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The Effect of Maternal Immunisation During Pregnancy on Infant Vaccine Responses

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ABSTRACT

Introduction: Immunisation during pregnancy to protect infants against tetanus, pertussis and influenza is recommended in many countries. However, maternal antibodies can interfere with infant vaccine responses. We investigated the effect of antenatal diphtheria-tetanus-acellular pertussis (dTpa) and trivalent inactivated influenza (TIV) immunisation on specific and heterologous antibody responses to routine immunisations given in the first year of life.

Methods: In total, 471 healthy infants were included. At 7 and 13 months of age, antibodies to the primary course of routine vaccines given at 6 weeks, 4 and 6 months of age (pertussis (pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN)), polio (type 1, 2, 3), *Haemophilus influenzae* type b (Hib), pneumococcus (serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F)) were measured, and at 13 months of age, antibodies to the 12-month routine vaccines (Hib, meningococcus C, measles, mumps and rubella). The seroprotection rates for each vaccine and the geometric mean concentrations (GMC) of antibodies were compared between infants whose mothers did or did not receive dTpa or TIV immunisation during pregnancy.

Results: A total of 369 infants were included in the final analysis. Maternal dTpa immunisation was associated with reduced antibody responses to both specific (diphtheria and pertussis) and heterologous (polio and pneumococcus) vaccine antigens. This effect was stronger for persistence of antibodies at 13 months of age than it was at 7 months of age. At 7 months of age, adjusted average antibody concentrations were significantly lower for diphtheria, pertussis (PT, FHA, PRN) and polio type 2, and at 13 months of age, for diphtheria, pertussis (PT, FHA, PRN), polio type 1–3 and pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 18C and 23F. Additionally, at 13 months of age, seroprotection rates for diphtheria, PT, pneumococcal serotype 1, 6A and 6B were significantly lower in infants after maternal dTpa immunisation. In contrast, for Hib, in infants with maternal dTpa immunisation, the adjusted average antibody concentration and the seroprotection rate were higher, particularly at 7 months of age. Maternal TIV immunisation had minimal effect on infant vaccine responses.

Conclusion: Whilst maternal immunisation protects infants in the first few months of life, it might interfere with both specific and heterologous (unrelated) vaccines responses in infants.

Research in context: Evidence before this study: Maternal immunisation during pregnancy helps to protect infants during the period before they complete their primary immunisations. It has been proven to be safe and beneficial. However, pre-existing maternal antibodies can influence antibody responses following infant immunisation, an effect called 'blunting'. Previous studies have investigated the influence of dTpa but not influenza immunisation during pregnancy on infant vaccine responses. The majority of studies investigated antibody concentrations only to the specific vaccine antigens included in the maternal immunisation, and there is scarce data available on heterologous vaccine responses, particularly pneumococcal responses.

Abbreviations: BCG, Bacillus Calmette-Guérin vaccine; CI, confidence interval; dTpa, diphtheria-tetanus-acellular pertussis vaccine; FHA, filamentous haemagglutinin; FIM, fimbriae; GMC, geometric mean antibody concentration; GMR, geometric mean antibody ratio; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; IgG, immunoglobulin G; IPV, inactivated polio vaccine; MenC, meningococcus type C; MIS BAIR, Melbourne Infant Study: BCG for Allergy and Infection Reduction; MMR, measles-mumps-rubella vaccine; PCV13, 13-valent conjugate pneumococcal vaccine; PT, pertussis toxin; PRN, pertactin; TCV, tetanus-containing vaccine; TIV, trivalent inactivated influenza vaccine.

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Added value of this study: In this study, we have shown that maternal dTpa immunisation during pregnancy is associated with reduced antibody responses to both specific (diphtheria and pertussis) and heterologous (polio and pneumococcus) vaccine antigens. This effect is stronger for persistence of antibodies at 13 months of age than after primary immunisation at 7 months of age. In contrast, for Hib, in infants with maternal dTpa immunisation, antibody concentrations are higher, particularly at 7 months of age. Maternal TIV immunisation has minimal effect on infant vaccine responses.
Implications of all the available evidence: Whilst maternal immunisation protects infants in the first few months of life, it might interfere with both specific and heterologous (unrelated) vaccines responses in infants. As most vaccines induce very high antibody responses, small differences in antibody concentrations may not be of clinical significance. However, since maternal immunisation during pregnancy also influences seroprotection rates, strategies, such as additional booster doses in the second year of life, particularly for pertussis and pneumococcus, might need to be considered to address this.

1. Introduction

Immunisation during pregnancy aims to protect infants during the period before they complete their primary immunisations. Antenatal immunisation against tetanus has been recommended in certain settings for decades and is estimated to have reduced the burden of neonatal tetanus by 96% [1]. Recently, many countries have reported a steep rise in pertussis cases, with high rates of disease in infants younger than 2 months of age, who are too young to have been vaccinated. This age group has the highest rates of pertussis-related hospitalisations and deaths. For this reason, maternal pertussis immunisation has been recommended in many countries since 2012 [2,3]. Similarly, because of the increased risk of severe influenza in pregnant women, as well as adverse outcomes for infants, influenza immunisation is also routinely recommended during pregnancy [4].

The transfer of maternal immunoglobulin G (IgG) to the foetus is an active process but not all IgG antibodies are transported to the same extent. This is reflected by the fact that, towards the end of pregnancy, IgG antibody concentrations against polysaccharide antigens are similar in the foetus and mother, whereas those against proteins are higher in the foetus [5]. Of the multiple factors that influence the transfer of IgG across the placenta, maternal antibody concentration is an important one. Infants whose mothers receive diphtheria, tetanus and acellular pertussis (dTpa) immunisation during pregnancy have higher antibody concentrations to these antigens at birth compared to those whose mothers do not receive the vaccine [6–12]. Following birth, maternal antibodies in infants wane with a half-life of approximately four to six weeks [13]. Higher antibody concentrations at birth are associated with a longer duration of protection [14].

Despite the benefits of maternal immunisation, there are also potential disadvantages. Pre-existing maternal antibodies influence antibody responses following infant immunisation, an effect called 'blunting'. A recent meta-analysis showed that for immunisation with inactivated polio vaccine (IPV), a two-fold higher maternal antibody concentration is associated with up to 28% lower post-immunisation antibodies in infants [13]. For acellular pertussis, tetanus and diphtheria, these estimates are 11%, 13% and 24%, respectively [13]. Apart from the type of vaccine, blunting of infant antibody production is also influenced by the age of infants at immunisation, the effect being stronger in younger infants [13]. Nevertheless, for acellular pertussis, diphtheria and IPV, the influence of maternal antibodies has been reported to be still evident after booster immunisation at 12 to 24 months of age [13].

Whilst a large number of studies have investigated the association between maternal antibody concentrations and infant antibody production [13], the effect of maternal immunisation on infant vaccine responses has been less extensively investigated [6–10,15–17]. Previous studies have investigated the influence of dTpa but not influenza immunisation during pregnancy [6–10]. The results of these studies show that antibody concentrations against diphtheria, tetanus and pertussis, as well as against hepatitis B (HepB), polio and Hib, are higher at birth in infants whose mothers received dTpa during pregnancy [6–10]. Notably, the majority of studies investigated antibody concentrations only to the specific vaccine antigens included in the maternal immunisation, and there is scarce data available on heterologous vaccine responses, particularly pneumococcal responses.

In this study, we investigated the effect of dTpa and influenza immunisation during pregnancy on specific and heterologous antibody responses to routine infant immunisations given in the first year of life.

