DR PETRA SABINE ZIMMERMANN (Orcid ID : 0000-0002-2388-4318)

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The immunomodulatory effects of measles-mumps-rubella (MMR) vaccination on persistence of heterologous vaccine responses

Petra Zimmermann^{1,2,3,4}, MD, Kirsten P Perrett^{5,6,7}, FRACP, PhD, Fiona R. M. van der Klis⁸, Nigel Curtis^{1,2,3}, FRCPCH, PhD

Affiliations:

¹ Department of Paediatrics, The University of Melbourne, Parkville, Australia

² Infectious Diseases Unit, The Royal Children's Hospital Melbourne, Parkville, Australia

³ Infectious Diseases & Microbiology Research Group, Murdoch Children's Research Institute, Parkville, Australia

⁴ Department of Paediatrics, Fribourg Hospital HFR and Faculty of Science and Medicine, University of Fribourg, Switzerland

⁵ Population Allergy Research Group and Melbourne Children's Trial Centre, Murdoch Children's Research Institute, Parkville, Australia

⁶ Departments of Allergy and Immunology and General Medicine, Royal Children's Hospital Melbourne, Parkville, Australia

⁷ School of Population and Global Health, The University of Melbourne, Melbourne, Australia

⁸ National Institute of Public Health and the Environment, Centre for Infectious Diseases, Bilthoven, the Netherlands

Address correspondence to: Dr Petra Zimmermann, Department of Paediatrics, The University of Melbourne, Royal Children's Hospital Melbourne, Parkville, VIC 3052, Australia, Tel: +61 3 9345 6366, petra.zimmermann@mcri.edu.au

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Running head: The effect of MMR vaccination on heterologous vaccine responses

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ABSTRACT

It is proposed that measles-containing vaccines (MCV) have immunomodulatory effects which include a reduction in all-cause childhood mortality. The antibody response to heterologous vaccines provides a means to explore these immunomodulatory effects. This is the first study to investigate the influence of measles-mumps-rubella (MMR) vaccine on the persistence of antibodies to a broad range of heterologous infant vaccinations given in the first year of life.

In total, 319 children were included in the study. All infants received routine vaccinations at 6 weeks, 4 and 6 months of age. At 12 months of age, 212 children were vaccinated with measles-mumps-rubella (MMR) and *Haemophilus influenzae* type b-meningococcus C (Hib-MenC) vaccine while the remaining 99 children had not yet received this vaccine. In the MMR/Hib-MenC-vaccinated group, blood was taken 28 ± 14 days after receiving these vaccines. Antibodies against diphtheria, tetanus, pertussis (pertussis toxin, filamentous haemagglutinin, pertactin), poliomyelitis (type 1, 2, 3) and 13 pneumococcal serotypes were measured. Geometric mean antibody concentrations (GMC) and seroprotection rates were compared between MMR/MenC-Hib-vaccinated and MMR/MenC-Hib-naïve participants.

In the final analysis, 311 children were included. Seroprotection rates were lower in MMR/Hib-MenC-vaccinated children against pertussis toxin and pneumococcus serotype 19A. After adjustment for pre-specified factors, MMR/Hib-MenC-vaccinated infants had significantly higher antibody concentrations against tetanus (likely explained by a boosting effect of the carrier protein, a tetanus toxoid), while for the other vaccine antigens there was no difference in antibody concentrations between the two groups.

MMR vaccination given at 12 months of age in a developed country does not significantly influence antibody concentrations to heterologous vaccines received in the first year of life.

