Vaccine 40 (2022) 7050–7056

Contents lists available at ScienceDirect

Vaccine

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

An observational, cohort, multi-centre, open label phase IV extension study comparing preschool DTAP-IPV booster vaccine responses in children whose mothers were randomised to one of two pertussis-containing vaccines or received no pertussis-containing vaccine in pregnancy in England

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ARTICLE INFO

Article history:
Received 3 March 2022
Received in revised form 23 September 2022
Accepted 5 October 2022
Available online 20 October 2022

Keywords:
Maternal vaccination
Immunisation
Pertussis
Immune
Response
Pregnancy
Vaccine
Blunting
Children
Booster

ABSTRACT

An antenatal pertussis vaccination programme was introduced in 2012 in the UK in the context of a national outbreak of pertussis. It has been shown that a lower antibody response to primary immunisation can be seen for certain pertussis antigens in infants born to women who received pertussis-containing antenatal vaccines, a phenomenon known as blunting. The longer-term impact of this has not been documented previously, and accordingly was evaluated in this study.

Children were predominantly recruited from a previous study in which their mothers had received acellular pertussis-containing antenatal vaccines ($dTaP_3$-IPV [diphtheria toxoid, tetanus toxoid, three antigen acellular pertussis and inactivated polio] or $dTaP_5$-IPV [diphtheria toxoid, tetanus toxoid, five antigen acellular pertussis and inactivated polio]), or no pertussis-containing vaccine. Blood samples were obtained prior to and one month after the acellular pertussis-containing preschool booster ($dTaP_5$-IPV) was given at around age 3 years 4 months. Pre- and post-booster immunoglobulin G (IgG) geometric mean concentrations (GMCs) against pertussis toxin, filamentous haemagglutinin, fimbriae 2 & 3, and pertactin, were compared.

Prior to the receipt of the preschool booster, there was no difference in the IgG GMCs against pertussis-specific antigens between children born to women vaccinated with $dTaP_3$-IPV and $dTaP_5$-IPV; however, IgG GMCs against pertussis toxin were significantly lower in children born to women vaccinated with $dTaP_3$-IPV compared with children born to unvaccinated women (geometric mean ratio 0.42 [95 % CI 0.22–0.78], p = 0.03). One month after the receipt of the preschool booster there was no differences between the groups.

The blunting effect of antenatal pertussis vaccine on pertussis responses in children can persist until preschool age, although it is overcome by the administration of a booster dose.

ClinicalTrials.gov registration number: NCT03578120

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https://doi.org/10.1016/j.vaccine.2022.10.005
0264-410X/

1. Introduction

Pertussis (whooping cough) is a vaccine-preventable acute bacterial respiratory infection caused mainly by the organism *Bordetella pertussis* [1]. It is characterised by a protracted coughing illness that can result in severe complications, including death, particularly in young infants [1].

A resurgence of pertussis infections, including pertussis-related infant deaths, has been reported from several countries [2], including those with longstanding childhood vaccination programmes that had replaced whole cell pertussis (wP) with acellular pertussis (aP) vaccines [3]. In the UK, a national outbreak of pertussis was declared in 2012 and in response a temporary immunisation programme for pregnant women was introduced [4,5]. A low-dose diphtheria-tetanus-acellular pertussis-inactivated polio combination vaccine (dTaP-IPV) was recommended. Initially this was given as REPEVAX®, and subsequently as BOOSTRIX-IPV® from 2014[5]. High vaccine effectiveness has been observed for both vaccines [2,6]. In 2019, the Joint Committee on Vaccination and Immunisation (JCVI) recommended that the antenatal pertussis vaccination programme become routine [4].

It is assumed that the effectiveness of the antenatal pertussis vaccination programme in preventing infant disease is largely due to the increased levels of transplacentally derived pertussis antigen-specific maternal immunoglobulin G (IgG) antibodies present in infants born to vaccinated women. One of the key questions regarding maternal vaccination however, is the clinical significance of the interference of maternally derived antibodies on the infant's own immune response to vaccination, a phenomenon known as blunting [5]. Blunting has been widely observed [5,7–11]. In a preceding study to this, known as *immunising Mums Against Pertussis 2* (iMAP2), which compared the IgG response to pertussis antigens following primary immunisation in infants born to mothers who received pertussis-containing vaccines (BOOSTRIX-IPV® or REPEVAX®), or no pertussis-containing vaccine in pregnancy [12]. Children born to vaccinated women had a lower IgG geometric mean concentration (GMC) against pertussis toxoid (PT) at 5 months of age, compared to infants of unvaccinated women [12], although this difference was not observed at 13 months of age [12].

