Vaccine 62 (2025) 127481

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

Pertussis antibody responses in infants born to mothers vaccinated at different time points in pregnancy

Olwenn Daniel [a,1,*], Sashank Srikanth [a,1], Paul Clarke [d,e], Kirsty Le Doare [a,b,c], Paul T. Heath [a], Christine E. Jones [f,g], Tim Scorrer [h], Matthew Snape [i,j], Anna Calvert [a]

[a] Centre for Neonatal and Paediatric Infection and Vaccine Institute, School of Health & Medical Sciences, City St George's University of London, London, UK
[b] Pathogen Immunology, UK Health Security Agency, Salisbury, UK
[c] Makerere University Johns Hopkins University, Kampala, Uganda
[d] Neonatal Intensive Care Unit, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK
[e] Norwich Medical School, University of East Anglia, Norwich, UK
[f] NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[g] Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK
[h] Portsmouth Hospitals University NHS Trust, Portsmouth, UK
[i] Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[j] Oxford Vaccine Group, University of Oxford Department of Paediatrics, and Oxford NIHR Biomedical Research Centre, Oxford, UK

ARTICLE INFO

Keywords:
Bordetella pertussis
Vaccine
Preterm
Immunoglobulin G
Serology
Multiplex

ABSTRACT

The optimal timing of pertussis vaccination in pregnancy is debated, especially to maximise antibody concentrations in infants born preterm. This study investigated immunoglobulin G (IgG) in preterm infants at 5 and 12 months, whose mothers had received a pertussis-containing vaccine at different gestations or were unvaccinated. Results show that vaccination in the early-mid second trimester may result in increased FHA specific IgG concentrations in preterm infants at 5 and 12 months.

The BEAR PAW study used residual serum samples from the BEAR Men B study (Babies born Early Antibody Response to Men B vaccination (NCT03125616)).

Pertussis is a highly infectious bacterial infection of the upper respiratory tract with a broad spectrum of presentations and potentially serious complications including apnoea, pneumonia, and death [1]. Infants aged less than three months who have not yet completed the primary vaccination series are most at risk, relying largely on maternally derived antibody for protection. Vaccination in pregnancy has been shown to be safe and effective [1–4], but there continues to be debate about the best time at which to offer the vaccine for optimal antibody concentrations in infants at delivery. The time window for vaccine administration was widened in the UK in 2016 from 28 to 32 to 16–32 weeks and a recent UK study investigating immunogenicity of pertussis vaccination in pregnancy given in three time windows has supported this [5], as has UK vaccine effectiveness data [6]. Furthermore, widening the window of vaccine administration resulted in a significant reduction in hospital admissions for pertussis in preterm infants [7]. Although pertussis vaccination in pregnancy has been shown to result in higher antibody concentrations at birth, it has also been shown to result in a blunted response to infants' own vaccinations, meaning that infants born to vaccinated mothers have lower antibody responses to some antigens following the primary series [8,9]. This blunting phenomenon has not been associated with any increase in cases of disease which suggests that this is unlikely to be clinically significant.

The impact of timing of administration of the pertussis containing vaccine Boostrix-IPV in pregnancy on antibody concentration in preterm infants following primary vaccines and prior to booster vaccines is unknown. We compared IgG concentrations against three pertussis specific antigens included in the vaccine: pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and also tetanus toxoid (TT) and diphtheria toxoid (DT). Serum samples were taken at 5 months (i.e. 1 month following completion of the primary vaccination course,

Abbreviations: DT, diphtheria toxoid; FHA, filamentous haemagglutinin; GMC, geometric mean concentration; GW, gestational weeks; IU, international units; PRN, pertactin; PT, pertussis toxin; TT, tetanus toxoid; UnV, unvaccinated.

* Corresponding author at: Infection and Immunity - City St George's, University of London - Cranmer Terrace, SW170RE London, UK.
E-mail address: odaniel@sgul.ac.uk (O. Daniel).