2. Methods

2.1. Study Design and Population

Participants were a subset of infants from the Melbourne Infant Study: BCG for Allergy and Infection Reduction (MIS BAIR). This randomised controlled trial comprises 1272 healthy infants whose mothers were recruited antenatally from 2013 to 2016 to investigate whether Bacillus Calmette-Guérin (BCG) immunisation at birth protects against childhood infection, allergy and asthma. Inclusion criteria were: >32 week gestation, birth weight > 1500 g and absence of symptoms or signs of illness. Three-monthly parent questionnaires were used to prospectively collect demographic and other data.

From participants whose parent/guardian provided consent, blood samples were obtained during study visits at 7 and 13 months of age, designed to be 4 weeks after the administration of routine scheduled immunisations. Only participants who had a blood taken between 28 ± 14 days after their 6-month and 12-month routine vaccines, respectively, were included in the final analysis (with the exception of the subset of infants who had their blood analysed at 13 months of age for persistence of antibodies to their primary course of vaccines ending at 6 months). Participants of twins were excluded, because they were not considered as being independent.

2.2. Infant Immunisation

All infants received routine immunisations according to the Australian National Immunisation Program: at birth: intramuscular HepB vaccine (H-B-Vax II Paediatric® (*bioCSL*)); at 6 weeks, 4 and 6 months of age: intramuscular combined diphtheria-tetanus-acellular pertussis (DTPa)-HepB-inactivated polio (IPV)-*Haemophilus influenzae* type b (Hib) vaccine (Infanrix® hexa (*GlaxoSmithKline*)), intramuscular 13-valent conjugate pneumococcal vaccine (PCV13) (conjugated to CRM197, a diphtheria toxin) (Prevenar13® (*Wyeth*)), and oral rotavirus vaccine (RotaTeq® (*Merck*)); at 12 months of age: subcutaneous measles-mumps-rubella (MMR) vaccine (Priorix® (*GlaxoSmithKline*)) or (M-M-R®II (*Seqirus*)) and intramuscular combined Hib and meningococcal C vaccine (conjugated to tetanus toxin) (Menitorix® (*GlaxoSmithKline*)). Approximately half of the infants were randomised to receive intradermal BCG-Denmark (*Statens Serum Institute, Copenhagen*) shortly after birth as part of the MIS BAIR. None of the infants received an influenza vaccine. Vaccine records were obtained from the

National Australian Immunisation register and/or individual immunisation records.

2.3. Maternal Immunisation

Maternal immunisation during pregnancy was self-reported. Participants' mothers received dTpa (Boostrix® (*GlaxoSmithKline*)) and/or a trivalent inactivated influenza vaccine (TIV), or neither during pregnancy.

2.4. Blood Collection

Blood samples were collected at study visits approximately 4 weeks after the scheduled 6-month routine vaccines ('7 months') and the scheduled 12-month routine vaccines ('13 months') in tubes containing sodium-heparin (S-monovette® (*Sarstedt*)). Plasma was stored at −80 °C until analysis.

2.5. Antibody Assay

Blood samples were analysed at the National Institute for Health and Environment, in Bilthoven, the Netherlands. IgG antibodies against 26 vaccine antigens (diphtheria, tetanus, pertussis (pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN)), polio (types 1, 2, 3), Hib, pneumococcus (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), meningococcus type C (MenC), measles, mumps and rubella) were measured in using fluorescent bead-based multiplex immune-assays (Luminex xMAP technology) [18–23]. In all assays, an international or in-house reference, controls and blanks were included on each plate. All analyses were performed with a Bio-Plex 200 in combination with Bio-Plex manager software (Bio-Rad Laboratories, Hercules, CA).

2.6. Statistical Analysis

The proportion of infants with an antibody concentration above the standard protective correlate value for each vaccine (seroprotection rate) [21,24,25] was calculated in each group of infants, together with 95% confidence intervals (CI) using the Clopper-Pearson method. For pertussis no clear correlate of protections exists. However, an antibody concentration against pertussis toxin of >25 IU/mL is generally considered as protective and was therefore used in this study, although there is no consensus on this. We did not calculate seroprotection rates of FHA and PRN for which no accepted protective correlate value exists. Proportions were compared using Fisher's exact test and 95% CIs for differences in proportions estimated. In each group, the geometric mean concentration (GMC) for each vaccine antibody (immunoglobulin G) was calculated. Geometric mean antibody ratios (GMR) with 95% confidence interval (CI) were derived from the anti-logged coefficient using a linear regression with log-concentrations as outcome and maternal immunisation status (dTpa or TIV) as covariate. Effect modification was assessed using the following pre-specified potential

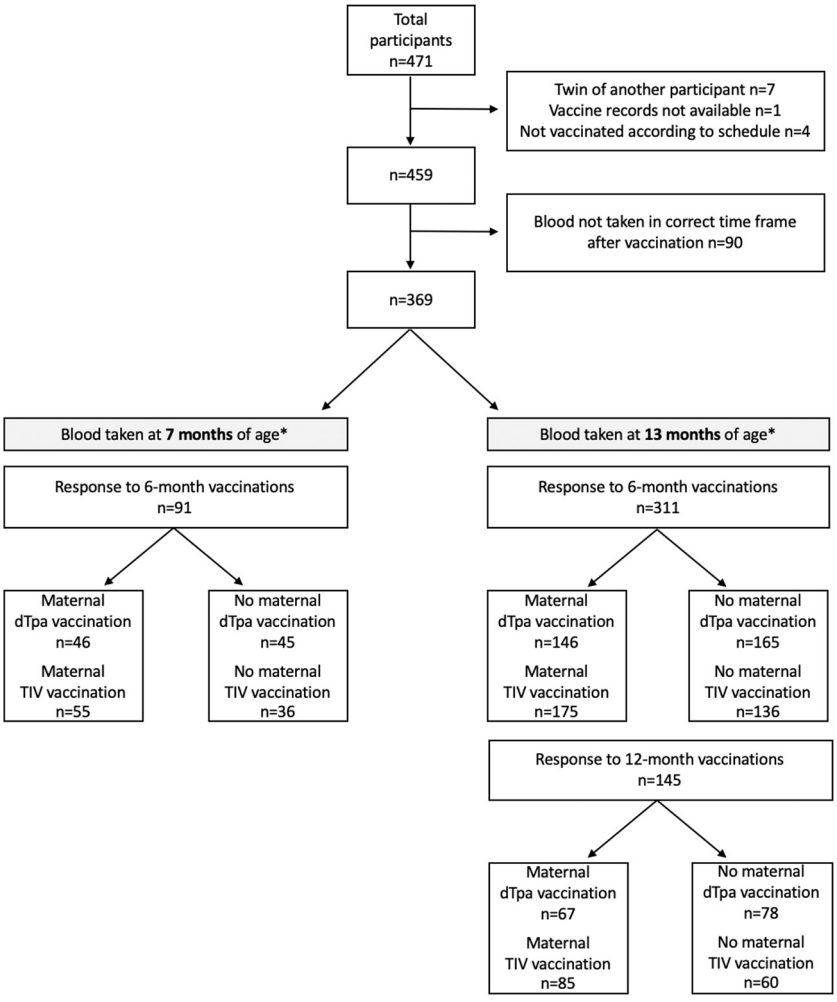

Fig. 1. Selection of participants.
* 33 participants had their blood analysed at 7 and 13 months of age dTpa = diphtheria-tetanus-acellular pertussis vaccine TIV = trivalent inactivated influenza vaccine.

confounding factors: maternal age, gestational age, delivery mode, sex, birth weight, age at first DTPa-HepB-IPV-Hib/PCV13 immunisation, infant BCG immunisation status, MMR/Hib-MenC immunisation status (for responses at 13 months of age), age at sampling and time between 6-month or 12-month immunisation and blood sampling. The GMR for each vaccine antigen was adjusted for those factors that had an effect on the vaccine antigen responses (detailed in each table). As Menitorix includes a tetanus toxoid and Hib component, infants who had received this vaccine before blood sampling at 13 months of age were excluded from the analysis of antibody persistence against these two vaccine antigens. A 5%-significance level was used. All statistical analyses were done using R version 3.4.3.