INTRODUCTION

It is proposed that vaccines, particularly live-vaccines such as Bacillus Calmette-Guérin (BCG) and measles-containing vaccines (MCV), have heterologous ('non-specific') immunomodulatory effects.¹⁻⁴ These are effects induced by vaccines beyond protection against their targeted disease. The reduced mortality has been attributed to decreased deaths from respiratory illnesses, diarrhoea and malnutrition.⁵ For MCV, a recent meta-analysis reported reduced childhood mortality from diseases other than measles by 26 to 49% in high-mortality settings.¹ However, a number of the included studies were deemed to be at risk of bias. More recent studies have also shown a beneficial effect of MCV on childhood survival, the effect being greater when MCV are given before the age of 12 months.^{6, 7} The immunomodulatory effects of MCV have also been used in the treatment of atopic dermatitis, for which the vaccine (given subcutaneously) has been reported to decrease serum immunological markers.⁸ In addition, in the treatment of cutaneous warts, it been hypothesised that injection of MCV into lesions accelerated the destruction of the papilloma virus and infected host cells.^{9, 10}

MCV induce both humoral and cell-mediated immune responses.^{11, 12} The mechanisms underlying the immunomodulatory effects of MCV remain unclear. The antibody response to heterologous vaccines provides one way to explore these effects. To date, only three studies have investigated the influence of MCV on heterologous vaccine responses and these reported inconsistent results.¹³⁻¹⁵ In these studies, a MCV was given at the same time as the other vaccines. We hypothesised that through effects on innate immunity, stimulation of B- and T-lymphocytes and expansion of pre-existing memory cells, a MCV might alter heterologous responses to previously administered vaccines. The aim of our study was to investigate the effect of a MCV vaccine given at 12 months of age on persistence of antibodies to a broad range of heterologous routine vaccines given in the first year of life.

RESULTS

Of 319 eligible participants, five were excluded because they were a twin of another participant, two because they were not vaccinated according to the schedule and one because vaccine records were not available (Figure 1). Of the remaining 311 participants, 212 had received the MMR/Hib-MenC vaccine 28 ± 14 days before the study. The remainder were MMR/Hib-MenC vaccine naïve (as they had not yet been taken to a clinic for vaccination). The background characteristics of participants are shown in Table 1. There were no

differences in sex, gestational age, birth weight, Caesarean section rate, maternal dTpa vaccination in pregnancy or infant BCG-vaccination status between the two groups. However, the MMR/Hib-MenC-naïve infants received their vaccines on average later than the MMR/Hib-MenC- vaccinated infants. The time interval between the 6-month vaccines and blood sampling at 13 months of age was longer in the MMR/Hib-MenC-vaccinated infants compared with the MMR/Hib-MenC-naïve infants.

Infants who were vaccinated with MMR/Hib-MenC had a lower seroprotection rate for 15/19 (79%) antigens compared with those who were MMR/Hib-MenC vaccine-naïve. This difference was statistically significant for PT (13%) and pneumococcus serotype 19A (17%) (Table 2 and Figure 2).

Unadjusted GMCs were lower in MMR/Hib-MenC-vaccinated children for 20/21 (95%) antigens. This reached statistical significance for 10/21 (48%) antigens. In contrast, MMR/Hib-MenC-vaccinated children had significantly higher GMCs against tetanus (Table 3, Figure 3 and 4). After adjusting for the pre-specified factors, a GMR above one, indicating higher average antibody concentrations against tetanus in MMR/Hib-MenC-vaccinated children was the only statistically significant finding (Table 3 and Figure 5).

DISCUSSION

Children who are infected with measles have a significantly higher mortality rate than children who are vaccinated against the disease.¹⁶ One explanation for the decreased mortality after measles vaccination is that by preventing measles infection, the vaccine also prevents the transient immunosuppressive state (also called measles virus immune amnesia) that is observed after measles infection.¹⁷ Measles virus commonly infects memory lymphocytes^{18, 19} and consequently, after measles infection, individuals lose their immune repertoire and are predisposed to a broad-range of infections for a period of up to several weeks or even years.¹⁷

