iMAP3

Immunising Mums Against Pertussis 3

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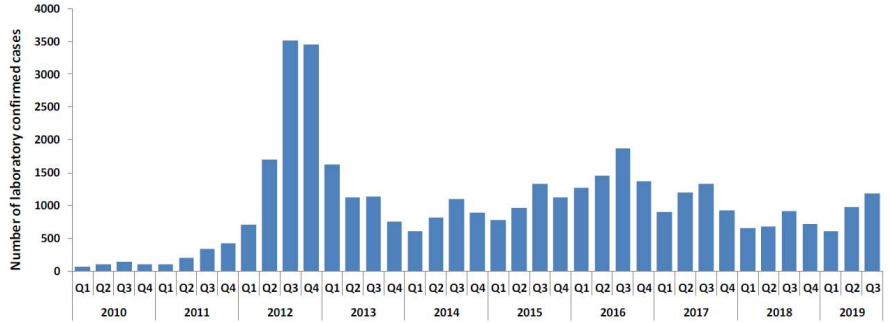
Background – Pertussis outbreak

- Pertussis (whooping cough) is a highly infectious respiratory disease, which can cause significant morbidity & mortality
- Childhood immunisation against pertussis led to a significant decline
- 2012: A national outbreak of pertussis was declared in the UK → a temporary antenatal pertussis vaccination programme was introduced
- Overall decrease in pertussis between 2013 - 2015
- A relative increase <-> decrease in pertussis between 2016 - 2019
- 2019: JCVI recommended for routine antenatal pertussis vaccination programme

Figure 1: Total number of laboratory-confirmed pertussis cases per quarter in England, 2010 to 2019 (Q3)



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Background – REPEVAX vs BOOSTRIX

- Antenatal pertussis vaccination programme changed from Repevax-IPV (REPEVAX; Sanofi Pasteur) to Boostrix-IPV (BOOSTRIX; GSK) in 2014 due to the national procurement & different supplier of vaccines
- There are differences between the DTAP-IPV vaccines (in red):

Vaccine	Repevax-IPV®	Boostrix-IPV®
Components	Diphteria – tetanus - 5-component acellular pertussis - inactivated polio combination vaccine (dT5ap-IPV)	Diphtheria – tetanus – 3 - component acellular pertussis - inactivated polio combination vaccine (dT3aP-IPV)
Pertussis toxin (PT)	2.5 µg	8 µg
Filamentous haemagglutinin (FHA)	5 µg	8 µg
Pertactin (PRN)	3 µg	2.5 µg
Fimbriae 2 & 3 (FIM)	5 µg	None

Background – iMAP2

- Maternal antibody can interfere with an infant's response to immunisation, known as "blunting"
- iMAP2: Phase IV RCT in 2014 - 2016 to compare anti-pertussis IgG responses one month following 1° immunisation (age 8, 12 & 16 weeks) & at 13 months age, in infants whose mothers received one of two antenatal pertussis-containing vaccines (REPEVAX or BOOSTRIX) or did not (CONTROL) (*Jones et al BMC Med 2021*)
- BOOSTRIX vs REPEVAX: post 1° immunisation & at 13 months age, no differences in all pertussis antigen IgG geometric mean concentration (GMC) levels
- BOOSTRIX/REPEVAX vs CONTROL:

  - prior to 1° immunisation, all anti-pertussis antigen levels were higher in BOOSTRIX & REPEVAX than in CONTROL

  - post 1° immunisation, levels were higher in CONTROL than in BOOSTRIX & REPEVAX for anti-PT & than in only REPEVAX for anti-FHA

  - at 13 months age, no differences for anti-PT but anti-FHA levels were higher in CONTROL than in BOOSTRIX & REPEVAX

iMAP3 - Methods

- An observational, cohort, open label phase IV extension study
- Comparing DTaP/IPV vaccine (preschool booster) responses in children whose mothers were randomised to one of two pertussis-containing vaccines as part of iMAP2 (BOOSTRIX or REPEVAX) or no pertussis-containing vaccine (CONTROL) in pregnancy
- Multisite: St George's Vaccine Institute, Oxford Vaccine Group & Gloucestershire NHS Trust
- Study period: 2018 - 2019 (iMAP2 children of age for preschool booster i.e., 3 years 4 months)
- Study visits: Blood samples obtained prior to preschool booster (Visit 1) & one month after (Visit 2)

iMAP3 - Methods

- Primary outcome measure: Fold-difference between groups (BOOSTRIX, REPEVAX & CONTROL) in anti-PT IgG GMC in children prior to preschool booster
- Secondary outcome measure:

  - Fold-difference between groups in anti-PT IgG GMC in children one month after preschool booster

  - Fold-difference between groups in IgG GMC to other pertussis antigens (FHA, FIM, pertactin), tetanus toxoid (TT) & diphtheria toxoid (DT) prior to & one month after preschool booster