When compared to infants born to unvaccinated women, blunting was observed for anti-PT IgG responses, although this effect was not sustained at the end of the first year of life.

The longer-term effects of blunting have not been assessed in the UK, where the first pertussis-containing booster vaccination after completing the primary immunisation (at sixteen weeks old) is given at pre-school age (aged at least 3 years and 4 months).

The primary objective of this study, known as *immunising Mums Against Pertussis 3* (iMAP3), was to assess the antibody persistence post-primary immunisation against PT at preschool age, before receipt of the preschool booster vaccination, in children born to women who were randomised in pregnancy to receive one of two pertussis-containing vaccines (BOOSTRIX-IPV® or REPEVAX®), and to compare these responses to those of children born to unvaccinated women. Antibody concentrations against diphtheria, tetanus and other pertussis-specific antigens before and after receipt of the preschool booster vaccination were also assessed and compared.

2. Methods

2.1. Study design

In this observational, multi-centre, open label phase IV extension study, children born to vaccinated and unvaccinated women who had taken part in the iMAP2 study were invited to participate. Another group of children who were in a similar age group and whose mothers had not received a pertussis-containing vaccine in pregnancy were also approached. These children had been in another study (Infanrix study, ClinicalTrials.gov registration number NCT01896596) conducted in parallel with the iMAP2 study, and using the same methodology (blood sampling time-points, age group, laboratory, and assays). Children in the Infanrix study had received primary immunisation with a 6-in-1 vaccine (Infanrix®-hexa; diphtheria toxoid [DT]: ≥30 IU; tetanus toxoid [TT]: ≥40 IU; PT: 25 μg; filamentous hemagglutinin [FHA]: 25 μg; pertactin [PRN]: 8 μg; no fimbriae types 2 and 3 [FIM]; IPV type 1: 40 D-antigen units [DAU]; IPV type 2: 8 DAU; IPV type 3: 32 DAU; *Haemophilus influenzae* type b [Hib]: 10 μg; recombinant hepatitis B surface antigen [HBsAg]: 10 μg; GlaxoSmithKline) as compared with children in iMAP2 who had received a 5-in-1 vaccine (PEDIACEL®; DT: ≥30 IU; TT: ≥40 IU; PT: 20 μg; FHA: 20 μg; PRN: 3 μg; FIM: 5 μg; IPV type 1: 40 DAU; IPV type 2: 8 DAU; IPV type 3: 32 DAU; Hib: 10 μg; Sanofi Pasteur).

Children at pre-school age and due for their preschool booster (aged at least 3 years and 4 months) were eligible to participate. Exclusion criteria included any of the contraindications to vaccination specified in The Green Book on Immunisation or receipt of an additional pertussis containing vaccine after the routine 16-week primary immunisation [13].

Following written, parental informed consent, a venous blood sample was collected at the first visit from the recruited child prior to the receipt of the preschool booster with REPEVAX® ($dTaP_5$-IPV; PT: 2.5 μg; FHA: 5 μg; PRN: 3 μg; FIM: 5 μg; Sanofi Pasteur) in accordance with the routine UK immunisation schedule. A further venous blood sample was collected at a second visit, around 1 month (range 28 to 35 days) later.

The study was approved by the NHS Health Research Authority and the London Brent Research Ethics Committee (18/NW/0095). Children were recruited from 3 sites in England; St George's University of London, University of Oxford and Gloucestershire Hospitals NHS Foundation Trust.