A further explanation for the decreased mortality after MCV is modulation of the immune system through the immunomodulatory effects of the vaccine.^{9, 10, 20} The precise mechanisms underlying the immunomodulatory effects of live-vaccines, particularly BCG and MMR, are the subject of on-going investigations. BCG vaccine, for example, influences the innate²¹⁻²³ and T cell immunity²⁴ by epigenetic reprogramming of immune cells^{25, 26} and by altering cytokine responses.^{22, 27} Fewer studies have investigated the mechanisms underlying the

immunomodulatory effects of MCV. Measles virus induces a predominately T helper (Th) type 1 responses, which leads to an increase in interferon (IFN)-gamma and interleukin (IL)-12 production.^{28,29} MCV induce both humoral and cell-mediated immune responses.^{11, 12} The mechanisms associated with the non-specific immunomodulatory effects of MCV include a decrease in leukocytes³⁰ and lymphocytes, with a decrease in CD4 cells³⁰ and an increase in CD8 cells,³¹ and induction of cross-reactive B- and T-lymphocyte responses.³² Additionally, functional assays show enhanced lymphoproliferation after stimulation.³⁰ Furthermore, following MCV, increases in soluble CD8 molecule and β -microglobulin have been observed.³³ It is also proposed that MCV induces 'trained' innate immune memory by epigenetic and transcriptional reprogramming of innate cells.³²

One way to explore the immunomodulatory effects of vaccines is to study their influence on the antibody responses to heterologous vaccines. For BCG, it has been shown that the vaccine, when administered prior, increases antibody responses to a number of heterologous vaccines.^{34,35} For MCV, much less data are available. Three studies have investigated the effect of co-administration of MCV with other vaccines. One study showed that female infants who are vaccinated with high-dose Edmonstron-Zagreb measles vaccine at the same time as receiving a rabies vaccine, have higher antibodies against rabies three months after vaccination compared to female infants who do not received the vaccine.¹³ Another study, showed that when MMR is given simultaneously with a yellow fever vaccine, antibody concentrations and seroprotection rates to yellow fever are lower than when the vaccines are given more than a month apart.¹⁴ In contrast, concurrent administration of MMR with a live-attenuated influenza vaccine does not influence antibody responses to influenza.¹⁵ In addition to the studies investigating the effect of co-administered MCV, one study investigated the effect of prior MCV on the response to a smallpox vaccine. Another study reported that when children received a varicella vaccination less than 30 days following MCV, they had a 2.5-fold increase in the incidence of breakthrough disease.³⁶

In our study, we did not find any significant differences in GMCs to heterologous vaccines between infants who did or did not receive a MCV. In contrast to previous studies, which investigated the effect of co-administration of vaccines, we investigated the influence of an MCV vaccine on the persistence of antibodies to vaccines given earlier in life. In our study, MMR was given at 12 months of age, while in many developing countries a MCV is given at 9 months of age or earlier. While age at first MCV does not influence cellular vaccine

responses,^{28, 37-39} younger age is associated with lower antibody responses, faster waning and lower avidity of antibodies.^{40, 41} In contrast, MCV were observed to have a stronger effect on the reduction in all-cause mortality when given at a younger age.^{6, 7} Further studies are needed to explore the effect of age of MCV vaccination on heterologous vaccine responses.

The lower unadjusted GMCs and seroprotection rates in MMR/MenC-Hib-vaccinated participants is most likely explained by waning of antibody levels as the interval between the 6-month immunisation and blood sampling at 13 months of age was an average of 28 days longer in this group. This was most marked in those vaccine antigens which wane most rapidly and therefore had the lowest seroprotection rates (PT, pneumococcal serotype 4 and 19A).

The higher seroprotection rate and GMC for tetanus in MMR/MenC-Hib-vaccinated infants is likely explained by a boosting effect of the carrier protein in the MenC-Hib vaccine, which is a tetanus toxoid.

The strengths of our study are the detailed participant demographic and clinical data allowing for adjustment for possible confounding factors, the homogeneity in the vaccines given and the wide range of measured antibody responses. The limitations of the study are the small sample size and consequent risk of type-2 error and the fact that MMR was co-administered with MenC-Hib.