[1] Contributed equally

https://doi.org/10.1016/j.vaccine.2025.127481
Received 19 December 2024; Received in revised form 2 July 2025; Accepted 2 July 2025
Available online 12 July 2025
0264-410X/© 2025 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

consisting in the UK of three doses of the 6-in-1 vaccine Infanrix hexa), and at 12 months, in a cohort of preterm infants whose mothers received either Boostrix-IPV at a range of gestational ages, or who were unvaccinated.

Serum samples were available for 91 preterm infants born to mothers vaccinated at different gestations: 22 vaccinated at ≤23 gestational weeks [GW], 15 vaccinated at 24–27 GW, 13 vaccinated at ≥28 GW and 41 in an unvaccinated control group. Infants were born at a median of 30 + 3 GW (IQR 27 + 1–32 + 5) (vaccinated group 32 + 3 GW [IQR 28 + 2–32 + 5]; unvaccinated group 28 + 2 GW (IQR 26 + 0–32 + 4 GW). The mean intervals between maternal vaccination and birth for each of the timing groups was 57 days (≤23 GW), 37.5 days (24–27 GW) and 14.5 days (≥28 GW).

FHA and TT specific IgG concentrations at 5 months (Fig. 1) were significantly lower in the infants whose mothers were vaccinated at ≤23 GW compared with those whose mothers were unvaccinated. This difference persisted for FHA at 12 months (Fig. 1). At five months, DT specific IgG was significantly reduced in those born to mothers vaccinated at 24–27 GW when compared with those born to unvaccinated mothers, this difference was not observed at 12 months. At 12 months, PT-specific IgG concentrations were higher in infants born to mothers vaccinated at ≥28 GW compared with those born to mothers vaccinated at ≤23 GW.

At five months of age, TT specific IgG concentrations in all samples, and DT concentrations in most samples (89/91) of both unvaccinated and vaccinated cohorts were protective, greater than the internationally defined correlate of protection of 0.1 IU/ml (4).

When analysed according to the interval between vaccination and birth, there was a trend to higher antigen-specific IgG concentrations at five (Fig. 2) and twelve months (Fig. 2) for infants with mothers vaccinated at less than 14 days before birth, regardless of the number of gestational weeks at vaccination.

Our results show that at 5 months of age, IgG concentrations against FHA, TT and DT are lower in preterm infants born to vaccinated women than in those born to unvaccinated women, resolving by 12 months except for FHA. These results may be explained by the phenomenon of immunological blunting, in which high levels of maternal IgG antibodies following vaccination in pregnancy can inhibit the infant's own antibody response to primary vaccinations [5,6]. This interpretation would suggest that there are higher maternally acquired antibody concentrations against FHA, TT and DT in preterm infants born to women who received vaccination in pregnancy compared with those who did not, as shown in a previous study [3]. For both FHA and TT this difference was seen only between unvaccinated mothers and those vaccinated at ≤23 GW which may suggest higher antibody concentrations at birth for those infants vaccinated in an earlier window. A previous study has shown that vaccination in the second trimester resulted in higher cord blood antibody concentrations for anti-PT and anti-FHA antibodies in preterm infants [7]. There are currently no agreed serological correlates of protection for pertussis, nor is there evidence to suggest that blunting produces a clinically relevant effect in susceptibility to pertussis infection [8,9].

Gross trends were also identified showing higher antigen-specific IgG concentrations at 5 and 12 months of age when vaccines were given within 14 days prior to birth, regardless of the gestational age at vaccination. The absence of a blunting effect in infants born to mothers vaccinated close to time of delivery is consistent with previous work showing that cord blood PT and FHA concentrations were not significantly different between unvaccinated mothers and mothers who were vaccinated less than 14 days prior to delivery [10].