2.2. Outcomes

The primary outcome was the fold-differences in anti-PT immunoglobulin G (IgG) GMCs in children at preschool age before receipt of the preschool booster, between those born to women who received one of the two pertussis-containing antenatal vaccines, REPEVAX® or BOOSTRIX-IPV® ($dTaP_3$-IPV; PT: 8 μg; FHA: 8 μg; PRN: 2.5 μg; Glaxo Smith Kline), to those born to women who did not. Secondary outcomes included the fold-differences in anti-PT IgG GMC in the children 1 month after the receipt of the preschool booster, and the fold-differences in anti-FHA, anti-FIM, anti-PRN, anti-diphtheria toxoid (anti-DT) and anti-tetanus toxoid (anti-TT) IgG GMCs in the children prior to and 1 month after the receipt of the preschool booster.

2.3. Laboratory

Blood samples were shipped on the same day of collection (or the next working day and stored in a temperature-monitored refrigerator between 2 °C and 8 °C until time of shipment) to the Immunoassay Group (IAG) Laboratory at Public Heath England (PHE) via tracked next-day delivery service, where the serum were separated, aliquoted and frozen at less than −60 °C, before being tested for the IgG antibodies against PT, FHA, FIM, PRN, DT and TT, using enzyme-linked immunosorbent assays (ELISAs). Further details are provided in the Supplementary Paragraph.

2.4. Statistical methods

The sample size calculation was based on an estimation that approximately 50 % of the children who participated in the iMAP2 study would be recruited to this study (i.e. 70 children, approximately 35 children whose mothers received REPEVAX® and 35 whose mothers had received BOOSTRIX-IPV®). The addition of a further 15 children whose mothers had not receive an antenatal pertussis-containing vaccine would provide 80 % power to detect a twofold difference in anti-PT IgG antibodies between the groups, based on a standard deviation (SD) of 0.28 IU/ml anti-PT IgG GMC reported post-primary immunisations in a previous study that utilised the same validated ELISA [14].

Missing data were assumed to be missing at random and excluded from analysis. Analyses were performed using Stata version 13. Baseline data including gender, age in months, duration in months since the children's last pertussis-containing vaccine and duration in days between preschool booster and post-vaccination blood sampling were presented and summarised categorically according to the three different groups (born to mothers who received REPEVAX®, BOOSTRIX-IPV® and no pertussis-containing vaccine in pregnancy) using Fisher's exact test for gender and Kruskal Wallis test for other variables.

For the primary endpoint analysis, antibody concentrations were log-transformed and compared between the three groups by normal errors regression and by calculating geometric means and geometric mean ratios (GMR) with 95 % CIs. All three groups were compared with one another in pairwise comparisons as well as combining the two vaccinated groups together to compare with the unvaccinated group. Adjustment for sex and interval since the last pertussis-containing and non-pertussis-containing vaccination were performed where data were skewed. Kruskal-Wallis test was also used to compare the groups where data were skewed (on a log-scale). Antibody concentration analyses for the secondary endpoints were assessed in the same way as for the primary endpoint. Comparisons of proportions above the established serocorrelates of protection thresholds for anti-DT and anti-TT (0.1 IU/ml for both) were performed by Fisher's exact test and by logistic regression to adjust for gender and time since vaccination.

The decline in anti-PT IgG GMCs from post primary to pre-preschool booster was modelled using a log-time log-titre relationship (normal errors regression) and plotted. The slopes were compared between groups as an interaction term in the model. The overall anti-PT IgG GMCfold decline was also calculated and compared between groups and the GMC post-primary vaccination in the iMAP2 study and in those children also recruited into the current study was also compared.

3. Results

3.1. Comparison of recruited versus non-recruited children from the preceding study

Between March 2018 and September 2019, 63 out of 144 children participating in the iMAP2 study and one child from the Infanrix study were recruited; 48 were born to women who received a pertussis-containing antenatal vaccine in pregnancy (26 BOOSTRIX-IPV®, 22 REPEVAX®) and 16 to women who did not receive a pertussis-containing antenatal vaccine. Details of those recruited are shown in Supplementary Table 1. There were no significant differences between recruited and non-recruited children from the iMAP2 study.

3.2. Comparison amongst recruited children

Details of those recruited to the three groups (mothers receiving BOOSTRIX-IPV®, REPEVAX® or no pertussis-containing vaccine in pregnancy) are shown in Table 1. No significant differences were observed.