METHODS

Study design and population

Participants were a subset of infants from a trial to determine whether neonatal BCG vaccination protects against childhood infection, allergy and asthma (the Melbourne Infant Study: BCG for Allergy and Infection Reduction (MIS BAIR)). Inclusion criteria included greater than 32 weeks gestation and birth weight greater than 1500 grams. Parent questionnaires were used to prospectively collect data. All infants received routine vaccinations according to the Australian National Immunisation Program: at birth: intramuscular hepatitis B vaccine (H-B-Vax II Paediatric[®] (*bioCSL*, Parkville, Victoria)); at 6 weeks, 4 months and 6 months of age: intramuscular combined diphtheria-tetanus-acellular pertussis (DTPa), hepatitis B (HepB), poliomyelitis (IPV), and *Haemophilus influenzae* type b (Hib) vaccine (Infanrix[®] Hexa (*GlaxoSmithKline*, Abbotsford, Victoria)), intramuscular 13-

valent conjugate pneumococcal vaccine (conjugated to CRM197, a diphtheria toxin) (Prevenar13[®] (Wyeth, West Ryde, New South Wales)), and oral rotavirus vaccine (RotaTeq[®] (Merck, Parkville, Victoria)). Approximately half of the infants also received intradermal BCG-Denmark shortly after birth as part of the MIS BAIR. At the time of the study, approximately two-thirds of the participants had received subcutaneous measles-mumps-rubella (MMR) vaccine (Priorix[®] (GlaxoSmithKline, Abbotsford, Victoria)) or M-M-R[®] II (Seqirus, Parkville, Victoria)) and intramuscular combined Hib and meningococcal C (MenC) vaccine (conjugated to tetanus toxin) (Menitorix[®] (GlaxoSmithKline, Abbotsford, Victoria)) scheduled at 12 months of age, while the other third had not yet received these vaccines. Vaccine records were obtained from the National Australian Immunisation register and/or individual vaccination records.

Blood samples were collected into sodium-heparin (S-monovette, Sarstedt[®], Mawson Lakes, South Australia) tubes during study visits at approximately 13 months of age and plasma stored at -80°C until analysis.

For the participants who had had their MMR/Hib-MenC before the study, only those who had blood taken 28 ± 14 days after the MMR/Hib-MenC vaccine were included in the final analysis. Participants of twins were excluded from the final analysis, because they were not considered independent.

Antibody assays

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), MenC, measles, mumps and rubella) were measured in duplicate using fluorescent bead-based multiplex immune-assays (Luminex xMAP technology). 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).⁴²⁻⁴⁷ Laboratory staff were blinded to MMR/Hib-MenC vaccine status.

Statistical analysis

The antibody response to each of the scheduled routine vaccines was compared between the participants who had received their 12 months MMR/MenC-Hib vaccine at the time of the study ('MMR/MenC-Hib-vaccinated') and those who had not ('MMR/MenC-Hib-naïve'). The proportion of children with an antibody concentration above the standard protective correlate value (seroprotection rate)^{45, 48, 49} for each vaccine was calculated in each group (with the exception of FHA and PRN for which no accepted protective correlate value exists). The Clopper-Pearson method was used to estimate the 95% confidence intervals (CIs) of the seroprotection rates. Proportions were compared using Fisher's exact test and 95% confidence interval (CI) for differences in proportions estimated. In each group, the geometric mean concentrations (GMC) for each vaccine antibody was calculated. The geometric mean ratio (GMR) with 95% CI was obtained as the anti-logged coefficient from a linear regression with log-concentrations as outcome and MMR/Hib-MenC vaccination status as covariate. Effect modification was assessed using the following pre-specified factors: maternal vaccination (dTpa and influenza) during pregnancy, birth weight, sex, gestational age, age at first routine vaccination, infant BCG vaccination status, age at sampling and time from 12-month vaccination to blood sampling. The GMR for each vaccine antigen was adjusted for those factors that differed between groups and had an effect on that vaccine antigen response. A 5%-significance level was used. All statistical analyses were done using R version 3.4.3.

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, approval no. 38124A). MIS BAIR is registered with the Australia & New Zealand Clinical Trials Registry (1051228) and the U.S. National Institutes of Health (NCT01906853).

COMPETING INTERESTS

The authors declare that they have no competing interests.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

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PZ drafted the initial manuscript. NC critically revised the manuscript and both authors approved the final manuscript as submitted.

