhani have conducted studies on behalf of St George's, University of London funded by vaccine manufacturers but do not receive any personal payments or travel support. All other authors have no financial relationships relevant to this article to disclose.

FUNDING: This was an investigator-led study funded by Pfizer Ltd. The funder had no input into the study design, data analysis or manuscript preparation. This study was supported by the National Institute for Health Research Clinical Research Network.

POTENTIAL CONFLICT OF INTEREST: Prof Heath and Dr Ladhani have conducted studies on behalf of St George's, University of London funded by vaccine manufacturers but do not receive any personal payments or travel support; the other authors have no conflicts of interest relevant to this article to disclose.

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Pediatrics 2016;138;
DOI: 10.1542/peds.2015-3854 originally published online June 2, 2016;

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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