2.7. Ethics

Informed consent was obtained from participants' parents or guardians. The study was approved by the Royal Children's Hospital Human Research Ethics Committee (HREC, authorisation (38124A)). MIS BAIR is registered with the Australia & New Zealand Clinical Trials Registry (1051228) and the U.S. National Institutes of Health (NCT01906853).

3. Results

Of the 471 potentially eligible participants, seven were excluded because they were a twin of another participant, four because they were not vaccinated according to the vaccine schedule and one because vaccine records were not available. Of the remaining 459 participants, 368 had blood taken in the predefined time frame (28 ± 14 days after their 6-month and 12-month vaccines, respectively (Fig. 1)). At 7 months of age, 91 (45 with and 46 without maternal dTpa immunisation, 55 with and 36 without maternal TIV immunisation) were included in the final analysis. At 13 months of age, 311 (146 with and 165 without maternal dTpa immunisation, 175 with and 136 without maternal TIV immunisation) were included for measurement of persistence of antibodies against the primary course of vaccines ending at 6-months and 145 (67 with and 78 without maternal dTpa immunisation, 85 with and 60 without maternal TIV immunisation) for responses to the 12-months vaccines. The number of participants who were included at both time points (n = 33) was too small to allow longitudinal analysis. Baseline characteristics are summarised in Table 1 and Supplementary Table 1.

A comparison of the GMCs for each of the vaccine antigens in infants with and without maternal dTpa immunisation is shown in Supplementary Figs. 1 and 2, and in infants with and without maternal TIV immunisations is shown in Supplementary Figs. 3 and 4.

3.1. The effect of Maternal dTpa Immunisation on Antibody Concentrations at 7 Months of Age

Adjusted GMRs at 7 months of age were less than one (indicating lower average antibody concentrations in the group with maternal dTpa immunisation) for all vaccine antigens except tetanus, Hib and pneumococcal serotype 3 and 4. These differences reached statistical significance for diphtheria, pertussis (PT, FHA and PRN), polio type 2 and Hib.

At 7 months of age, the large majority of infants had antibody concentrations above the standard protective correlate value (the seroprotection rate was above 95% for 16 of the 22 antigens). Low seroprotection rates were observed for Hib and pneumococcal serotype 4 (Table 2 and Fig. 2).

At 7 months of age, seroprotection rates were generally lower for infants with maternal dTpa immunisation, with the largest difference observed for pneumococcal serotype 4 and PT. In contrast, the seroprotection rate was higher for Hib in infants with maternal dTpa immunisation. None of these differences reached statistical significance (Table 3 and Fig. 3).

Table 1
Characteristics of participants whose mothers did or did not receive dTpa during pregnancy.

	To primary course of vaccines ending at 6 months of age						To 12-month vaccines		
	At 7 months of age n (%) or median (IQR)			At 13 months of age n (%) or median (IQR)			At 13 months of age n (%) or median (IQR)		
	Maternal dTpa (n = 46)	No maternal dTpa (n = 45)	p-Value	Maternal dTpa (n = 146)	No maternal dTpa (n = 165)	p-Value	Maternal dTpa (n = 67)	No maternal dTpa (n = 78)	p-Value
Maternal age at birth (y)	33.6 (32.1–35.1)	33.8 (32.3–36.2)	0.57	32.8 (30.5–36.4)	33.3 (30.1–46.5)	0.97	33.4 (31.1–36.5)	33.5 (30.5–38.6)	0.52
Gestational age (w)	40.1 (39.0–40.6)	39.1 (38.5–40.3)	0.06	39.3 (38.3–40.3)	39.3 (38.4–40.4)	0.71	39.2 (38.4–40.4)	39.2 (38.4–40.4)	0.81
Caesarean section	12 (26)	23 (51)	0.10	55 (38)	62 (38)	0.99	26 (39)	28 (36)	0.81
Sex (male)	20 (43)	23 (51)	0.66	66 (45)	86 (52)	0.47	30 (45)	42 (54)	0.53
Birth weight (kg)	3.48 (3.15–3.65)	3.48 (3.06–3.76)	0.65	3.46 (3.14–3.75)	3.43 (3.10–3.76)	0.49	3.42 (3.09–3.67)	3.36 (3.14–3.67)	0.55
BCG-vaccinated	18 (39)	27 (60)	0.25	85 (58)	84 (51)	0.48	38 (57)	38 (49)	0.59
MMR/Hib-MenC-vaccinated	–	–	–	101 (69)	110 (67)	0.84	–	–	–
Age at routine immunisation (d)									
- 6-w vaccines	44 (42–47)[a]	45 (43–48)	0.29	45 (43–47)	47 (44–52)	0.06	44 (43–47)	46 (43–50)	0.43
- 4-m vaccines	123 (115–127)	123 (119–127)	0.83	125 (122–130)	125 (120–134)	0.16	125 (122–130)	124 (119–132)	0.90
- 6-m vaccines	187 (180–192)	187 (182–195)	0.23	191 (186–200)	191 (184–212)	0.44	191 (186–198)	191 (184–212)	0.90
- 12-m vaccines	–	–	–	–	–	–	377 (369–383)	375 (369–384)	0.60
Interval between (d)									
- 6-m vaccines to 7-m blood sample	29 (22–36)	28 (21–39)	0.74	–	–	–	–	–	–
- 6-w vaccines to 13-m blood sample	–	–	–	213 (197–224)	204 (186–225)	0.95	–	–	–
- 12-m vaccines to 13-m blood sample	–	–	–	–	–	–	29 (23–36)	28 (21–36)	0.46
Age at sampling (d)	216 (207–225)	223 (208–228)	0.20	402 (390–418)	400 (388–415)	0.41	403 (398–415)	406 (396–414)	1.00

p-values were determined by t-test for continuous variables and Pearson's Chi-squared test for categorical variables.
d = days, dTpa = diphtheria-tetanus-acellular pertussis vaccine, m = month, w = week, y = years.
[a] Age for one participant not available.

Table 2
Geometric mean antibody concentrations (GMCs) and geometric mean antibody ratios (GMRs) at 7 and 13 months of age in infants whose mothers did or did not receive dTpa immunisation during pregnancy. Bold denotes results with p-value < 0.05.