  - Fold-difference between groups in anti-DT & anti-TT IgG GMC above the established serocorrelates of protection thresholds (0.1 IU/ml) one month after preschool booster

iMAP3 - Results

- *Sapuan S et al. Vaccine. 2022. 40(49):7050-7056. doi: 10.1016/j.vaccine.2022.10.005*
- 64 children recruited: 26 BOOSTRIX + 22 REPEVAX + 16 CONTROL
- No difference in demographics & most recent antibody responses to DTaP-IPV between recruited & non-recruited participants from iMAP2

Supplementary Table 1. Comparison of recruited and non-recruited children from the iMAP2 study

Factor	Level	Recruited	Non-recruited	Total	Recruited	p-value
Group	BOOSTRIX-IPV® in pregnancy	26	54	80	33%	0.70
	REPEVAX® in pregnancy	22	57	79	28%	
	no vaccine in pregnancy	15	30	46	33%	
Sex	Female	33	66	99	33%	0.48
	Male	31	66	97	32%	
Ethnicity	Asian	6	10	16	38%	0.11
	Black	5	6	11	45%	
	Chinese	3	0	3	100%	
	Mixed	2	6	8	25%	
	Other	0	1	1	0%	
	White	48	118	166	29%	
Age at last DTaP-IPV dose	Median days	123	121			0.10
Age at last MMR & PCV dose	Median days	372	372			0.24
Anti-FHA post-last DTaP-IPV dose#	GMC (95%CI)	59.8 (52.1-68.6)	54.0 (48.0-60.7)			0.28*
Anti-FIM post-last DTaP-IPV dose#	GMC (95%CI)	5.4 (3.9-7.3)	6.4 (4.8-8.5)			0.56*
Anti-PT post-last DTaP-IPV dose#	GMC (95%CI)	33.2 (28.8-38.4)	35.6 (31.4-40.4)			0.54*
Anti-PRN post-last DTaP-IPV dose#	GMC (95%CI)	61.8 (52.4-72.9)	64.0 (51.5-79.5)			0.36*
Anti-DT post-last DTaP-IPV dose#	GMC (95%CI)	0.75 (0.58-0.99)	0.67 (0.56-0.81)			0.51*
Anti-TT post-last DTaP-IPV dose#	GMC (95%CI)	6.3 (5.1-7.8)	6.7 (5.6-8)			0.69*

*regression adjusting for group; #last DTaP dose was at around age 16 weeks and last blood sampling was at around age 5 months; MMR, measles, mumps and rubella vaccine; PCV, pneumococcal conjugate vaccine.

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iMAP3 - Results

- No difference in demographics & routine vaccine intervals between groups

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

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iMAP3 - Results

Vaccine responses to pertussis toxin (PT):

- Pre-booster: Lower in BOOSTRIX than in CONTROL (GMR 0.42 [95% CI 0.22-0.78], p=0.03), no difference between BOOSTRIX & REPEVAX
- Post-booster: No difference between groups

Antibody	Timeline	Group	N	GMC (95 % CI)	GMR Vaccine: Control (95 % CI)	P-value*	GMR REPEVAX®: BOOSTRIX® (95 % CI)	P-value*
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)				

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iMAP3 - Results

Vaccine responses to other pertussis antigens (filamentous haemagglutinin (FHA), Fimbriae 2&3 (FIM) & pertactin (PRN)):

- Pre-booster: No difference between groups
- Post-booster: No difference between groups

Antibody	Timeline	Group	N	GMC (95 % CI)	GMR Vaccine: Control (95 % CI)	P-value*	GMR REPEVAX®: BOOSTRIX® (95 % CI)	P-value*
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)				

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iMAP3 - Results

Vaccine responses to diphtheria toxoid (DT) and tetanus toxoid (TT):

- Pre-booster: No difference between groups
- Post-booster: No difference between groups, all above established serocorrelates of protection thresholds

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 (%)**
Anti-DT	Pre-booster	BOOSTRIX-IPV®	25	0.07 (0.05–0.10)	1.02 (0.54–1.93)	0.96			11 (44 %)
		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 %)
		Both vaccines	46	0.06 (0.04–0.08)	0.79 (0.44–1.43)	0.44			17 (37 %)
		Control	16	0.07 (0.05–0.11)					4 (25 %)
	Post-booster	BOOSTRIX-IPV®	24	3.87 (2.82–5.32)	0.88 (0.52–1.48)	0.63			24 (100 %)
		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 %)
		Both vaccines	42	3.56 (2.78–4.57)	0.81 (0.50–1.30)	0.38			42 (100 %)
		Control	16	4.40 (2.75–7.04)					16 (100 %)
Anti-TT	Pre-booster	BOOSTRIX-IPV®	25	0.46 (0.30–0.70)	1.05 (0.52–2.11)	0.89			23 (92 %)
		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 %)
		Both vaccines	46	0.34 (0.24–0.49)	0.84 (0.45–1.58)	0.59			37 (80 %)
		Control	16	0.39 (0.22–0.68)					14 (88 %)
	Post-booster	BOOSTRIX-IPV®	24	15.93 (12.78–19.86)	1.04 (0.67–1.61)	0.85			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 %)
		Both vaccines	42	15.96 (12.92–19.73)	1.04 (0.71–1.55)	0.83			42 (100 %)
		Control	16	15.29 (10.59–22.06)					16 (100 %)

