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Short communication

Effect of maternal immunisation with multivalent vaccines containing inactivated poliovirus vaccine (IPV) on infant IPV immune response: A phase 4, multi-centre randomised trial ☆

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ABSTRACT

Multivalent diphtheria, tetanus, acellular pertussis and inactivated poliovirus vaccine (DTaP/IPV) has been offered to pregnant women in the United Kingdom since 2012. To assess the impact of maternal DTaP/IPV immunisation on the infant immune response to IPV, we measured poliovirus-specific neutralising antibodies at 2, 5 and 13 months of age in a randomised, phase 4 study of Repevax or Boostrix/IPV in pregnancy and in a non-randomised group born to women not given DTaP/IPV in pregnancy. Infants whose mothers received DTaP/IPV were less likely to seroconvert after three IPV doses than those whose mothers did not receive DTaP/IPV. At 13 months of age, 63/110 (57.2 %), 46/108 (42.6 %) and 40/108 (37.0 %) were seropositive to types 1 to 3, compared with 20/22 (90.9 %), 20/22 (90.9 %) and 14/20 (70.0 %) (p-values 0.003, <0.001 and 0.012). UK infants whose mothers are given DTaP/IPV in pregnancy may be insufficiently protected against poliomyelitis until their pre-school booster.

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1. Introduction

The persistence of wild-type and vaccine-derived poliovirus transmission in South Asia and Africa, despite intensive vaccination activities, is a major challenge to the success of the Global Polio Eradication Initiative (GPEI). It also exposes all countries to the risk of poliovirus importation and spread, as was recently highlighted by the detection of poliovirus circulation in London, which has now been linked to detections in Israel and the United States [1]. The international spread of poliovirus is designated a Public Health Emergency of International Concern (PHEIC) by the World Health Organisation [2]. It is therefore vital that national immunisation programmes maximise protection of children against poliomyelitis through the implementation of optimal, evidence-based immunisation schedules.

In the UK, immunisation of pregnant women with multivalent vaccine containing diphtheria, tetanus and pertussis antigens as well as inactivated poliovirus vaccine (DTaP/IPV) began in October 2012 in response to an increased incidence of pertussis cases and mortality in young infants. The resulting boost in maternally-derived pertussis-specific antibodies in infants was shown to be highly effective (>90 %) against pertussis and is estimated to have prevented between 82 and 170 infant deaths between 2012 and 2017 [3,4]. However, high levels of maternally-derived antibodies in the infant may be accompanied by a reduced humoral immune response to the same vaccine antigens given in the infant schedule [5–9]. In the case of protection against polio, it is known that the infant humoral immune response to inactivated poliovirus vaccine

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(IPV) is lower when given at younger ages or to infants with higher concentrations of maternally-derived, poliovirus-specific neutralising antibodies in their blood [10–15]. However, the impact on the infant immune response to IPV of maternal immunisation with IPV-containing vaccines, which may boost maternal antibodies to levels exceeding that observed in these studies, is unknown.

Unlike most other European countries with a three dose IPV schedule at 2, 3 and 4 months of age, the UK does not give an IPV booster in the second year of life, the first booster offered pre-school to 3-year-old children. In addition, the UK offers an IPV-containing pertussis vaccine in pregnancy, whereas the vaccine recommended by most other countries does not contain IPV. Coverage of the maternal immunisation programme in England was 64 % during January to March 2022, whilst pre-school booster coverage by 5 years of age was 85 % over the same time period (45 % and 73 % for each vaccination respectively in London) [16,17]. Lack of a booster in the second year of life, incomplete coverage with the preschool booster and potential interference with the primary series by maternal vaccination risks an immunity gap to poliomyelitis in children in the UK.

To assess the impact of maternal vaccination on the infant response to IPV in the UK, we measured poliovirus-specific serum neutralising antibodies at 2, 5 and 13 months of age in infants born to mothers with and without DTaP/IPV administered in pregnancy. Samples were collected as part of a randomised clinical trial (iMAP2) conducted by the National Vaccine Evaluation Consortium to investigate responses to immunisation in infants whose mothers had received DTaP/IPV in pregnancy. Our findings have implications for the risk of poliomyelitis outbreaks in the UK and the consideration of a revised childhood immunisation schedule by the UK's Joint Committee on Vaccines and Immunisation.