Vaccine antigen	Antibodies to primary course of vaccines ending at 6 months of age measured at 7 months of age						Antibodies to primary course of vaccines ending at 6 months of age measured at 13 months of age					
	Maternal dTpa (n = 46)	No maternal dTpa (n = 45)	Unadjusted GMR (95% CI)	p-value	Adjusted GMR (95% CI)	p-value	Maternal dTpa (n = 146)	No maternal dTpa (n = 165)	Unadjusted GMR (95% CI)	p-value	Adjusted GMR (95% CI)	p-value
	GMC (95% CI)	GMC (95% CI)					GMC (95% CI)	GMC (95% CI)				
Diphtheria[1]	**0.31 (0.25, 0.39)**	**0.51 (0.41, 0.63)**	**0.61 (0.45, 0.82)**	**<0.01**	**0.68 (0.50, 0.93)**[b,f,h]	**0.02**	**0.06 (0.05, 0.07)**	**0.11 (0.09, 0.12)**	**0.54 (0.43, 0.67)**	**<0.01**	**0.57 (0.46, 0.70)**[g,h,i,j]	**<0.01**
Tetanus[1]	1.22 (0.98, 1.51)	1.01 (0.83, 1.23)	1.21 (0.91, 1.62)	0.19	1.24 (0.93, 1.64)[d]	0.14	0.45 (0.35, 0.58)[3]	0.44 (0.34, 0.56)[3]	1.03 (0.72, 1.46)[3]	0.89[3]	0.98 (0.70, 1.37)[3,j]	0.89[3]
PT[1]	**49.69 (40.50, 69.96)**	**99.60 (79.34, 125.02)**	**0.50 (0.37, 0.67)**	**<0.01**	**0.53 (0.39, 0.72)**[a]	**<0.01**	**12.21 (10.45, 14.26)**	**24.15 (20.79, 28.06)**	**0.51 (0.41, 0.63)**	**<0.01**	**0.53 (0.43, 0.66)**[g,h,i,j]	**<0.01**
FHA[1]	**49.01 (38.93, 61.70)**	**83.36 (65.77, 105.65)**	**0.59 (0.42, 0.81)**	**<0.01**	**0.68 (0.49, 0.93)**[b,d,g]	**0.02**	**14.14 (12.04, 16.62)**	**25.06 (21.90, 28.68)**	**0.56 (0.46, 0.70)**	**<0.01**	**0.57 (0.47, 0.70)**[d,g,i]	**<0.01**
PRN[1]	**48.31 (37.36, 62.47)**	**76.12 (56.23, 103.03)**	**0.63 (0.43, 0.94)**	**0.02**	**0.67 (0.45, 0.98)**[b,e]	**0.04**	**8.94 (7.31, 10.95)**	**15.85 (13.30, 18.88)**	**0.56 (0.43, 0.74)**	**<0.01**	**0.59 (0.45, 0.76)**[d,i]	**<0.01**
Hib[2]	0.62 (0.39, 0.97)	0.42 (0.26, 0.68)	1.46 (0.76, 2.79)	0.26	**2.01 (1.08, 3.77)**[b,d,g,h]	**0.03**	1.32 (0.78, 2.24)[3]	1.03 (0.64, 1.66)[3]	1.28 (0.63, 2.60)[3]	0.49[3]	1.36 (0.70, 2.64)[3,c,h]	0.36[3]
Polio type 1[1]	29.42 (20.75, 41.71)	40.87 (31.43, 53.14)	0.72 (0.47, 1.11)	0.13	0.78 (0.50, 1.21)[b,e]	0.26	**9.25 (7.70, 11.10)**	**13.28 (11.17, 15.78)**	**0.70 (0.54, 0.89)**	**<0.01**	**0.71 (0.56, 0.91)**[g,i,j]	**<0.01**
Polio type 2[1]	**48.59 (33.71, 70.04)**	**82.10 (64.97, 103.76)**	**0.59 (0.38, 0.91)**	**0.02**	**0.59 (0.39, 0.90)**[a,i]	**0.02**	**16.44 (13.48, 20.04)**	**27.66 (22.75, 33.62)**	**0.59 (0.45, 0.78)**	**<0.01**	**0.61 (0.46, 0.80)**[g,i]	**<0.01**
Polio type 3[1]	21.00 (14.79, 29.81)	21.89 (15.94, 30.06)	0.96 (0.60, 1.53)	0.86	0.95 (0.60, 1.49)[i]	0.81	**6.87 (5.50, 8.59)**	**11.35 (9.41, 13.69)**	**0.61 (0.45, 0.81)**	**<0.01**	**0.61 (0.46, 0.81)**[d,g,i,j]	**<0.01**
Pn 1[2]	3.83 (2.78, 5.29)	4.99 (3.76, 6.63)	0.77 (0.50, 1.17)	0.22	0.89 (0.60, 1.33)[f,h,i]	0.56	**1.03 (0.89, 1.19)**	**1.31 (1.15, 1.49)**	**0.79 (0.65, 0.96)**	**0.02**	**0.80 (0.67, 0.97)**[i]	**0.02**
Pn 3[2]	1.43 (1.15, 1.78)	1.44 (1.20, 1.73)	0.99 (0.75, 1.31)	0.94	1.06 (0.80, 1.39)[g]	0.70	0.504 (0.44, 0.57)	0.58 (0.51, 0.66)	0.87 (0.72, 1.04)	0.11	0.87 (0.73, 1.03)[i]	0.11
Pn 4[2]	0.53 (0.40, 0.70)	0.50 (0.41, 0.62)	1.04 (0.73, 1.48)	0.81	1.12 (0.80, 1.57)[h]	0.49	**0.19 (0.18, 0.22)**	**0.24 (0.21, 0.27)**	**0.82 (0.70, 0.95)**	**<0.01**	**0.83 (0.72, 0.96)**[b,f,g,i]	**0.01**
Pn 5[2]	2.81 (2.10, 3.77)	3.56 (2.77, 4.56)	0.79 (0.54, 1.16)	0.22	0.91 (0.63, 1.30)[f,h,i]	0.59	**0.80 (0.68, 0.93)**	**1.05 (0.91, 1.20)**	**0.76 (0.62, 0.93)**	**<0.01**	**0.78 (0.64, 0.95)**[h,i,j]	**0.01**
Pn 6A[2]	**3.98 (2.99, 5.28)**	**5.85 (4.73, 7.25)**	**0.68 (0.48, 0.97)**	**0.03**	0.80 (0.57, 1.12)[f,g,h]	0.19	**0.82 (0.68, 0.97)**	**1.20 (1.05, 1.38)**	**0.68 (0.54, 0.85)**	**<0.01**	**0.70 (0.57, 0.86)**[h,i]	**<0.01**
Pn 6B[2]	1.51 (0.98, 2.32)	2.44 (1.53, 3.89)	0.62 (0.33, 1.16)	0.13	0.77 (0.41, 1.45)[c,h]	0.41	**0.42 (0.35, 0.51)**	**0.62 (0.53, 0.74)**	**0.68 (0.52, 0.87)**	**<0.01**	**0.69 (0.54, 0.88)**[i]	**<0.01**
Pn 7F[2]	5.37 (4.14, 6.96)	7.03 (5.80, 8.51)	0.76 (0.55, 1.05)	0.10	0.80 (0.58, 1.10)[h]	0.17	**1.69 (1.49, 1.91)**	**2.06 (1.83, 2.32)**	**0.82 (0.69, 0.97)**	**0.02**	**0.83 (0.70, 0.98)**[a,i,j]	**0.03**
Pn 9V[2]	2.15 (1.62, 2.85)	2.82 (2.28, 3.49)	0.76 (0.54, 1.08)	0.12	0.92 (0.66, 1.27)[f,g,h,i]	0.61	0.55 (0.48, 0.64)	0.64 (0.56, 0.73)	0.86 (0.71, 1.04)	0.12	0.88 (0.73, 1.06)[h,i,j]	0.17
Pn 14[2]	2.47 (1.72, 3.54)	2.89 (1.96, 4.26)	0.85 (0.51, 1.44)	0.55	0.85 (0.51, 1.44)	0.55	1.02 (0.86, 1.21)	1.08 (0.93, 1.25)	0.94 (0.75, 1.18)	0.62	0.94 (0.75, 1.18)[g,h,i,j]	0.59
Pn 18C[2]	2.80 (2.09, 3.76)	3.09 (2.36, 4.04)	0.91 (0.61, 1.34)	0.63	0.97 (0.66, 1.42)[h]	0.86	**0.58 (0.51, 0.66)**	**0.73 (0.64, 0.83)**	**0.79 (0.66, 0.95)**	**0.01**	**0.81 (0.68, 0.97)**[h,i,j]	**0.02**
Pn 19A[2]	1.45 (1.10, 1.91)	2.04 (1.54, 2.71)	0.71 (0.48, 1.05)	0.09	0.76 (0.52, 1.13)[b]	0.18	0.45 (0.36, 0.57)	0.47 (0.39, 0.56)	0.97 (0.72, 1.29)	0.81	1.00 (0.75, 1.33)[i,j]	0.99
Pn 19F[2]	**9.62 (7.26, 12.76)**	**13.87 (10.97, 17.55)**	**0.69 (0.48, 1.00)**	**0.05**	0.74 (0.52, 1.05)[h]	0.09	2.97 (2.45, 3.61)	3.19 (2.76, 3.70)	0.93 (0.73, 1.18)	0.56	0.96 (0.76, 1.21)[h,i,j]	0.73
Pn 23F[2]	2.11 (1.51, 2.95)	2.59 (1.84, 3.65)	0.81 (0.51, 1.31)	0.39	0.94 (0.59, 1.50)[f,h]	0.78	**0.48 (0.39, 0.58)**	**0.65 (0.54, 0.79)**	**0.73 (0.56, 0.96)**	**0.03**	**0.72 (0.55, 0.94)**[d,e]	**0.01**