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

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iMAP3 - Results

- All antibody results from iMAP2 and iMAP3 in BOOSTRIX/REPEVAX and CONTROL groups:

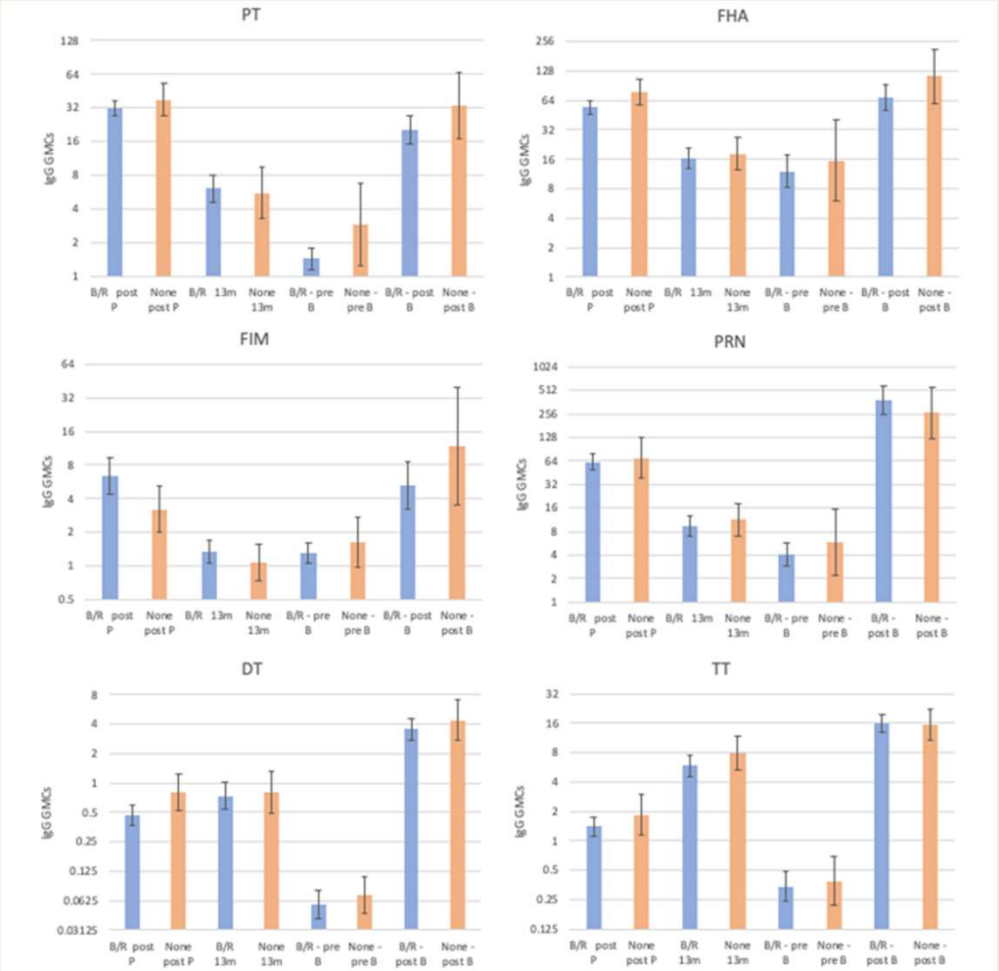

Fig. 1. Children's antibody responses by antigen post-primary immunisations, at age 13 months, pre- and post-booster according to their mothers' antenatal vaccination status (BOOSTRIX-IPV®, REPEVAX® or none). B, BOOSTRIX-IPV® group; R, REPEVAX® group; post P, post-primary immunisations; pre B, pre-booster;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

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iMAP3 - Discussions

- The first study to explore the influence of antenatal pertussis vaccination on children's antibody responses beyond 18 months of age
- Prior to preschool booster, anti-PT was the only pertussis antibody concentrations found at lower level in children born to pertussis-vaccinated mothers in BOOSTRIX (TdaP3-IPV) which may reflect blunting due to higher level of PT in BOOSTRIX compared to REPEVAX (TdaP5-IPV), which resolved post preschool booster
- Clinical significance of lower pertussis antibody concentrations is uncertain due to absence of a serocorrelate of protection for pertussis antibodies

iMAP3 - Discussions

- The presence or absence of FIM in a pertussis-containing antenatal vaccine did not have an impact on vaccine responses to FIM in preschool age children
- No differential effects between REPEVAX and BOOSTRIX on vaccine responses in children into 3rd year of life, suggesting either may be used in pregnancy
- 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

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