This study is limited by the lack of cord or infant pre-primary vaccination blood samples, which would have allowed us to better understand the impact of vaccination timing in pregnancy. Previous studies have demonstrated that a minimum of 6–7.5 weeks between vaccination and delivery is associated with maximal antibody concentrations at birth [11], however shorter periods between vaccination and delivery are inevitable in a preterm population. Our conclusions are also further limited as we performed no correction for multiple comparisons increasing the risk of type 1 error. Finally, small sample sizes limited our ability to assess the relationship between time of vaccination and delivery and between gestational age and timing of vaccination.

In conclusion our data suggests that for FHA, TT and DT antigens, vaccination in pregnancy may result in blunting of the response to primary vaccination in infants born preterm. We infer that preterm infants have higher antibody concentrations in the early months of life following maternal vaccination, suggesting benefit from the vaccine. Despite the proven benefits of maternal vaccination against pertussis, it remains essential to investigate further the blunting phenomenon and establish a serological correlate of protection.

1. Methods

1.1. Study samples

The BEAR PAW study used residual serum samples from the BEAR Men B study (Babies born Early Antibody Response to Men B vaccination (NCT03125616)), which had been stored at -80 °C. Ethical approval for BEAR PAW was given by REC West Midlands-Edgbaston (19/WM/0198) and for the BEAR Men B study by York and Humber Research Ethics Committee (17/YH/0150) and the Health Research Authority. In the BEAR Men B study, 136 infants were recruited in England between August 2017 and September 2018 and samples were collected at 5, 12 and 13 months. All the infants in the BEAR Men B study received Men B vaccination and were randomised either to receive the routine schedule which at the time was 2 and 4 months, or an extended schedule with an additional dose at 3 months. Samples were eligible for the BEAR PAW study if permission had been given for retention of the sample, and if information was available about gestational age at vaccination and birth. Because the infants were recruited to BEAR Men B after birth, whether women received vaccination and the timing of this vaccination was entirely independent of the trial but would be expected to have taken place within the national recommendations at 16–32 weeks of gestation).

1.2. Vaccination

The vaccine in the national programme at the time was Boostrix-inactivated poliovirus vaccine (GlaxoSmithKline; London, UK). Boostrix-IPV contains pertussis toxin (8 μg), filamentous haemagglutinin (8 μg), pertactin (2·5 μg), diphtheria toxoid (not less than two international units), tetanus toxoid (not less than 20 international units), and inactivated polio virus types 1–3 (type-1 40 D-antigen unit, type-2 8 D-antigen unit, and type-3 32 D-antigen unit). All babies in the trial received routine vaccines according to the UK schedule with one study group in the BEAR Men B study randomised to receive an additional dose of Bexsero at 12 weeks in addition to 8 and 16 weeks.

1.3. Laboratory assay

An in-house Multiplex assay was used to measure antigen-specific serum IgG. MagPlex microspheres (Luminex DiaSorin, Italy) were conjugated to five antigens: pertussis toxin, pertactin, diphtheria toxoid, tetanus toxoid (181, 187, 151 and 191B respectively, List Biological Laboratories, Campbell, United-States), and filamentous haemagglutinin (QTOX, QTXAG-131). Serum samples were diluted to 1:100, 1:1000 and 1:10.000, next to a curve prepared from the Pertussis Antiserum WHO International standard (1:60 dilution and 3-fold serial dilution, NIBSC 06/140, UK). Serum and microspheres were incubated for two hours at 300 rpm, and R-Phycoerythrin-conjugated goat anti-human IgG secondary antibody (1:200, 50ul/well, 109–115-098, Jackson ImmunoResearch, Ely, UK) was added for 30 min at 300 rpm. Plates were read with Bio-Plex 200 (Bio-Rad, Hercules, United-States).

