Open Forum Infectious Diseases

BRIEF REPORT

Decay Rates of Maternal Tetanus, Diphtheria, and Pertussis Antibody Levels in Early and Moderate-to-Late Preterm and Term Infants at Birth and at Two Months

Maarten M. Immink,[1,2,a] Nicoline A. T. van der Maas,[1,a] Mireille N. Bekker,[2] Hester E. de Melker,[1] Gerco den Hartog,[1,3] Nynke Y. Rots,[1] Pieter G. M. van Gageldonk,[1] Floris Groenendaal,[4] and Elisabeth A. M. Sanders[1,5]

[1]Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands, [2]Department of Obstetrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, and Utrecht University, Utrecht, The Netherlands, [3]Laboratory of Medical Immunology, Radboudumc, Nijmegen, The Netherlands, [4]Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, and Utrecht University, Utrecht, The Netherlands, and [5]Department of Pediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital, University Medical Center Utrecht, and Utrecht University, Utrecht, The Netherlands

A post hoc analysis of maternally derived antibodies at birth and age 2 months following second trimester maternal Tdap vaccination between 20 and 24 weeks' gestational age (GA) showed a faster decay rate of Tdap-related immunoglobulin G in early preterms born before 32 weeks' GA compared with moderate-to-late preterms and full-terms. This is different from previous studies and merits further research.

Keywords. antibody decay; full-term; immunogenicity; maternal immunization; pertussis; preterm.

Before the first immunizations against pertussis at age 2–3 months, infants, and particularly preterms, remain vulnerable for developing severe pertussis [1]. Maternal tetanus-diphtheria-and-acellular-pertussis (Tdap) vaccination has been shown to be 90% effective in the protection of newborns against pertussis during this period [2]. The height of maternally derived antipertussis antibodies at birth and at 2 months of age after maternal Tdap vaccination is determined by many factors, for example, gestational age (GA), the time interval between maternal vaccination and birth, placental function, and postnatal antibody decay [3, 4]. Therefore, antipertussis antibodies at 2 months may differ between full-terms and preterms [5]. However, knowledge about the persistence of pertussis-specific vaccine-induced maternal antibodies, in particular in the case of early second trimester Tdap vaccination and early preterms born before 32 weeks' GA, is limited.

We recently reported on a prospective study on transplacental immunoglobulin G (IgG) transfer following maternal Tdap vaccination between 20 and 24 weeks' GA, that is, early during the advised immunization period, in full-terms and preterms [6]. We compared anti–*B. pertussis* IgG levels at birth and 2 months. In this post hoc analysis, we compared antibody levels in cord blood and at 2 months between early and moderate-to-late preterms vs full-terms and estimated Tdap-specific antibody decay rates between birth and 2 months of age in these groups.

For the analysis, 3 groups were defined: mother–infant pairs of early preterms (birth $25^{0/7}$–$31^{6/7}$ weeks' GA), moderate-to-late preterms ($32^{0/7}$–$34^{6/7}$ weeks' GA), and full-terms ($37^{0/7}$–$42^{0/7}$ weeks' GA). We did not include 35–36 weeks' GA preterms because their antibody transfer resembles transfer in full-terms due to active transplacental transport [7]. Blood was collected from mothers within 24 hours after delivery, from the umbilical cord, and from infants at age 6–9 weeks in case of preterms and 2 months ± 5 days in full-terms; blood was collected in all cases before the first pertussis immunization. The study was approved by the Central Committee on Research Involving Human Subjects (NL66966.000.18). Informed consent was obtained from parents or legal guardians [8, 9].

IgG antibody concentrations against pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (Prn), and toxoids of diphtheria (DT) and tetanus (TT) were determined as described [10] and were log-transformed. Geometric mean concentrations (GMCs) with corresponding 95% CIs were calculated. GMC differences between the groups and at different time points were compared by utilizing a marginal generalized estimating equation model, taking into account the between variation.

The decay rate (ie, time in which antibody concentrations decrease 2-fold) of maternal antibodies in infants until 2 months of age was estimated with a linear mixed-effects model of $\log^2$-transposed antibody concentrations with random slope, adjusted for timeliness of blood sampling. The antibody decay rate was expressed as the inverse of the regression slope in days. An infant was included in the analysis if measurements of Tdap-specific antibody concentrations for cord blood and

Received 16 September 2024; editorial decision 02 December 2024; accepted 09 December 2024; published online 10 December 2024

[a]Equal contribution.