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Figure 1. Selection of participants

Figure 2. Seroprotection rates in MMR/Hib-MenC-vaccinated (n = 212, dark grey bars) and MMR/Hib-MenC-naïve (n = 99, light grey bars) participants at 13 months of age

Figure 3. GMCs of antibodies against DTPa-IPV in MMR/Hib-MenC-vaccinated (n=212) and MMR/Hib-MenC-naïve participants (n=99) at 13 months of age (box-and-whisker plots showing interquartile range (IQR) with whiskers depicting 1.5-times the IQR)

Figure 4. GMCs of antibodies against pneumococcus in MMR/Hib-MenC-vaccinated (n=212) and MMR/Hib-MenC-naïve participants (n=99) at 13 months of age (box-and-whisker plots showing interquartile range (IQR) with whiskers depicting 1.5-times the IQR)

Figure 5. GMRs with 95% CI of antibodies to vaccine antigens in participants at 13 months of age (MMR/Hib-MenC-vaccinated (n=212) and MMR/Hib-MenC-naïve participants (n=99))

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Table 1 Characteristics of participants

	MMR/Hib-MenC- vaccinated (n=212) n (%) or median (IQR)	MMR/Hib-MenC- naïve (n=99) n (%) or median (IQR)	P-value
Sex (male)	102 (48)	50 (50)	0.70
Gestational age (weeks)	39.2 (38.4-40.4)	39.3 (38.4-40.3)	0.77
Birth weight (kg)	3.42 (3.12-3.73)	3.55 (3.19-3.88)	0.29
Caesarean section	77 (36)	40 (40)	0.49
Maternal dTpa in pregnancy	101 (48)	45 (45)	0.72
BCG-vaccinated	111 (52)	58 (59)	0.31
Age at routine vaccinations (days)			
- 6-week vaccines	45 (43-48)	47 (44-52)	0.01
- 4-month vaccines	124 (120-130)	127 (123-137)	<0.01
- 6-month vaccines	189 (184-200)	193 (186-220)	<0.01
- 12-month vaccines	375 (369-383)	-	
Interval between (days)			
- 6-month-vaccines to blood sampling at 13 months of age	218 (204-230)	190 (166-203)	<0.01
- 12-month-vaccines to blood sampling at 13 months of age	32 (21-43)	-	
Age at blood sampling (days)	410 (397-421)	385 (378-398)	<0.01

dTpa – diphtheria-tetanus-acellular pertussis vaccine

P-values are from *t*-test for continuous variables and χ^2 test for categorical variables

Table 2 Proportions of participants at 13 months of age with antibody concentrations above protective correlate