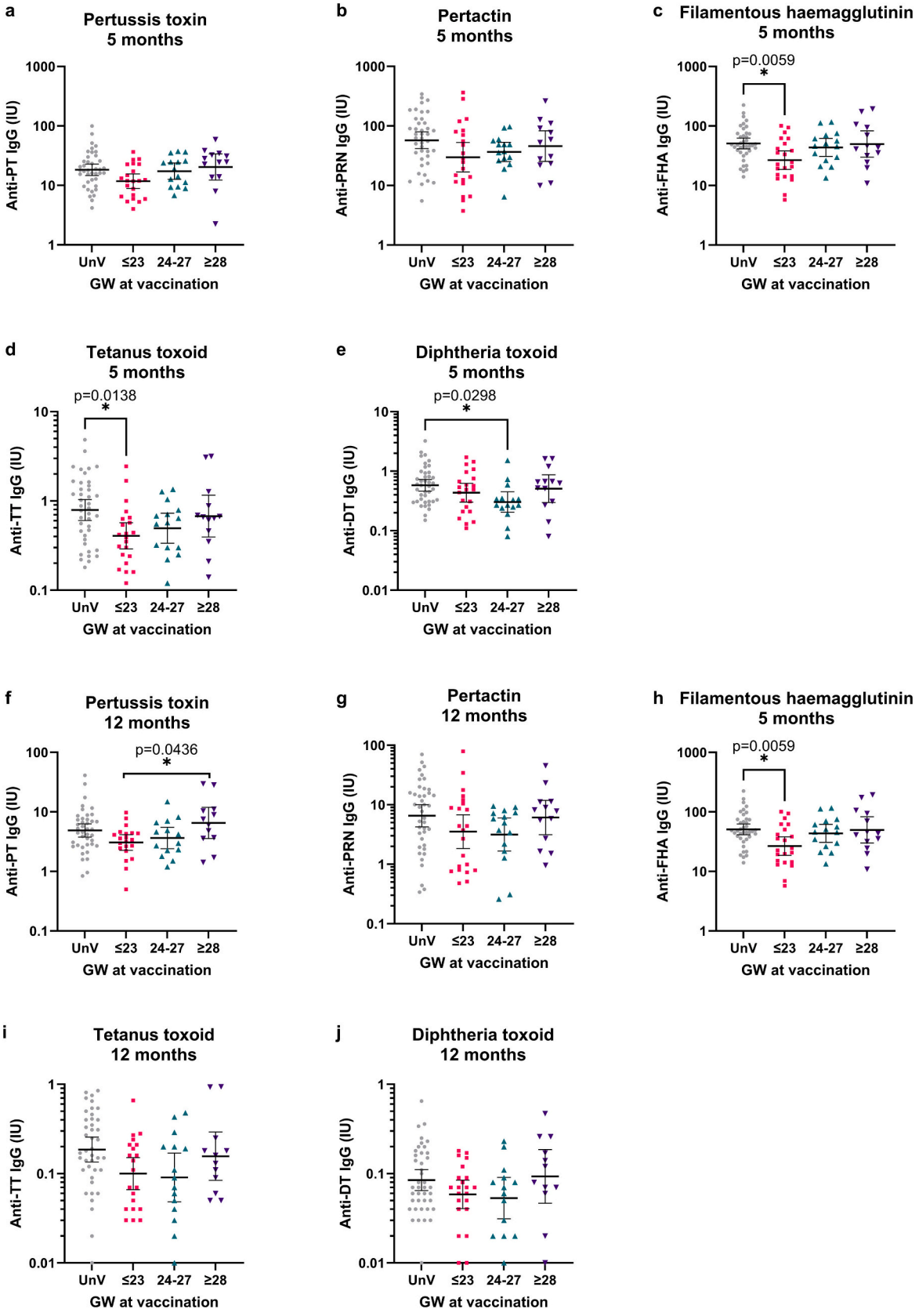

Fig. 1. Infant serum PT, PRN, FHA, TT, and DT specific IgG at 5 and 12 months. Mothers are unvaccinated (UnV) or vaccinated at different gestational weeks with a Boostrix-IPV vaccine. The geometric mean concentration (GMC) of antigen specific IgG (IU) in infant serum and 95 % confidence interval are plotted. Groups were compared with ANOVA tests with a significance level of 5 %.