Correspondence: N. A. T. van der Maas, MD, PhD, PO Box 1, 3720BA Bilthoven, The Netherlands (nicoline.van.der.maas@rivm.nl); or E. A. M. Sanders, MD, PhD, PO box 1, 3720BA Bilthoven, The Netherlands (lieke.sanders@rivm.nl).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofae717

blood taken at 2 months were available, if they were above the lower limit of quantification, and if they indicated decay. Baseline characteristics are reported as means and standard deviations or as absolute numbers and percentages. Comparison of baseline characteristics was done using either the *t* test, Mann-Whitney *U* test, or Fisher exact test.

Complete data were available from 37 early and 36 moderate-to-late preterms and 66 full-terms (Supplementary Table 1). Mean GA at Tdap vaccination was 22.6, 22.7, and 22.0 weeks for mothers of early and moderate-to-late preterms and full-terms, respectively. This corresponded with mean time intervals between maternal Tdap vaccination and delivery of 6.3, 10.5, and 18.3 weeks.

At age 2 months, anti-PT GMCs were 8.63 IU/mL (95% CI, 5.52–13.48; early preterms), 14.58 IU/mL (95% CI, 9.25–22.99; moderate-to-late preterms), and 14.70 IU/mL (95% CI, 10.58–20.41; full-terms) (Figure 1). Though lower in early preterms, differences between the small groups were nonsignificant. Anti-FHA and -Prn GMCs in early preterms were significantly lower compared with moderate-to-late preterms and full-terms (Figure 1; Supplementary Table 2). Anti-TT GMC in early preterms was significantly lower compared with full-terms, but not with moderate-to-late preterms. For anti-DT GMC, no significant differences were found between the groups.

In cord blood, no differences were observed for anti-PT GMCs: 56.24 IU/mL (95% CI, 39.98–79.12), 49.30 IU/mL (95% CI, 32.50–74.78), and 58.65 IU/mL (95% CI, 46.38–74.16) for the groups. For anti-FHA and anti-Prn, GMC in early preterms was significantly lower than in full-terms, but not compared with moderate-to-late preterms (Supplementary Table 2; Figure 1). For anti-DT GMC and anti-TT GMC, no significant differences were found.

In mothers of early preterms, anti-PT GMC at delivery was 75.24 IU/mL (95% CI, 48.90–115.79), compared with 47.64 IU/mL (95% CI, 29.85–76.03; mothers of moderate-to-late preterms) and 32.88 IU/mL (95% CI, 26.01–41.57; mothers of full-terms), and was associated with the time interval between Tdap vaccination and delivery (data not shown). Maternal anti-FHA and anti-Prn GMCs did not differ between the groups (Figure 1; Supplementary Table 2). Anti-DT and -TT GMCs were significantly higher in mothers of early preterms compared with mothers of moderate-to-late preterms and full-terms.

Decay rates of maternal antibodies were significantly faster in early preterms compared with moderate-to-late preterms or full-terms for all antigens; for example, for PT, this was 21.7 days vs 32.9 days and 32.2 days, respectively. No differences were found between moderate-to-late preterms and full-terms (Table 1).

We recently described that maternal Tdap vaccination between $20^{0/7}$–$24^{0/7}$ weeks' GA resulted in comparable antibody concentrations against PT, Dt and TT at birth and 2 months in preterms (ie all infants born $25^{0/7}$–$34^{6/7}$ weeks GA) and full-terms, although Tdap vaccination before 24 weeks' GA resulted in at least 2-fold lower anti-PT antibody levels compared with maternal Tdap between $30^{0/7}$–$33^{0/7}$ weeks' GA [6]. The results of this post hoc analysis of the study data suggest that Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' GA leads to lower Tdap-related antibody concentrations at 2 months of age in early preterms but that levels in moderate-to-late preterms born after 32 weeks' GA are very similar to those of full-terms. This would indicate that lower levels in early preterms at age 2 months are not only explained by the sometimes lower maternally derived IgG levels at birth, but also by faster decay rates of maternal antibodies in the first months of life.