Vaccine antigen	Protective correlate	MMR/ Hib-MenC- vaccinated (n=212) % (n); 95% CI	MMR/ Hib-MenC- naïve (n=99) % (n); 95% CI	Difference % (95% CI)	P-value
Diphtheria	0.01 IU mL ⁻¹	97.6 (207); (94.6, 99.2)	100 (99); (97.3, 100)	-2.4 (-4.5, 1.4)	0.18
Tetanus	0.01 IU mL ⁻¹	100 (212); (98.3, 100)	100 (99); (96.3, 100)	0 (-1.8, 3.7)	-
Pertussis toxin	25 IU mL ⁻¹	26.4 (56); (20.6, 32.9)	39.4 (29); (29.7, 49.7)	-13.0 (-24.4, -1.9)	0.02
Polio					
type 1	0.23 IU mL ⁻¹	100 (212); (98.3, 100)	100 (99); (96.3, 100)	0 (-1.8, 3.7)	-
type 2	0.29 IU mL ⁻¹	99.5 (211); (97.4, 100)	100 (99); (96.3, 100)	-0.5 (-2.6, 3.3)	1
type 3	0.12 IU mL ⁻¹	100 (212); (98.3, 100)	100 (99); (96.3, 100)	0 (-1.8, 3.7)	-
Pneumococcus (Pn)					
serotype 1	0.35 µg mL ⁻¹	92.0 (195); (87.5, 95.3)	97.0 (96); (91.4, 99.3)	-5.0 (-10.0, 1.1)	0.14
serotype 3	0.35 µg mL ⁻¹	69.3 (147); (62.7, 75.5)	70.8 (70); (60.7, 79.4)	-1.4 (-11.2, 9.9)	0.89
serotype 4	0.35 µg mL ⁻¹	20.3 (43); (15.0, 26.3)	30.3 (30); (21.5, 40.4)	-10.0 (-20.9, 0.1)	0.06
serotype 5	0.35 µg mL ⁻¹	85.8 (182); (80.4, 90.2)	89.9 (89); (82.2, 95.0)	-4.0 (-11.1, 4.5)	0.37
serotype 6A	0.35 µg mL ⁻¹	86.3 (183); (80.9, 90.6)	86.9 (86); (78.6, 92.8)	-0.6 (-8.1, 8.5)	1
serotype 6B	0.35 µg mL ⁻¹	63.7 (135); (56.8, 70.2)	65.7 (65); (55.4, 74.9)	-2.0 (-13.0, 9.7)	0.80
serotype 7F	0.35 µg mL ⁻¹	99.5 (211); (97.4, 100)	99.0 (98); (94.5, 100)	0.5 (-1.7, 5.1)	0.54
serotype 9V	0.35 µg mL ⁻¹	75.5 (160); (69.1, 81.1)	76.8 (76); (67.2, 84.7)	-1.3 (-10.9, 9.4)	0.89
serotype 14	0.35 µg mL ⁻¹	84.4 (179); (78.8, 89.0)	90.9 (90); (83.4, 95.8)	-6.5 (-13.6, 1.9)	0.15
serotype 18C	0.35 µg mL ⁻¹	73.6 (156); (67.1, 79.4)	83.8 (83); (75.1, 90.5)	-10.3 (-19.1, -0.1)	0.06
serotype 19A	0.35 µg mL ⁻¹	44.3 (94); (37.5, 51.3)	61.6 (61); (51.3, 71.2)	-17.3 (-18.5, 5.3)	<0.01
serotype 19F	0.35 µg mL ⁻¹	99.1 (210); (96.6, 99.9)	100 (99); (96.3, 100)	-0.9 (-3.4, 2.8)	1

serotype 23F	0.35 µg mL ⁻¹	60.8 (129); (53.9, 67.5)	62.6 (62); (52.3, 72.1)	-1.8 (-13.0,10.0)	0.80
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Bold denotes statistically significant results

P-values are from *t*-test for continuous variables and χ^2 test for categorical variables

CI – confidence interval

Table 3 Geometric mean antibody concentrations (GMCs) and geometric mean antibody ratios (GMRs) in participants at 13 months of age

Vaccine antigen	MMR/ Hib-MenC- vaccinated (n=212) GMC 95% CI	MMR/ Hib-MenC- naïve (n=99) GMC 95% CI	Unadjusted GMR (95% CI)	<i>P</i> -value	Adjusted GMR (95% CI)	Adjusted <i>P</i> -value
Diphtheria (IU mL ⁻¹)	0.07 (0.06, 0.08)	0.09 (0.07, 0.12)	0.77 (0.60, 0.98)	0.03	1.04 (0.81, 1.33) ^{a,g,h,i}	0.76
Tetanus (IU mL ⁻¹)	0.90 (0.76, 1.06)	0.32 (0.26, 0.39)	2.80 (2.13, 3.69)	<0.01	2.82 (2.15, 3.71)^d	<0.01
Pertussis (IU mL ⁻¹)						
pertussis toxin	15.94 (13.96, 18.21)	21.48 (17.33, 26.63)	0.74 (0.58, 0.95)	0.02	0.97 (0.75, 1.25) ^{a,g,h,i}	0.82
filamentous haemagglutinin	18.03 (15.82, 20.54)	21.84 (17.98, 26.53)	0.83 (0.65, 1.04)	0.10	1.00 (0.79, 1.27) ^{a,d,g,i}	0.98
pertactin	11.39 (9.72, 13.34)	13.84 (10.66, 17.96)	0.82 (0.61, 1.10)	0.19	1.04 (0.77, 1.40) ^{a,d,g,i}	0.80
Polio (IU mL ⁻¹)						
type 1	9.82 (8.41, 11.48)	14.84 (12.04, 18.30)	0.66 (0.51, 0.87)	<0.01	0.76 (0.57, 1.01) ^{a,g,i}	0.06
type 2	20.44 (17.09, 24.44)	24.54 (19.53, 30.84)	0.83 (0.61, 1.13)	0.24	1.00 (0.72, 1.38) ^{a,g,i}	0.98
type 3	8.08 (6.68, 9.76)	11.23 (9.06, 13.92)	0.72 (0.53, 0.98)	0.04	0.88 (0.63, 1.22) ^{a,d,g,i}	0.45
Pneumococcus (Pn) (µg mL ⁻¹)						
serotype 1	1.11 (0.98, 1.25)	1.31 (1.10, 1.55)	0.85 (0.69, 1.04)	0.12	1.02 (0.82, 1.26) ^{a,c,i}	0.87
serotype 3	0.52 (0.47, 0.58)	0.58 (0.48, 0.70)	0.90 (0.74, 1.09)	0.26	1.06 (0.86, 1.30) ⁱ	0.57