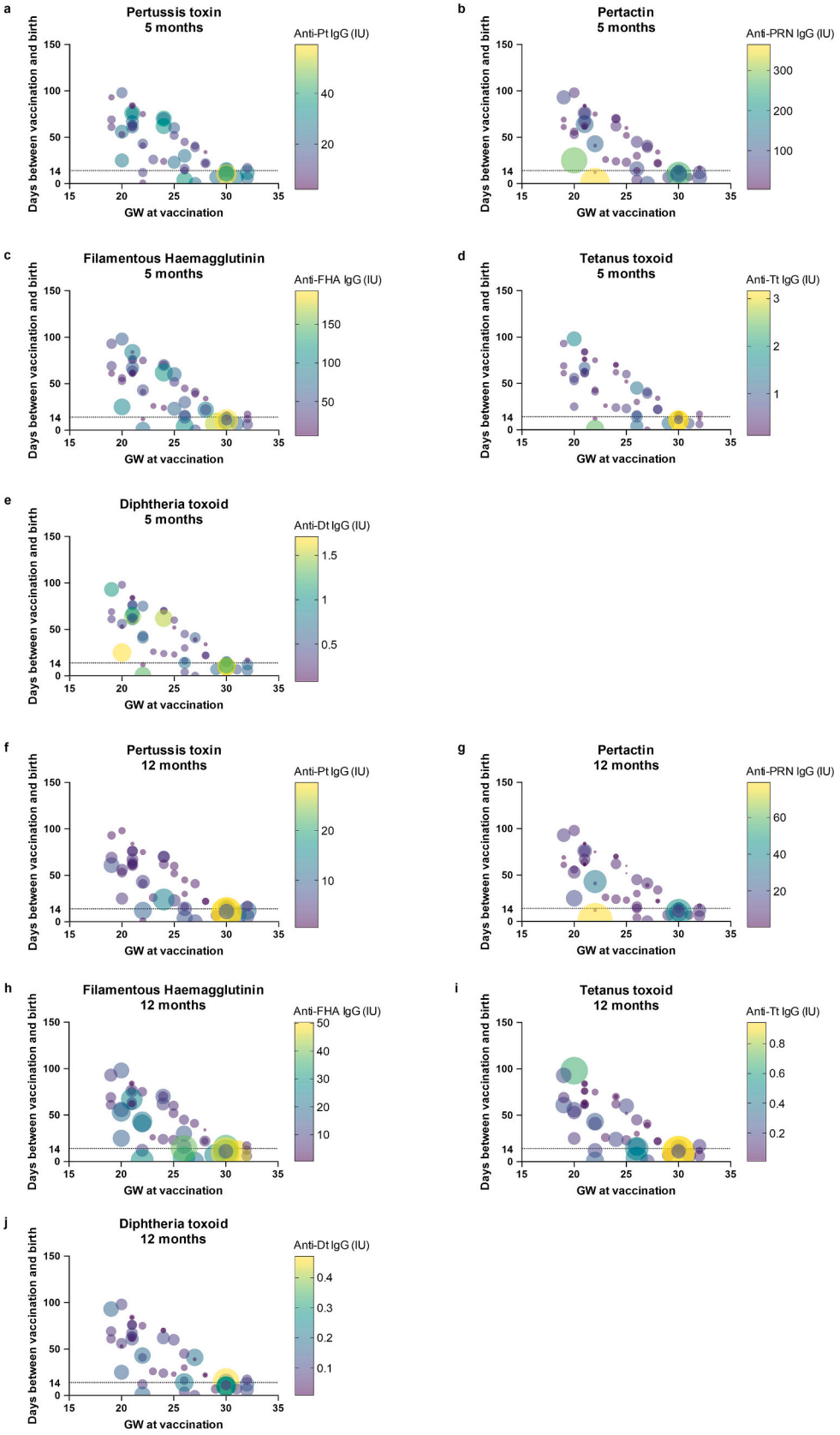

Fig. 2. Infant serum IgG at 5 months and 12 months of age relative to timings of maternal vaccination and birth. Antigen specific IgG concentration (IU) is proportional to the points size and colour coded. IgG is then plotted according to number of days between maternal vaccination and birth and number of gestational weeks at vaccination. Higher IgG levels are found under 14 days between vaccination and birth.