When we compared our data with an individual-participant meta-analysis (n = 1426, mainly full-terms), point estimates of the half-lives of Tdap-related antibodies ranged from 28.7 days for anti-TT to 35.1 days for anti-Prn [4], similar to the decay rates we observed for moderate-to-late preterms and full-terms, but different from the much faster decay rates of 21 days we observed in early preterms. The faster decay rate in early preterms is in contrast with findings in preterms by Maertens et al., who reported longer half-lives of maternal Tdap-related IgG levels after birth in preterms vs full-terms [11]. Data from the Maertens study combined with another study on maternal Tdap vaccination in mother–term infant pairs performed in Thailand were included in a detailed study by Embacher et al. on determinants of half-lives of maternally derived antibodies after Tdap vaccination. The authors found that being term, having a higher maternal antibody concentration at birth, an increased change in infant weight in the first 2 months of life, and no breastfeeding shortened IgG half-life, whereas female sex and a longer interval between maternal vaccination and delivery was associated with an increased half-life. Taking all covariates from both studies together (if applicable), the authors found longer half-lives in preterms vs full-terms, which differs from the shorter half-life in early preterms in our post hoc analysis [5]. While the method to estimate decay rates in our study is similar to the studies from Embacher, Maertens, and Oguti et al. [4, 5, 11], there are, however, important differences between our post hoc study and the 2 studies Embacher used for analyses. First, in our study women were vaccinated much earlier during pregnancy: mean GA, 22.6, 22.7 and 22.0 weeks for the 3 groups, compared with 29.3 weeks (full-terms) and 28.8 weeks (preterms) in Maertens et al. and 30.7 weeks (full-terms) in the Thai study by Wanlapakorn et al. without preterms [11, 12]. Second, our early preterms had a much lower GA, with a mean GA at birth of 28.9 weeks, while this was 33.2 weeks for moderate-to-late preterms and 34.0 weeks for all preterms described by Maertens et al.

Besides the lower gestational age of early preterms and the earlier Tdap vaccination around 22 weeks, other factors like relative weight gain, more frequent blood withdrawal, and