Vaccine antigen	Antibodies to 12-month vaccines measured at 13 months of age					
	Maternal dTpa (n = 69)	No maternal dTpa (n = 79)	Unadjusted GMR (95% CI)	p-value	Adjusted GMR (95% CI)	p-value
	GMC (95% CI)	GMC (95% CI)				
Measles[1]	3.50 (2.84, 4.30)	2.67 (2.01, 3.54)	1.31 (0.92, 1.87)	0.14	1.27 (0.90, 1.81)[d]	0.18
Mumps[1]	62.27 (44.46, 87.21)	57.66 (42.96, 75.90)	1.09 (0.71, 1.68)	0.69	1.02 (0.72, 1.45)[a,h,i]	0.89
Rubella[1]	58.51 (41.39, 82.70)	50.48 (36.71, 69.40)	1.16 (0.73, 1.85)	0.53	1.03 (0.73, 1.47)[h,i]	0.85
MenC[2]	19.40 (15.91, 23.64)	16.49 (13.69, 19.87)	1.18 (0.90, 1.54)	0.24	1.08 (0.79, 1.49)[a,d,i]	0.63
Hib[2]	19.11 (13.22, 27.63)	12.93 (9.02, 18.54)	1.48 (0.88, 2.47)	0.13	1.47 (0.90, 2.41)[c,i]	0.12
Tetanus[1]	1.09 (0.80, 1.49)	0.93 (0.72, 1.20)	1.17 (0.79, 1.73)	0.43	1.17 (0.79, 1.73)	0.43

CI = confidence interval, dTpa = diphtheria-tetanus-acellular pertussis vaccine, FHA = filamentous haemagglutinin, GMC = geometric mean antibody concentration, GMR = geometric mean antibody ratio, Hib = *H. influenzae* type b, MenC = meningococcus C, Pn = pneumococcus serotype, PRN = pertactin, PT = pertussis toxin.

[1] IU/mL
[2] μg/mL
[3] only participants who have not had Hib-MenC
[a] maternal influenza immunisation during pregnancy
[b] gestational age
[c] delivery mode
[d] sex
[e] birth weight
[f] BCG immunisation
[g] age at first DTPa-HepB-IPV-Hib / PCV13 immunisation
[h] age at bleeding
[i] time between immunisation and bleeding
[j] MMR/Hib-MenC immunisation

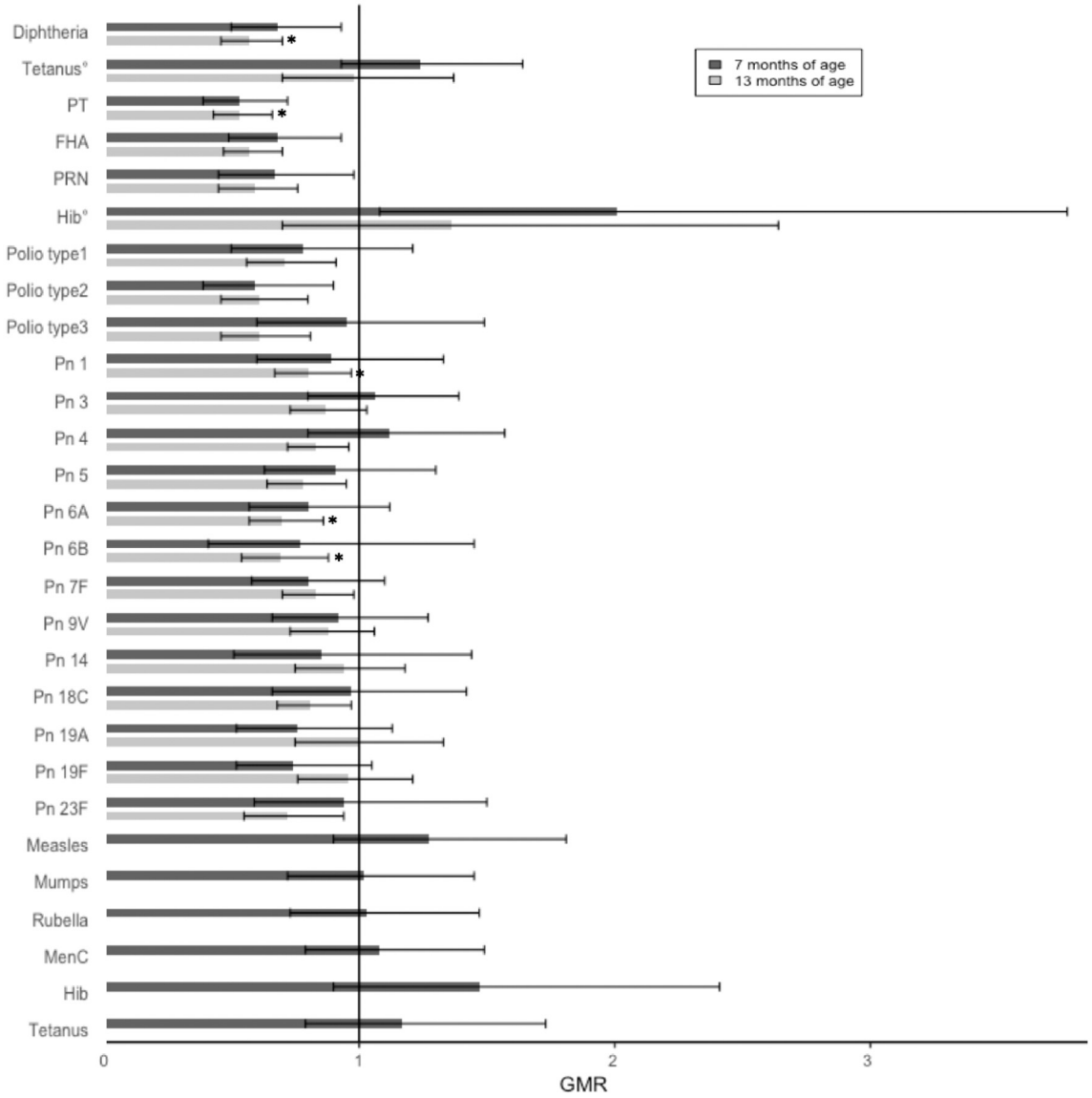

Fig. 2. Geometric mean antibody ratios (GMRs) with 95% CI in participants with or without maternal dTpa immunisation in pregnancy at 7 and 13 months of age.
° participants who have not yet received Hib-MenC, * $p < 0.05$.