3.3. Antibody concentrations prior to preschool booster

Prior to receipt of the preschool booster, there was no significant difference in the IgG GMCs against any pertussis-specific antigens between children born to women vaccinated with BOOSTRIX-IPV® and REPEVAX®. Only anti-PT IgG GMCs were significantly lower (p = 0.03) in the children born to BOOSTRIX-IPV® vaccinated women compared with those born to unvaccinated women (GMR 0.42 [95 % CI 0.22–0.78). There was no significant difference but only an apparent trend for lower IgG GMCs against all pertussis antigens in the children born to vaccinated women than in the children born to unvaccinated women. There was also no significant difference in the anti-DT and anti-TT IgG GMCs between groups (Table 2).

3.4. Antibody concentrations 1 month after the preschool booster

One month after the receipt of the preschool booster, there was no significant difference but only an apparent trend for lower IgG GMCs against all pertussis antigens (except PRN) in children born to vaccinated women than in children born to unvaccinated women. There was also no significant difference in the IgG GMCs against DT and TT between groups and all achieved levels above the established serocorrelates of protection (Table 2).

Table 1
Comparison of recruited children in the current study iMAP3.

Factor	Level	BOOSTRIX-IPV® (n = 26)	REPEVAX® (n = 22)	Control (n = 16)	P-value
Sex	Female	10 (38 %)	14 (64 %)	9 (56 %)	0.22
	Male	16 (62 %)	8 (36 %)	7 (44 %)	
Age at receipt of preschool booster (months)	39	2 (8 %)	1 (4 %)	0 (0 %)	
	40	16 (61 %)	14 (64 %)	11 (69 %)	
	41	4 (15 %)	3 (14 %)	2 (12 %)	
	42	2 (8 %)	4 (18 %)	3 (19 %)	
	43	1 (4 %)	0 (0 %)	0 (0 %)	
	44	1 (4 %)	0 (0 %)	0 (0 %)	
	Median (months)	40.5	40.7	40.7	0.69
Interval since last DTaP dose (months)	Median [range]	36.3 [35.4–40.1]	36.9 [35.7–39.1]	36.7 [35.0–38.7]	0.70
Interval since last MMR/PCV doses (months)	Median [range]	28.3 [27.6–32.1]	28.5 [27.5–30.6]	28.4 [27.9–30.1]	0.86
Interval of blood sampling post preschool booster (days)	Median [range]	30 [28–35]	33 [28–35]	29.5 [28–35]	0.89

Table 2
Summary of antibody concentrations pre- and post-booster.