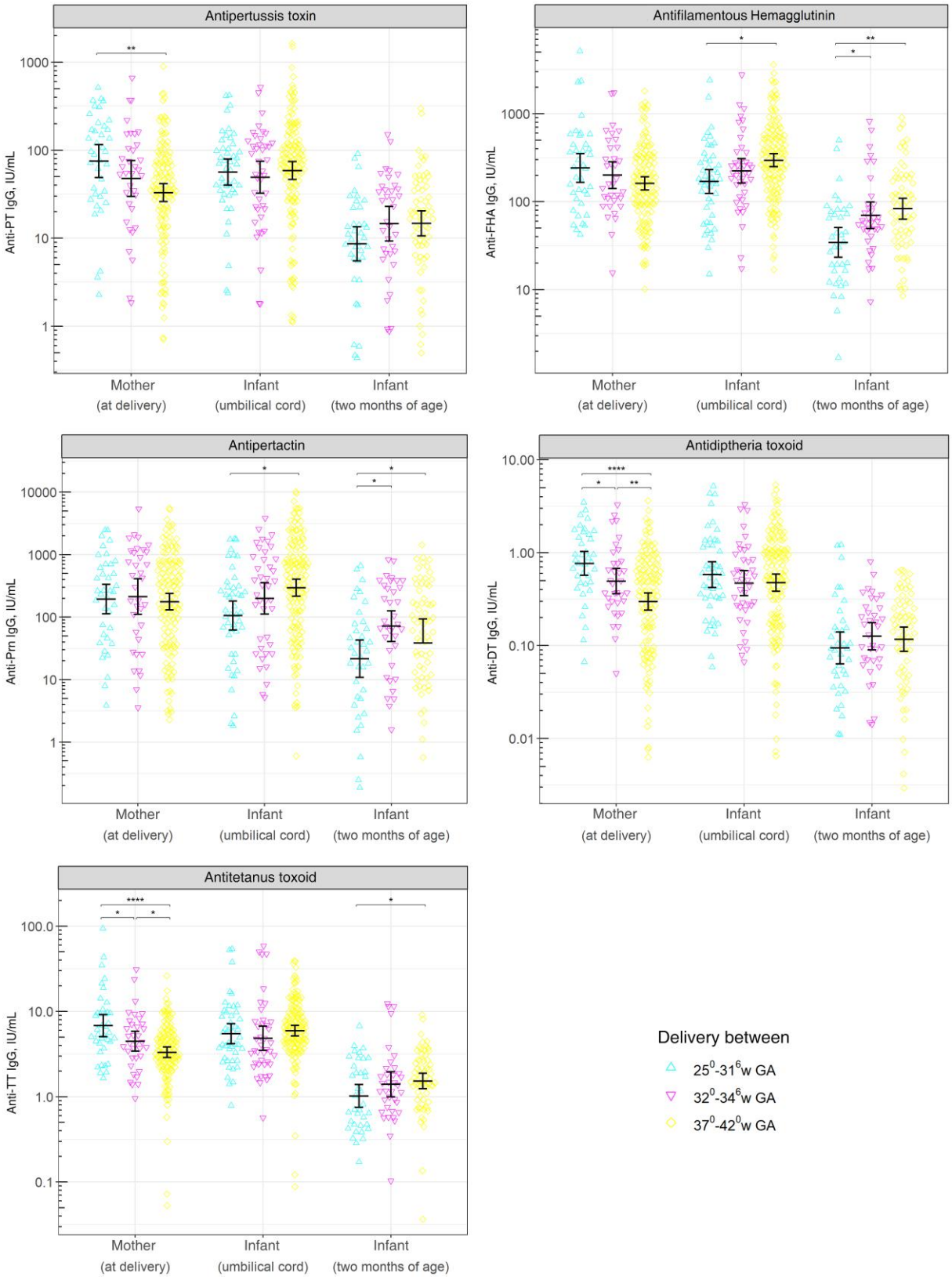

Figure 1. Individual IgG antibody concentrations and GMCs with 95% CIs after $20^{0/7}$–$24^{0/7}$ weeks' GA Tdap vaccination in preterm and term mother–infant pairs at different time points. Whiskers represent GMCs with corresponding 95% CIs. Difference labels are only presented in case of a significant effect. $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$; $^{****}P < .0001$. Abbreviations: DT, diphtheria toxoid; FHA, filamentous hemagglutinin; GA, gestational age; GMC, geometric mean concentration; Prn, pertactin; PT, pertussis toxin; TT, tetanus toxoid.

Table 1. Antibody Decay Estimates With Corresponding 95% CIs in Number of Days at Which Half of All Measured Antibody Concentrations Remained in Early and Late Preterms and Full-term Infants

IgG Antibody	Delivery Between $25^{0/7}$–$31^{6/7}$ Weeks' GA	Delivery Between $32^{0/7}$–$34^{6/7}$ Weeks' GA	Delivery between $37^{0/7}$–$42^{0/7}$ Weeks' GA
Antipertussis toxin	21.7 (19.2–24.4)	32.6 (29.1–34.6)	32.1 (30.6–33.7)
Antifilamentous hemagglutinin	22.0 (20.0–24.5)	33.0 (30.2–36.5)	33.5 (32.1–35.0)
Antipertactin	21.8 (19.6–24.5)	31.8 (28.4–33.6)	31.9 (30.4–33.6)
Antidiphtheria toxoid	20.8 (19.1–22.9)	28.7 (26.8–31.4)	29.4 (28.3–30.7)
Antitetanus toxoid	22.0 (19.9–24.5)	29.3 (27.1–31.9)	30.8 (29.5–32.2)

Abbreviations: GA, gestational age; IgG, immunoglobulin G.

breastfeeding practices in early preterms between birth and 2 months of age may have contributed to the contrasting results between our post hoc analysis and the studies of Embacher and Maertens [5, 11]. Furthermore, antibody concentrations at delivery were relatively high in mothers of early preterms after maternal Tdap vaccination before 24 weeks' GA; for example, anti-PT GMC in mothers of early preterms was 75.24 compared with 47.64 in mothers of moderate-to-late preterms and 32.88 in mothers of full-terms. Besides quantitative characteristics, the qualitative characteristics of maternally derived IgG antibodies may affect protection against pertussis and may be different following timing of maternal Tdap vaccination and delivery [13].

This study represents the post hoc analyses of a larger study investigating disease-specific transplacental antibody transfer following $20^{0/7}$–$24^{0/7}$-week Tdap vaccination in full-terms and all preterms born between 25 and 35 weeks' GA [6]. Our findings on early and moderate-to-late preterms therefore come with limited power and should be interpreted with caution.

In the Netherlands, infant DTaP-IPV-Hib-HepB vaccinations are administered at 3, 5, and 12 months of age, provided that the mother is Tdap-vaccinated during pregnancy at least 14 days before delivery and the infant is full-term. Preterms born before 37 weeks' GA obtain an additional dose between 6 and 9 weeks of age. Further studies are needed to confirm similar antibody levels and IgG half-lives compared with full-terms in case the child is born after 32 weeks' GA and with a sufficient interval between maternal vaccination and delivery. This may impact vaccination strategies in case of moderate-to-late preterm birth.