3.2. The Effect of Maternal dTpa Immunisation on Antibody Concentrations at 13 Months of Age to the Primary Course of Vaccines

At 13 months of age, adjusted GMRs were below one (indicating lower antibody concentrations in the group with maternal dTpa immunisation) for all antigens, except tetanus. The differences reached statistical significance for diphtheria, pertussis (PT, FHA and PRN), polio type 1–3, pneumococcal serotype 1, 4, 5, 6A, 6B, 7F, 18C and 23F (Table 2 and Fig. 2).

At 13 months of age, infants with maternal dTpa immunisation had lower seroprotection rates for the large majority of vaccine antigens. These differences reached statistical significance for diphtheria, PT, pneumococcal serotype 1, 6A and 6B (Table 3 and Fig. 3).

3.3. The Effect of Maternal dTpa Immunisation on Antibody Concentrations at 13 Months of Age to the 12-Month Vaccines

Following the 12-month immunisations, GMRs were above one for measles, mumps and rubella, MenC and Hib. Seroprotection rates were higher in infants with maternal dTpa immunisation for measles, mumps and rubella and, but these findings did not reach statistical significance (Tables 2–3 and Figs. 2–3).

3.4. The Effect of Maternal TIV Immunisation on Antibody Concentrations at 7 Months of Age

Adjusted GMRs at 7 months of age were greater than one (indicating higher average antibody concentrations in the group with TIV immunisation). However, this only reached statistical significance for pneumococcal serotype 1 and 19F. In contrast, the adjusted GMR for PT was statistically significantly less than one (Supplementary Table 2).

Maternal TIV immunisation did not influence seroprotection rates at 7 months of age in any consistent direction and differences in seroprotection rates were smaller than those observed between infants whose mothers did or did not receive dTpa immunisation (Supplementary Table 3).

Table 3
Seroprotection rates at 7 and 13 months of age in infants whose mothers did or did not receive dTpa immunisation during pregnancy. Bold denotes results with p-value < 0.05.

Vaccine antigen	Protective correlate	Antibodies to primary course of vaccines ending at 6 months of age measured at 7 months of age				Antibodies to primary course of vaccines ending at 6 months of age measured at 13 months of age			
		Maternal dTpa (n = 46)	No maternal dTpa (n = 45)	Difference % (95% CI)	p-value	Maternal dTpa (n = 146)	No maternal dTpa (n = 165)	Difference % (95% CI)	p-value
		% (n); (95% CI)	% (n); (95% CI)			% (n); (95% CI)	% (n); (95% CI)		
Diphtheria	0.1 IU/mL[a]	95.7 (44); (85.2, 99.5)	97.8 (44); (88.2, 99.9)	-2.1 (-12.7, 7.8)	1	**96.6 (141); (92.2, 98.9)**	**100 (165); (97.8, 100)**	**-3.4 (-7.8, -1.1)**	**0.02**
Tetanus	0.1 IU/mL[b]	100 (46); (92.3, 100)	100 (45); (92.1, 100[b]	0 (-7.8, 7.9)	-	100 (79); (95.4, 100)[b]	100 (87); (95.8, 100)[b]	0 (-4.7, 4.3)[2]	-
PT	25 IU/mL	84.8 (39); (71.1, 94.7)	95.6 (43); (84.9, 99.5)	-10.8 (-24.6, 1.8)	0.16	**18.5 (27); (12.6, 25.8)**	**41.2 (68); (33.6, 49.1)**	**-22.6 (-32.3, 12.7)**	**<0.01**
Hib	0.15 μg/mL	82.6 (38); (68.6, 92.2)	71.1 (32); (55.7, 83.6)	11.5 (-6.0, 28.9)	0.22	79.7 (63); (69.2, 88.0)[b]	74.7 (65); (64.3, 83.4)[b]	5.0 (-8.0, 17.8)[2]	0.47[b]
Polio type 1	0.23 IU/mL	100 (46); (92.3, 100)	100 (45); (92.1, 100)	0 (-7.8, 7.9)	-	100 (146); (97.6, 100)	100 (165); (97.8, 100)	0 (-2.6, 2.3)	-
Polio type 2	0.29 IU/mL	100 (46); (92.3, 100)	100 (45); (92.1, 100)	0 (-7.8, 7.9)	-	99.3 (145); (96.2, 100)	100 (165); (97.8, 100)	-0.7 (-3.8, 1.6)	0.47
Polio type 3	0.12 IU/mL	100 (46); (92.3, 100)	100 (45); (92.1, 100)	0 (-7.8, 7.9)	-	100 (146); (97.6, 100)	100 (165); (97.8, 100)	0 (-2.6, 2.3)	-
Pn 1	0.35 μg/mL	95.7 (44); (85.2, 99.5)	97.8 (44); (88.2, 99.9)	-2.1 (-12.7, 7.8)	1	**89.0 (130); (82.8, 93.6)**	**97.6 (161); (93.9, 99.3)**	**-8.5 (-14.9, 3.3)**	**<0.01**
Pn 3	0.35 μg/mL	97.8 (45); (88.5, 99.9)	100 (45); (92.1, 100)	-2.2 (-11.4, 5.9)	1	67.8 (99); (59.6, 75.3)	71.5 (118; (64.0, 78.3)	-3.7 (-14.0, 6.5)	0.54
Pn 4	0.35 μg/mL	63.0 (29); (47.5, 76.8)	75.6 (34); (60.4, 87.1)	-12.5 (-30.8, 6.7)	0.26	19.2 (28); (13.1, 26.5)	27.3 (45); (20.6, 34.7)	-8.1 (-17.4, 1.4)	0.11
Pn 5	0.35 μg/mL	95.7 (44); (85.2, 99.5)	100 (45); (92.1, 100)	-4.3 (-14.6, 3.8)	0.49	84.9 (124); (78.1, 90.3)	89.1 (147); (83.3, 93.4)	-4.2 (-12.0, 3.3)	0.31
Pn 6A	0.35 μg/mL	95.7 (44); (85.2, 99.5)	100 (45); (92.1, 100)	-4.3 (-14.6, 3.8)	0.49	**80.1 (117); (72.7, 86.3)**	**92.1 (152); (86.9, 95.7)**	**-12.0 (-20.0, 4.4)**	**<0.01**
Pn 6B	0.35 μg/mL	87.0 (40); (73.7, 95.1)	91.1 (41); (78.8, 97.5)	-4.2 (-18.3, 9.7)	0.74	**57.5 (84); (49.1, 65.7)**	**70.3 (116); (62.7, 77.2)**	**-12.8 (-23.3, 2.1)**	**0.02**
Pn 7F	0.35 μg/mL	100 (46); (92.3, 100)	100 (45); (92.1, 100)	0 (-7.8, 7.9)	-	99.3 (145); (96.2, 100)	99.4 (164); (96.7, 100)	-0.1 (-3.2, 2.7)	1
Pn 9V	0.35 μg/mL	95.7 (44); (85.2, 99.5)	100 (45); (92.1, 100)	-4.3 (-14.6, 3.8)	0.49	73.3 (107); (65.3, 80.3)	78.2 (129); (71.1, 84.2)	-4.9 (-14.5, 4.6)	0.35
Pn 14	0.35 μg/mL	93.5 (43); (82.1, 98.6)	88.9 (40); (75.9, 96.3)	4.6 (-8,1, 18.1)	0.49	84.2 (123); (77.3, 89.7)	88.5 (146); (82.6, 92.9)	-4.2 (-12.2, 3.4)	0.32
Pn 18C	0.35 μg/mL	95.7 (44); (85.2, 99.5)	95.6 (43); (85.9, 99.5)	0 (-10.8, 11.2)	1	72.6 (106); (64.6, 79.7)	80.6 (133); (73.7, 86.3)	-8.0 (-17.6, 1.4)	0.11
Pn 19A	0.35 μg/mL	89.1 (41); (76.4, 96.4)	97.8 (44); (88.2, 99.9)	-8.6 (-21.3, 2.1)	0.20	47.3 (69); (38.9, 55.7)	52.1 (86); (44.2, 59.9)	-4.9 (-15.9, 6.3)	0.43
Pn 19F	0.35 μg/mL	100 (46); (92.3, 100)	100 (45); (92.1, 100)	0 (-7.8, 7.9)	-	98.6 (144); (95.1, 99.8)	100 (165); (97.8, 100)	-1.4 (-4.9, 0.9)	0.22
Pn 23F	0.35 μg/mL	93.5 (43); (82.1, 98.6)	93.3 (42); (81.7, 98.6)	0.1 (-11.9, 12.4)	1	56.2 (82); (47.7, 64.4)	66.1 (109); (58.3, 73.2)	-9.9 (-20.6, 1.0)	0.08