serotype 4	0.21 (0.19, 0.23)	0.24 (0.21, 0.27)	0.87 (0.74, 1.03)	0.11	1.02 (0.85, 1.22) ^{a,b,t,g,i}	0.85
serotype 5	0.85 (0.76, 0.96)	1.08 (0.89, 1.32)	0.79 (0.63, 0.98)	0.03	0.95 (0.75, 1.20) ^{a,h,i}	0.67
serotype 6A	0.95 (0.83, 1.08)	1.13 (0.92, 1.40)	0.83 (0.66, 1.06)	0.14	1.16 (0.90, 1.50) ^{a,g,h,i}	0.24
serotype 6B	0.51 (0.44, 0.60)	0.53 (0.41, 0.69)	0.96 (0.73, 1.28)	0.80	1.30 (0.97, 1.74) ^{a,g,i}	0.08
serotype 7F	1.80 (1.63, 2.00)	2.05 (1.74, 2.40)	0.88 (0.73, 1.06)	0.18	1.08 (0.88, 1.32) ^{a,h,i}	0.46
serotype 9V	0.56 (0.50, 0.63)	0.68 (0.57, 0.81)	0.83 (0.68, 1.03)	0.09	1.04 (0.83, 1.29) ^{h,i}	0.75
serotype 14	0.96 (0.84, 1.10)	1.26 (1.02, 1.56)	0.77 (0.60, 0.98)	0.03	0.94 (0.72, 1.23) ^{h,i}	0.67
serotype 18C	0.60 (0.54, 0.68)	0.76 (0.65, 0.90)	0.79 (0.65, 0.97)	0.02	1.00 (0.81, 1.24) ^{a,g,h,i}	0.89
serotype 19A	0.39 (0.33, 0.47)	0.64 (0.49, 0.85)	0.61 (0.45, 0.84)	<0.01	0.81 (0.58, 1.12) ⁱ	0.20
serotype 19F	2.79 (2.42, 3.20)	3.85 (3.07, 4.82)	0.72 (0.56, 0.93)	0.01	0.90 (0.68, 1.19) ^{h,i}	0.46
serotype 23F	0.55 (0.47, 0.65)	0.59 (0.46, 0.75)	0.94 (0.70, 1.26)	0.67	1.18 (0.87, 1.61) ^{a,d,e,i}	0.87

Bold denotes statistically significant results

CI – confidence interval

^a maternal dTpa immunisation during pregnancy

^b gestational age

^c delivery mode

^d sex

^e birth weight

^f BCG immunisation

^g age at 6-weeks immunisation

^h age at bleeding

ⁱ time between immunisation and bleeding

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Author/s:

Zimmermann, P;Perrett, KP;van der Klis, FRM;Curtis, N

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