In conclusion, in early preterms Tdap vaccination between $20^{0/7}$ and $24^{0/7}$ weeks' GA led to 3-fold lower IgG antibody levels against several Tdap-included antigens at 2 months of age due to lower levels at birth but also faster IgG decay rates when born $<32^{0/7}$ weeks' GA, while moderate-to-late preterms had similar antibody levels at birth and similar IgG decay rates as full-terms.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Author contributions. M.I., M.B., H.d.M., N.R., E.S., and N.v.d.M. designed the study. M.I. prepared, executed, and coordinated the study in the antenatal care facilities and hospitals under supervision of N.v.d.M., M.B., and E.S. P.v.G. performed laboratory analyses. M.I. performed statistical analyses. M.I., M.B., H.d.M., G.d.H., N.R., F.G., E.S., and N.v.d.M. interpreted results. M.I., N.v.d.M., and E.S. wrote the first draft of the manuscript, and all authors contributed to subsequent drafts. All read and approved the final manuscript.

Financial support. This study was funded by the Netherlands Organization for Health Research and Development (522004008220004008).

Potential conflicts of interest. All authors: No reported conflicts.

References

1. Kandeil W, van den Ende C, Bunge EM, Jenkins VA, Ceregido MA, Guignard A. A systematic review of the burden of pertussis disease in infants and the effectiveness of maternal immunization against pertussis. Expert Rev Vaccines **2020;** 19:621–38.
2. Vygen-Bonnet S, Hellenbrand W, Garbe E, et al. Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review. BMC Infect Dis **2020;** 20:136.
3. Voysey M, Kelly DF, Fanshawe TR, et al. The influence of maternally derived antibody and infant age at vaccination on infant vaccine responses: an individual participant meta-analysis. JAMA Pediatr **2017;** 171: 637–46.
4. Oguti B, Ali A, Andrews N, et al. The half-life of maternal transplacental antibodies against diphtheria, tetanus, and pertussis in infants: an individual participant data meta-analysis. Vaccine **2022;** 40:450–8.
5. Embacher S, Maertens K, Herzog SA. Half-life estimation of pertussis-specific maternal antibodies in (pre)term infants after in-pregnancy tetanus, diphtheria, acellular pertussis vaccination. J Infect Dis **2023;** 228:1640–8.
6. Immink MM, Bekker MN, de Melker HE, et al. Maternal pertussis immunization and immunoglobulin G levels in early- to late-term and preterm infants. JAMA Netw Open **2024;** 7:e2424608.
7. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. Am J Reprod Immunol **1996;** 36:248–55.
8. Immink MM, Bekker MN, de Melker HE, Rots NY, Sanders EAM, van der Maas NAT. Study protocol of the PIMPI-project, a cohort study on acceptance, tolerability and immunogenicity of second trimester maternal pertussis immunization in relation to term and preterm infants. BMC Infect Dis **2021;** 21:897.
9. Immink MM, Bekker MN, de Melker HE, et al. Maternal pertussis immunization before 24w of gestation and IgG-levels in term and preterm infants. JAMA **2024**; 7:e2424608.
10. van Gageldonk PGM, van Schaijk FG, van der Klis FR, Berbers GAM. Development and validation of a multiplex immunoassay for the simultaneous determination of serum antibodies to *Bordetella pertussis*, diphtheria and tetanus. J Immunol Methods **2008;** 335:79–89.
11. Maertens K, Orije MRP, Herzog SA, et al. Pertussis immunization during pregnancy: assessment of the role of maternal antibodies on immune responses in term and preterm-born infants. Clin Infect Dis **2022;** 74:189–98.
12. Wanlapakorn N, Maertens K, Thongmee T, et al. Levels of antibodies specific to diphtheria toxoid, tetanus toxoid, and *Haemophilus influenzae* type B in healthy children born to Tdap-vaccinated mothers. Vaccine **2020;** 38:6914–21.
13. Abu Raya B, Bamberger E, Almog M, Peri R, Srugo I, Kessel A. Immunization of pregnant women against pertussis: the effect of timing on antibody avidity. Vaccine **2015;** 33:1948–52.