Antibody	Timeline	Group	N	GMC (95 % CI)	GMR Vaccine: Control (95 % CI)	P-value*	GMR REPEVAX®: BOOSTRIX® (95 % CI)	P-value*	N >=0.1 IU/ml (%)**	N >=1 IU/ml (%)**
Anti-PT	Pre-booster	BOOSTRIX-IPV®	25	1.19 (1.04–1.36)	0.42 (0.22–0.78)	0.03				
		REPEVAX®	21	1.75 (1.13–2.73)	0.61 (0.32–1.18)	0.32	1.47 (0.82–2.64)	0.21		
		Both vaccines	46	1.42 (1.15–1.76)	0.50 (0.28–0.88)	0.06				
		Control	16	2.86 (1.22–6.68)						
	Post-booster	BOOSTRIX-IPV®	24	18.04 (11.53–28.23)	0.54 (0.28–1.04)	0.07				
		REPEVAX®	18	24.22 (17.08–34.36)	0.73 (0.36–1.46)	0.37	1.34 (0.71–2.53)	0.36		
		Both vaccines	42	20.47 (15.34–27.32)	0.61 (0.34–1.11)	0.11				
		Control	16	33.3 (16.84–65.83)						
Anti-FHA	Pre-booster	BOOSTRIX-IPV®	25	11.86 (6.63–21.22)	0.77 (0.31–1.88)	0.56				
		REPEVAX®	21	12.35 (7.5–20.34)	0.80 (0.32–2.02)	0.64	1.04 (0.46–2.38)	0.92		
		Both vaccines	46	12.08 (8.3–17.58)	0.78 (0.35–1.75)	0.55				
		Control	16	15.45 (5.94–40.24)						
	Post-booster	BOOSTRIX-IPV®	24	60.83 (39.58–93.50)	0.54 (0.28–1.04)	0.06				
		REPEVAX®	18	79.62 (51.15–123.94)	0.71 (0.35–1.41)	0.33	1.31 (0.70–2.46)	0.40		
		Both vaccines	42	68.27 (50.57–92.17)	0.61 (0.33–1.09)	0.10				
		Control	16	112.79 (59.93–212.26)						
Anti-FIM	Pre-booster	BOOSTRIX-IPV®	25	1.18 (0.89–1.58)	0.72 (0.44–1.19)	0.20				
		REPEVAX®	21	1.49 (1.05–2.1)	0.91 (0.54–1.52)	0.72	1.26 (0.80–1.99)	0.33		
		Both vaccines	46	1.31 (1.06–1.63)	0.80 (0.51–1.26)	0.34				
		Control	16	1.63 (0.98–2.71)						
	Post-booster	BOOSTRIX-IPV®	24	4.79 (2.75–8.32)	0.41 (0.13–1.25)	0.12				
		REPEVAX®	18	5.91 (2.39–14.63)	0.50 (0.15–1.66)	0.26	1.24 (0.42–3.64)	0.70		
		Both vaccines	42	5.24 (3.25–8.45)	0.45 (0.16–1.23)	0.12				
		Control	16	11.75 (3.53–39.13)						
Anti-PRN	Pre-booster	BOOSTRIX-IPV®	25	5.3 (3.6–7.8)	0.91 (0.40–2.09)	0.822				
		REPEVAX®	21	2.9 (1.7–5.2)	0.51 (0.22–1.20)	0.124	0.56 (0.26–1.21)	0.14		
		Both vaccines	46	4.0 (2.9–5.7)	0.70 (0.33–1.49)	0.351				
		Control	16	5.8 (2.2–15.4)						
	Post-booster	BOOSTRIX-IPV®	24	398.2 (253.3–626.1)	1.51 (0.63–3.6)	0.358				
		REPEVAX®	18	362.1 (156.1–840.0)	1.37 (0.54–3.47)	0.508	0.91 (0.39–2.11)	0.825		
		Both vaccines	42	382.3 (250.7–583.0)	1.45 (0.66–3.18)	0.359				
		Control	16	264.5 (125.1–559.3)						
Anti-DT	Pre-booster	BOOSTRIX-IPV®	25	0.07 (0.05–0.10)	1.02 (0.54–1.93)	0.96			11 (44 %)	0 (0 %)
		REPEVAX®	21	0.04 (0.02–0.08)	0.59 (0.3–1.15)	0.12	0.58 (0.32–1.05)	0.07	6 (29 %)	0 (0 %)
		Both vaccines	46	0.06 (0.04–0.08)	0.79 (0.44–1.43)	0.44			17 (37 %)	0 (0 %)
		Control	16	0.07 (0.05–0.11)					4 (25 %)	0 (0 %)
	Post-booster	BOOSTRIX-IPV®	24	3.87 (2.82–5.32)	0.88 (0.52–1.48)	0.63			24 (100 %)	23 (96 %)
		REPEVAX®	18	3.19 (2.08–4.90)	0.72 (0.42–1.26)	0.26	0.82 (0.50–1.36)	0.45	18 (100 %)	16 (89 %)
		Both vaccines	42	3.56 (2.78–4.57)	0.81 (0.50–1.30)	0.38			42 (100 %)	39 (93 %)
		Control	16	4.40 (2.75–7.04)					16 (100 %)	15 (94 %)
Anti-TT	Pre-booster	BOOSTRIX-IPV®	25	0.46 (0.30–0.70)	1.05 (0.52–2.11)	0.89			23 (92 %)	5 (20 %)
		REPEVAX®	21	0.24 (0.13–0.44)	0.65 (0.32–1.34)	0.24	0.62 (0.32–1.20)	0.16	14 (67 %)	3 (14 %)
		Both vaccines	46	0.34 (0.24–0.49)	0.84 (0.45–1.58)	0.59			37 (80 %)	8 (17 %)
		Control	16	0.39 (0.22–0.68)					14 (88 %)	2 (13 %)
	Post-booster	BOOSTRIX-IPV®	24	15.93 (12.78–19.86)	1.04 (0.67–1.61)	0.85			24 (100 %)	24 (100 %)
		REPEVAX®	18	16.01 (10.42–24.59)	1.05 (0.66–1.66)	0.85	1.00 (0.66–1.53)	0.98	18 (100 %)	18 (100 %)
		Both vaccines	42	15.96 (12.92–19.73)	1.04 (0.71–1.55)	0.83			42 (100 %)	42 (100 %)
		Control	16	15.29 (10.59–22.06)					16 (100 %)	16 (100 %)