2. Methods

2.1. Study design

A phase 4, multi-centre parallel arm randomised trial was conducted to examine the effect of maternal immunisation with DTaP/IPV vaccines (either Repevax (Sanofi Pasteur) or Boostrix-IPV (GlaxoSmithKline)) on infant humoral immune responses to routine vaccines given in the UK [9]. A non-randomised comparator group of infants born to unvaccinated mothers was recruited at the same time. Infant response to IPV was not included as a primary outcome but included *post hoc* to inform decisions about the need for an IPV booster in the UK vaccination schedule in the second year of life.

The study design has been previously described [9]. In brief, pregnant women aged 16–45 years receiving antenatal care at St George's University Hospitals NHS Foundation Trust or in primary care sites in Hertfordshire and Gloucestershire were eligible to participate. Following informed consent, they were randomised 1:1 to receive Repevax or Boostrix-IPV at 28–32 weeks of gestation using computer block randomisation with a block size of 8. Exclusion criteria included receipt of a pertussis-containing vaccine in the previous 12 months, receipt of a blood product in the previous 3 months, a bleeding disorder and any contraindication to vaccination. Each pentavalent vaccine administered to pregnant women included IPV consisting of 40, 8 and 32 D-antigen units of poliovirus seroypes 1, 2 and 3 respectively. Infants were vaccinated according to the UK schedule at the time including Infanrix-Penta™ (DTaP/IPV/Hib; GlaxoSmithKline) at 2, 3 and 4 months of age. Cord or infant peripheral blood samples were collected at birth or within 7 days respectively. Infant blood samples were collected at 2, 5 and 13 months of age, including from infants born to mothers not randomised to receive a maternal booster immunisation. Women were observed for 20 min after vaccination and safety data collected during study follow-up. Sample size was based on the primary outcome comparing anti-pertussis toxin immunoglobulin G between study arms.

The study was approved by the MHRA, NHS Health Research Authority and City & East Research Ethics Committee (14/LO/0141). The study was registered with ClinicalTrials.gov (NCT02145624).

2.2. Poliovirus specific neutralising antibodies

Poliovirus serum neutralizing antibodies to the three poliovirus serotypes were measured at the UK National Institute of Biological Standards and Control following the WHO protocol with Sabin poliovirus as challenge [18]. The International Reference for anti-poliovirus serum (82/585) was used as a working reference and tested in parallel to confirm the validity and sensitivity of the tests. Laboratory staff were blinded to the study arm. Quality assurance included the use of an in-house negative serum control.

2.3. Statistical analysis

The proportion with a protective neutralisation titre (>= 8), geometric mean titres (GMTs) and seroconversion were stratified by maternal vaccine type and compared to those for infants born to mothers who were not vaccinated in pregnancy using Fisher's exact test for proportions and by normal errors regression on logged GMTs with adjustment for maternal age and gestation. Seroconversion was defined as a fourfold rise in antibody titre above that predicted at 5 months of age (one month after the third infant dose) based on a half-life for the decay in maternal antibodies of 28 days and the assumption that the baseline measurement at 2 months of age represent purely maternally-derived antibody. Sensitivity analysis included seroconversion defined by a twofold rise over the predicted antibody titre. To maximise power when comparing to the group with no maternal vaccination, the two vaccinated study arms were combined after checking that these groups did not significantly differ. All analysis was performed in Stata version 14 (StataCorp, Texas).

3. Results

3.1. Study enrolment

A total of 154 pregnant women were enrolled and randomised to receive Repevax (n = 77) or Boostrix-IPV (n = 77) between October 2014 and October 2015. 159 babies were born to these women and 144 completed the study. An additional 27 infants born to unvaccinated mothers were recruited during the postnatal period as part of the iMAP2 study. The CONSORT flow diagram for the study and baseline demographic characteristics have been published previously [9]. No Serious Adverse Events were reported as related to maternal or infant vaccination.