Vaccine antigen	Protective correlate	Antibodies to 12-month vaccines measured at 13 months of age			
		Maternal dTpa (n = 67)	No maternal dTpa (n = 78)	Difference % (95% CI)	p-value
		% (n); (95% CI)	% (n); (95% CI)		
Measles	0.12 IU/mL	100 (67); (94.6, 100)	96.2 (75); (89.2, 99.2)	3.8 (-1.7, 10.7)	0.25
Mumps	45 IU/mL	64.2 (43); (51.5, 75.5)	59.0 (46); (47.3, 70.0)	5.2 (-10.7, 20.7)	0.61
Rubella	10 IU/mL	88.1 (59); (77.8, 94.7)	85.9 (67); (76.2, 92.7)	2.2 (-9.5, 13.4)	0.83
MenC	2 μg/mL	100 (67); (94.6, 100)	98.7 (77); (93.1, 100)	1.3 (-4.2, 6.9)	1
Hib	0.15 μg/mL	98.5 (66); (92.0, 100)	98.7 (77); (93.1, 100)	-0.2 (-6.9, 5.6)	1
Tetanus	0.01 IU/mL	100 (67); (94.6, 100)	100 (78); (95.4, 100)	0 (-5.5, 4.7)	-

CI = confidence interval, dTpa = diphtheria-tetanus-acellular pertussis vaccine, Hib = *H. influenzae* type b, Pn = pneumococcus serotype, PT = pertussis toxin, MenC = meningococcus C

[a] 0.01 IU/mL at 13 months of age

[b] only participants who have not had Hib-MenC

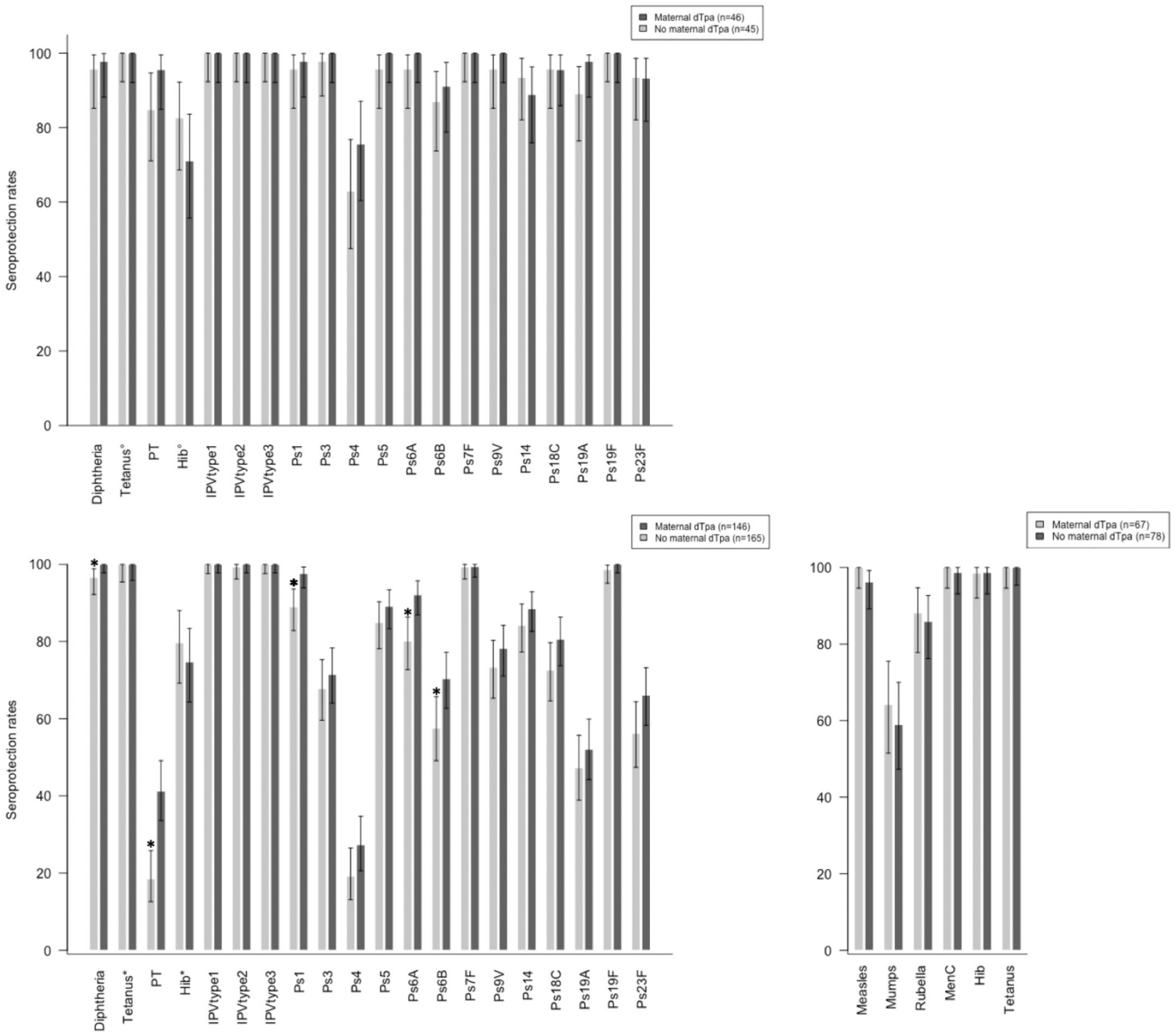

Fig. 3. Seroprotection rates with 95% CI in participants with or without maternal dTpa immunisation in pregnancy at 7 and 13 months of age.
° participants who have not yet received Hib-MenC, * $p < 0.05$.