*K-wallis test; **available for anti-DT & anti-TT.

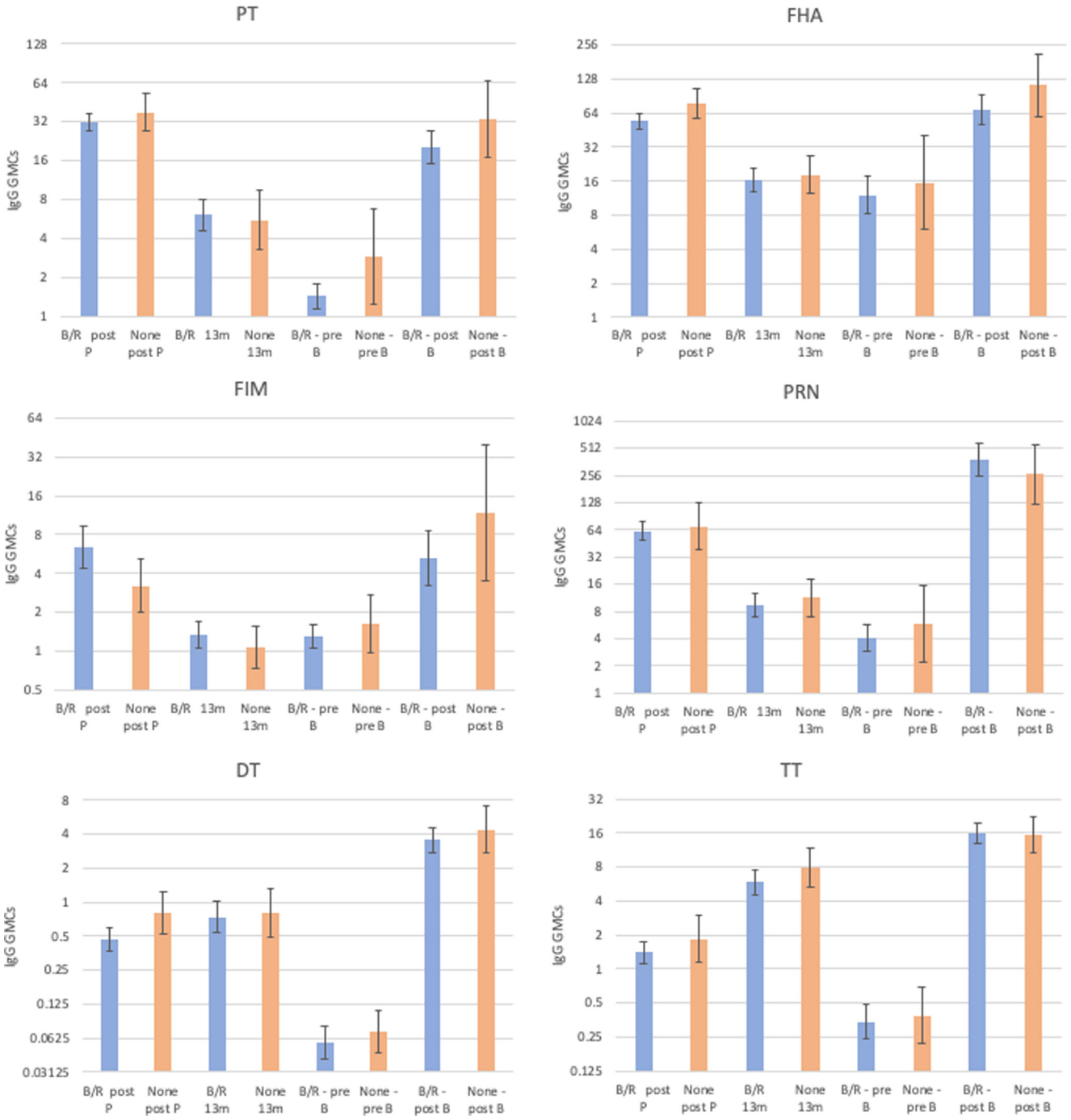

Fig. 1. Children's antibody responses by antigen post-primary immunisations, at age 13 months, pre- and post-booster according to their mothers' antenatal vaccination status (BOOSTRIX-IPV®, REPEVAX® or none). B, BOOSTRIX-IPV® group; R, REPEVAX® group; post P, post-primary immunisations; pre B, pre-booster; post B, post-booster.

3.5. Antibody concentrations across infancy and pre-school age

Fig. 1 shows all antibody results from both the iMAP2 and iMAP3 studies: post-primary immunisations (aged 5 months, iMAP2), 13 months of age (iMAP2), prior to and 1 month after the preschool booster (iMAP3). Both groups of children with mothers who received pertussis-containing vaccines (BOOSTRIX-IPV® and REPEVAX®) were combined at all time points as there were no significant differences between them.

3.6. Antibody decline

Supplementary Table 2 shows the IgG GMRs for all antibodies, comparing the IgG GMCs at 13 months of age and at pre-booster. Overall, larger declines between the two time-points were seen in anti-DT antibodies (GMR 0.08 [95 % CI 0.07–0.1] and anti-TT antibodies 0.06 [95 % CI 0.05–0.07] than in pertussis-specific antibodies (GMR 0.28 [95 % CI 0.21–0.39], 0.73 [95 % CI 0.47–1.15], 0.97 [95 % CI 0.72–1.32], and 0.51 [95 % CI 0.34–0.77] in anti-PT,

anti-FHA, anti-FIM and anti-PRN respectively). There was no clear evidence that the rate of decline between the two time-points differed by different pregnancy vaccination groups.

When comparing the IgG GMCs at 13 months age and pre-booster for anti-PT, four children displayed an increase in their anti-PT IgG GMC, three of whom were born to women who had not received a pertussis-containing vaccine in pregnancy (Supplementary Fig. 1). Supplementary Fig. 2 shows the IgG GMCs fold change between pre- and post-booster, which shows that higher anti-PT IgG GMCs following the preschool booster were related to higher levels prior to receipt of the booster. Supplementary Fig. 1 also shows the IgG GMCs fold change between 13 months and pre-booster for other pertussis-specific antibodies and for DT and TT antibodies. Some individuals displayed an increase in their IgG GMCs against other pertussis-specific antigens between these two time-points.