3.2. Infant immune responses

Compared with infants of unvaccinated mothers, poliovirus neutralising antibody titres in infants of vaccinated mothers were significantly higher at 2 months of age, but substantially lower post-immunisation, particularly at 13 months of age (Table 1). The proportion of infants with protective antibody titres (>=8) at 13 months was 32 % to 63 %, depending on serotype, for infants born to immunised mothers compared with 70 % to 91 % for infants born to unvaccinated mothers. The lower proportion with protective antibodies at 13 months of age is consistent with significantly

Table 1
Serum neutralising antibodies against poliovirus serotypes at 2, 5 and 13 months of age in infants born to mothers given Boostrix-IPV, Repevax or no DTaP/IPV in pregnancy.

age	polio type	Boostrix-IPV no. >=8 (%)	GMT (95 % CI)	Repevax no. >=8 (%)	GMT (95 % CI)	None no. >=8 (%)	GMT (95 % CI)
2 mo							
	1	57/57 (100.0)	634.4 (452.4–889.7)	66/66 (100.0)	829.5 (563.9–1220.2)	21/26 (80.8)**	49.8 (22–112.8)***
	2	56/59 (94.9)	235.3 (147.3–375.7)	68/68 (100.0)	375.6 (263.5–535.5)	22/26 (84.6)*	30.4 (14.5–63.8)***
	3	56/59 (94.9)	257.7 (161.7–410.6)	65/67 (97.0)	271.5 (174–423.7)	8/26 (30.8)**	5.4 (2.5–11.9)***
5 mo							
	1	55/57 (96.5)	90 (62.2–130.4)	56/56 (100.0)	127.6 (91.8–177.4)	24/24 (100.0)	180.6 (104.1–313.4)
	2	55/57 (96.5)	41.2 (31.2–54.3)	57/57 (100.0)	54.4 (40.2–73.6)	24/25 (96.0)	96.9 (49.4–190.3)**
	3	52/53 (98.1)	107.7 (69.9–165.9)	55/56 (98.2)	115.8 (80.9–165.6)	23/25 (92.0)	204.3 (87.2–478.5)
13 mo							
	1	35/56 (62.5)	13.3 (7.9–22.5)	28/54 (51.9)	7.5 (4.7–12.2)	20/22 (90.9)**	22.8 (13.4–38.7)*
	2	29/55 (52.7)	6.1 (4.2–8.8)	17/53 (32.1)	3.7 (2.6–5.3)	20/22 (90.9)***	33.9 (16.1–71.8)***
	3	23/55 (41.8)	6.5 (3.8–10.9)	17/53 (32.1)	3.7 (2.3–5.9)	14/20 (70.0)*	21.3 (11.0–41.2)***

The proportion with antibodies at a titre of >=8 are shown together with the GMT; The denominator is the number of infants with a sufficient sample volume collected at that visit to complete the serotype-specific neutralisation assay; *p < 0.05 ** p < 0.01 ***p < 0.001 comparing none with Boostrix-IPV and Repevax combined, by Fisher's exact test (proportions) or by regression on logged GMTs with adjustment for maternal age and gestation. mo = month. GMT = geometric mean titre.

* p < 0.05.
** p < 0.01.
*** p < 0.001.

lower seroconversion in infants born to vaccinated mothers following the three infant doses (Table 2). Seroconversion at 5 months of age was 18 % to 44 %, depending on serotype, for infants born to immunised mothers compared with 71 % to 92 % for infants born to unvaccinated mothers. When seroconversion was defined as a twofold rather than fourfold increase over predicted antibody titres, seroconversion was 27 % to 56 % compared with 78 % to 92 % respectively (Supplementary Table 1).

There were no significant differences in antibody titres or seroconversion between infants born to mothers given Repevax compared with Boostrix/IPV. At 13 months of age, 63/110 (57.2 %), 46/108 (42.6 %) and 40/108 (37.0 %) of infants born to mothers given Repevax or Boostrix/IPV had protective antibodies (>=8) to serotypes 1, 2 and 3 respectively. GMTs were 10.1 (95 % Confidence Interval: 7.1–14.4), 4.8 (3.7–6.2) and 4.9 (3.5–7) in this combined group for serotypes 1, 2 and 3 respectively.