3.5. The Effect of Maternal TIV Immunisation on Antibody Concentrations at 13 Months of Age (to the Primary Course of Vaccines and to the 12-Month Vaccines)

There was no consistent effect of maternal TIV immunisation on GMRs or seroprotection rates at 13 months of age (Supplementary Tables 2 and 3).

4. Discussion

Maternal immunisation has been proven to be safe and beneficial, and is now widely recommended [11,26–28]. For pertussis, for example, maternal immunisation leads to higher infant antibody concentrations at birth and during the first few months of life, which is highly effective in preventing severe pertussis in infants. The vaccine effectiveness against hospitalisation is estimated to be 91–94% and for preventing infection or mild disease 69–90% [29–31].

Our study investigated the effect of maternal dTpa immunisation on infant antibody responses to a large number of specific and heterologous vaccines, including measurement of the persistence of antibodies at 13 months of age. It is the first study to investigate the influence of maternal influenza immunisation on heterologous infant vaccine responses. Our results show that antenatal maternal dTpa immunisation strongly influences infant antibody responses at both 7 and 13 months of age and is associated with both reduced specific (diphtheria and pertussis) and heterologous (polio and pneumococcal) vaccine responses, but higher Hib responses at 7 months of age. In contrast, maternal TIV immunisation during pregnancy has no consistent effect on infant vaccine responses.

The findings of our study in relation to the primary course of vaccines are consistent with previous studies. To date, four studies have compared antibody concentrations one month after completion of primary immunisations between infants whose mother did or did not receive dTpa during pregnancy. These report higher GMCs for tetanus [7, 10,32] and Hib [10,32] in infants with maternal dTpa immunisation

during pregnancy, but lower GMCs for diphtheria [7,10,16,32], pertussis (FHA, fimbriae (FIM), PRN and PT) [7,10,16], HepB [10] and polio [10]. Two additional studies report higher GMCs for tetanus [8,33] and Hib [33], and lower GMCs for diphtheria [8] and pertussis (PRN, PT, FHA, FIM) [8,33], in infants whose mother received a pertussis-containing vaccine during pregnancy compared with those whose mother received a tetanus-containing vaccine (TCV) only.

Our findings in relation to persistence of antibodies before a booster-dose are also consistent with two studies which found higher GMCs for tetanus [10,16] and Hib [10], and lower GMCs for diphtheria [16], pertussis (FHA, FIM, PRN and PT) [10,16] and polio [10], in infants whose mothers received dTpa during pregnancy. Additionally, one larger study found higher GMCs for tetanus and Hib, and lower GMCs for pertussis (FHA, FIM, PRN and PT), in infants whose mother received a pertussis-containing vaccine during pregnancy compared with those whose mother received a TCV only [33].

Two previous studies have compared pneumococcal vaccine responses between infants whose mother did and did not receive dTpa during pregnancy. Both reported significantly lower GMCs against pneumococcal serotype 1, 3, 4, 5, 6A, 7F, 9V, 14 and 19A and lower seroprotection rates for serotype 3, 5 and 9V one month after primary immunisation [32,34]. The second study also measured vaccine responses 2.5 months after a booster dose of pneumococcal immunisation at 12 months of age and reported that GMCs remained lower in infants whose mother received a vaccine during pregnancy for serotype 1 and 4, without a difference in seroprotection rates [34].

One proposed mechanism for the inhibition of infant antibody production after maternal immunisation is that maternal antibodies bind to vaccine epitopes and mask them from infant B lymphocytes, leading to attenuation of responses to these antigens. Hence, the ratio between maternal antibody concentrations and dose of vaccine antigen might influence the degree of inhibition [35,36]. Since the carrier protein CRM197 in PCV13 is a modified diphtheria toxin, maternal antibodies against diphtheria might also mitigate responses to pneumococcal conjugate immunisation, which might explains the lower infant pneumococcal vaccine responses. Hib is conjugated to tetanus toxin as a carrier protein and responses to both tetanus and Hib are consistently (although not always significantly) higher in infants whose mother received dTpa during pregnancy. An unexpected finding in our study, which cannot be explained by a carrier protein, is that infants whose mothers received dTpa immunisation during pregnancy also had lower antibody responses to IPV.

Previously, it has been suggested that because of the short half-life of maternal antibodies (e.g. pertussis-specific IgGs are undetectable by the age of 2 months in infants of unvaccinated mothers) [37], maternal antibody interference of infant antibody production is only relevant during the first few months of life. However, in our study the effect of maternal dTpa immunisation during pregnancy (both reduced GMCs and seroprotection rates) was stronger at 13 months of age than at 7 months of age. Furthermore, three studies that compared vaccine responses in infants whose mothers received dTpa during pregnancy after booster immunisations given in the second year of age reported consistently (although not statistically significant) lower antibody concentrations for diphtheria [7,10,38], pertussis (FHA, FIM, PRN and PT) [7,10,38], Hib [10], HepB [10] and polio [10]. This suggests that the effect of maternal immunisation during pregnancy persists even after booster doses.

In our study, the lowest seroprotection rates were observed for pertussis (although the protection correlate value is debated) and pneumococcus. For pertussis, the main aim is to protect infants during the highest risk period occurring during the first few months of life and hence, the shift of the disease to a later period, as a result of maternal pertussis immunisation [39], might by an acceptable trade-off. However, the low seroprotection rates against pneumococcus at the age of 13 months are a concern, as this is a vulnerable age group for invasive pneumococcal disease.

Priming also occurs in infants after maternal vaccination. As most vaccines induce very high antibody responses, small differences in antibody concentrations may not be of clinical significance in terms of protective efficacy or may only impact the duration of protection. However, seroprotection rates are defined as correlates of clinical significance. Therefore, the differences in seroprotection rates found in our study might influence clinical outcomes. Nevertheless, protection induced by vaccines may not relate only to antibody concentration, but also to the quality of antibodies and cellular and cytokine responses. For example, for pertussis, there is no clear correlation between antibody concentration and protection rates. Nevertheless, countries that implement maternal immunisation might consider adapting their infant immunisation schedule to a later start (starting at 3 months of age with a 2-dose primary schedule results in higher antibody responses than a 3-dose schedule started at 2 months of age) [40] or including additional booster doses (e.g. pneumococcal vaccine in the second year of life to ensure protection during the at-risk period up to 5 years of age). Of note, new vaccines which interfere less with maternal antibodies are in development: animal studies show that co-injection of antigen and antigen-specific IgM increases antibody responses in the presence of inhibitory IgGs [41].

The strengths of our study include the low variation in background characteristics between groups, the detailed demographic and clinical data available from participants allowing for adjustment for potential confounding factors, the homogeneity in the vaccines given and the broad range of antibodies measured. The limitations of the study include the non-random allocation of maternal immunisations during pregnancy, the fact that maternal vaccines were given at different time points during pregnancy, that not all infants had antibody response measured exactly 4 weeks after immunisation and that not all infants had received their 12-month immunisation by the time blood samples were taken at 13 months, meaning a smaller number of participants available for assessment of responses to the 12-month vaccines, and that the number of infants included at both time points was too low to allow longitudal analysis. In addition, in the interpretation of our results, the lack of consensus on the protective correlate value for PT and the use of multiple significance testing need to be taken into consideration.

In conclusion, whilst maternal immunisation protects infant in the first few months of life, it might increase the risk of disease in older infants as a result of blunting of responses to both related (specific) and unrelated (heterologous) vaccines. Since the risk of hospitalisation and death is less in older infants, this might be an acceptable trade-off. Strategies, such as additional booster doses in the second year of life, particularly for pertussis and pneumococcus, should be considered to address this.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2019.06.010.

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