4. Discussion

It is now well recognised that antenatal pertussis vaccination is an effective strategy for the prevention of pertussis disease in early infancy [2,5,6]. However, the consequences of blunting of the infant's own immune response to primary pertussis immunisation remains a critical question, particularly in settings where booster doses are not given until later in childhood, as in the UK. To our knowledge, this is the first study to explore the influence of antenatal pertussis vaccination on children's antibody responses beyond 19 months of age.

At around 3 and a half years of age, and prior to receipt of the preschool booster, the only pertussis-specific antibody response found to be at a significantly lower level in those born to mothers who received a pertussis-containing antenatal vaccine was anti-PT in the $TdaP_3$-IPV group. This might reflect blunting due to the higher level of PT antigen contained in $TdaP_3$-IPV compared to $TdaP_5$-IPV. The clinical significance of lower pertussis antibody concentrations is uncertain, given the absence of a serocorrelate of protection for pertussis. None of the participants were reported to have had confirmed or suspected pertussis disease at any time. National surveillance data has also not shown any excess in later cases of disease in infants born to vaccinated mothers [2]. However, it is notable that three of the four children who displayed an increase in their anti-PT IgG GMCs between 13 months and 3 years 4 months were born to unvaccinated women, which could suggest that unrecognised pertussis infection may have occurred more frequently in this group and could explain their generally higher pertussis antibody concentrations; this interpretation however must be taken with caution in view of the small number of children concerned. The lower pertussis-specific antibody responses to PT in the antenatally vaccinated TdaP3-IPV group when compared to the unvaccinated group may support an argument for an earlier pertussis booster dose, such as in the second year of life. Such a decision would need to be based on robust epidemiological data.