4. Discussion

Maternal immunisation with DTaP/IPV results in higher poliovirus-specific infant antibody titres in the first few months of life but a diminished response to three doses of IPV at 2, 3 and 4 months of age as currently recommended in the UK. This results in a substantial immunity gap, evident at 13 months of age when approximately half of those children born to mothers immunised in pregnancy lack protective levels of antibodies to each serotype. Under the current UK vaccination schedule, this immunity gap will persist until the preschool booster at 3 years 4 months of age. By contrast, 70–91 % of children born to mothers not given DTaP/IPV in pregnancy were protected against polio at 13 months of age (depending on the serotype).

These findings differ from those for pertussis antigens measured in the same study, where infants born to mothers vaccinated or not in pregnancy had comparable antibody levels at 13 months of age despite evidence for a blunted immune response to infant pertussis vaccination in the former group [9].

Our study is the first we are aware of to measure IPV responses in infants born to mothers given an IPV containing vaccine in pregnancy. In Australia and the United States, studies have measured IPV response in infants born to mothers receiving DTaP in pregnancy, but not IPV [19,20].

Our study had a few limitations. Firstly, we inferred seroconversion one month after infant vaccination based on the predicted levels of maternally-derived antibodies. This is standard practice, and our finding of reduced seroconversion in infants born to boosted mothers was robust to differing definitions of seroconversion. However, it may have underestimated seroconversion rates if compared with the observed antibody titres at 13 months of age when maternally-derived antibodies are no longer present at appreciable levels. Secondly, although mothers were randomised to the two DTaP/IPV vaccines, infants born to unvaccinated mothers were a convenience sample recruited at the same time and were not part of the randomisation procedure. This could have resulted in systematic differences between the infants born to vaccinated and unvaccinated mothers in our study. We expect these differences to be minimal given their equivalent recruitment locations and timing. Moreover, there were no differences between groups in factors (other than maternally-derived antibodies) known to influence IPV immunogenicity, such as age of infant at vaccination. Finally, blood samples and neutralisation data were not available for all infants because of inadequate sample volumes.

Our findings have implications for the UK immunisation schedule. They support the introduction of an earlier booster with an IPV-containing vaccine in the second year of life, and/or the administration of a pertussis-containing vaccine in pregnancy that does not include an IPV component. While DTaP vaccines are available,

Table 2
Seroconversion after three doses of DTaP/IPV/Hib at 2,3 and 4 months of age in 5-month old infants born to mothers given Boostrix-IPV, Repevax or no DTaP/IPV in pregnancy.

serotype	Boostrix-IPV n/N	% seroconversion (95 % CI)	Repevax n/N	% seroconversion (95 % CI)	None n/N	% seroconversion (95 % CI)
1	10/52	19.2 (9.6–32.5)	12/53	22.6 (12.3–36.2)	17/23	73.9 (51.6–89.8)***
2	11/54	20.4 (10.6–33.5)	10/56	17.9 (8.9–30.4)	17/24	70.8 (48.9–87.4)***
3	18/50	36.0 (22.9–50.8)	24/54	44.4 (30.9–58.6)	22/24	91.7 (73.0–99.0)***

*** p < 0.01 comparing none with Boosterix-IPV or Repevax combined by Fisher's exact test. Seroconversion is defined as a >= 4-fold rise in antibody titre above that predicted in the absence of vaccination assuming passive decay of maternal antibody levels from the 2-month sample with a half-life of 28 days. n = number; N = total number.

the use of a DTaP/IPV vaccine in the UK maternal programme was a pragmatic decision as it is already used in the national pre-school boosting programme, obviating the need to contract for supply of a different product. Any policy changes would need to be carefully considered together with cost data and known variability in coverage of vaccines in pregnancy and pre-school by region. In the meantime, pregnant women should continue to be offered a pertussis-containing vaccine in pregnancy, which has been demonstrated to be a safe and highly effective strategy for prevention of severe pertussis in infants and death.

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Authors' contributions

iMAP2 study design EM, JS, NA, CJ, PH; study conduct AC, JS, EM CJ, PH laboratory testing GC, LS, JM; data management PW; data analysis NA with advice from NG; drafting the paper NG; obtained funding EM. All authors read and approved the final manuscript.

Data availability

Data will be made available on request.

Declaration of Competing Interest

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

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Appendix A. Supplementary data

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