1.4. Data analysis

MFI were interpolated into concentrations with Bio-Plex Manager Software 6.2. On Graph Pad Prism 10.2.2, the geometric mean concentration (GMC) levels of IgG in infant serum were compared between groups using ANOVA tests with a significance level of 5 %. Impact of the number of gestational weeks at vaccination and number of days between vaccination and birth was visually assessed, no regression models were performed due to small sample sizes.

CRediT authorship contribution statement

Olwenn Daniel: Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis. **Sashank Srikanth:** Writing – original draft, Investigation, Formal analysis. **Paul Clarke:** Writing – review & editing, Resources, Investigation. **Kirsty Le Doare:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Conceptualization. **Paul T. Heath:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Conceptualization. **Christine E. Jones:** Writing – review & editing, Resources, Investigation. **Tim Scorrer:** Writing – review & editing, Resources, Investigation. **Matthew Snape:** Writing – review & editing, Resources, Investigation. **Anna Calvert:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors for the additional work performed for the BEAR PAW study. The original BEAR Men B trial was funded by Meningitis Now and GSK.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data collected for the study, including individual (deidentified) participant data and a data dictionary defining each field in the set, can be made available for suitable applications submitted to the Chief Investigator (pheath@sgul.ac.uk). Additional related documents are available on request.

References

[1] Switzer C, D'Heilly C, Macina D. Immunological and clinical benefits of maternal immunisation against pertussis: a systematic review. Infect Dis Ther 2019;8:499–541.
[2] Munoz FM. Pertussis in infants, children and adolescents: diagnosis, treatment and prevention. Seminars in Paediatric Infect Dis 2006;17:14–9.
[3] Kent A, Ladhani SN, Andrews NJ, Matheson M, England A, et al. Pertussis antibody concentrations in infants born prematurely to mothers vaccinated in pregnancy. Paediatrics 2016;138.
[4] Roper M, Wassilak S, Henderson D, Poland GA. Tetanus Toxoid. 746–772. In: Plotkin SA, Orenstein W, Offit PA, editors. Vaccines. 6th ed. Elsevier; 2013.
[5] Abu-Raya B, Maertens K, Munoz FM, Zimmermann P, Curtis N, et al. Factors affecting antibody responses to immunizations in infants born to women immunized against pertussis in pregnancy and unimmunized women: individual-participant data Meta-analysis. Vaccine 2021;39:6545–52.
[6] Niewiesk S. Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Front Immunol 2014;16:446.
[7] Eberhardt CS, Blanchard-Rohner G, Lemaître B, Combescure C, Othenin-Girard V, Chilin A, et al. Pertussis antibody transfer to preterm neonates after second- versus third-trimester maternal immunization. Clin Infect Dis 2017;64:1129–32.
[8] Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol 2010;17:1055–65.
[9] Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine response. J Infect Dis 1990;161:487–92.
[10] EberharDT CS, Blanchard-Rohner G, Lemaitre B, Boukrid M, Combescure C, et al. Maternal immunisation earlier in pregnancy Maximises antibody transfer and expected infant Seropositivity against pertussis. Clin Infect Dis 2016;62:829–36.
[11] Gomme J, Wanlapakorn N, Ha Htt, Leuridan E, Herzog SA, et al. The impact of timing of pertussis vaccination during pregnancy on infant antibody levels at birth: a multi-country analysis. Front Immunol 2022;28(13):913922.