The presence or absence of FIM antigen in a pertussis-containing antenatal vaccine received by the vaccinated women did not appear to have any statistically significant impact on the level of anti-FIM IgG GMCs in their children.

Several studies have looked at the influence of antenatal pertussis vaccination on children's antibody response in the first two years of life, including some that have shown blunting post-primary and post-booster immunisation [5,7–11,15,16]. We identified one study performed in Belgium that looked beyond the first year of life at age 15 months, which is the age when a pertussis-containing booster vaccine (Infanrix-hexa®) is given according to the country's routine immunisation programme [17]. Persistence of blunting was shown both before and after receipt of the booster, significantly so for anti-PRN before, and for anti-PT after [17]. We also identified one study performed in Thailand that looked at the influence of antenatal pertussis vaccination on children's antibody response up to 19 months of age to either acellular (Infanrix-hexa®) or whole-cell pertussis (Quinvaxem®) vaccines administered at 2, 4, 6 (primary) and 18 months of age (booster) but without a control group of unvaccinated women [18]. Blunting was shown, persisting until after the booster at 19 months of age, more so in the children that received whole-cell pertussis vaccines [18].

It is therefore reassuring that following receipt of a booster at an older age in our study no statistically significant difference was found in any pertussis-specific antibody responses between the groups. This was also true for anti-DT and anti-TT IgG GMCs. It is reassuring that although potential blunting in the antibody response to PT was seen pre-booster for children in the TdaP3-IPV group, this did not persist after receipt of the preschool booster.

There are some limitations to this study. The group of children born to women who had not received a pertussis-containing antenatal vaccine were not randomised to this group, as it had been deemed unethical to do so in the context of the national outbreak. One infant received a different pertussis-containing vaccine during primary immunisation to the other infants; we did not analyse these 2 groups separately. However, no significant difference was found in the baseline data amongst all recruited participants. As the cohort for this study was essentially restricted to those included in the previous study, the sample size is relatively small, which reduced the statistical power of the analysis, as more than anticipated were lost to follow-up.

In conclusion, this is the first study to explore the influence of antenatal pertussis vaccination on children's antibody response beyond 2 years of age. It generates data on the impact of antenatal pertussis vaccination on responses to a booster dose given around 3 years of age. In an era of widespread use of antenatal pertussis vaccination, we provide evidence to suggest that either $TdaP_5$-IPV or $TdaP_3$-IPV vaccines may be used in pregnancy, with no major differential effects between the vaccines on the antibody responses against pertussis into the third year of life. There is some evidence of blunting of pertussis-specific antibody responses as a result of antenatal pertussis vaccination, which appears to persist until pre-school age, although this is overcome by the administration of a booster dose and the clinical significance of this blunting remains unclear.

Funding

This research is funded by the National Institute for Health Research (NIHR) Policy Research Programme (PR-R17-0916-22001). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'Matthew Snape is the director of NISEC, and Paul Heath and Bassam Hallis are members of the NISEC steering committee, but none of them have received any personal funding from NISEC. Christine Jones and Paul Heath have conducted studies on behalf

of St George's University of London (Paul Heath), University of Southampton (Christine Jones) and University Hospital Southampton NHS Foundation Trust (Christine Jones), funded by vaccine manufacturers, including Glaxo Smith Kline (Paul Heath), Medicago (Christine Jones), MinervaX (Christine Jones, Paul Heath), Moderna (Christine Jones), Novovax (Christine Jones), Pfizer (Christine Jones) and ReViral (Christine Jones) within the last three years, but received no personal funding from these sources. Christine Jones has carried out consultancy or been a member of an advisory board or data safety and monitoring board for Moderna, MSD, Pfizer, and Sanofi in the last three years, and she has received remuneration for these activities.'

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.10.005.

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