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Title: A phase III, open-label, randomised multicentre study to evaluate the immunogenicity and safety of a booster dose of two different reduced antigen diphtheria-tetanus-acellular pertussis-polio vaccines, when co-administered with measles-mumps-rubella vaccine in 3 and 4-year-old healthy children in the UK.

Article Type: Original article

Keywords: preschool booster; dTap-IPV; RCT; child; UK

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Abstract: Aim - To evaluate the immunogenicity and safety of a reduced antigen diphtheria-tetanus-acellular pertussis-inactivated poliovirus (dTap-IPVB) vaccine (Boostrix-IPV, GSK) as a pre-school booster in 3-4 year old children as compared to dTap-IPVR (Repevax, Sanofi Pasteur), when co-administered with mumps-measles-rubella vaccine (MMRV).
Methods - This phase III, open label, randomised study was conducted in the UK between April 2011 and April 2012. Children due their pre-school dTap-IPV booster vaccination were randomised 2:1 to receive one of two different dTap-IPV vaccines (dTap-IPVB or dTap-IPVR) with blood sample for immunogenicity assessment just prior and one month after vaccination. Immune responses to diphtheria, tetanus and polio antigens were compared between the study vaccines (inferential comparison). In the absence of an accepted pertussis correlate of protection, the immunogenicity of dTap-IPVB vaccine against pertussis was compared with historical pertussis efficacy data (inferential comparison). Safety and reactogenicity of both study vaccines were evaluated.
Results - 387 children were randomised and 385 vaccinated: 255 in the dTap-IPVB group and 130 in the dTap-IPVR group. Prior to vaccination, ≥76.8% of children had anti-diphtheria and ≥65.5% had anti-tetanus titres above the protection threshold; for pertussis, the pre-vaccination seropositivity rate ranged between 18.1 and 70.6%. Both vaccines were immunogenic with 99.2-100% of children achieving titres above the pre-specified seroprotection /seropositivity thresholds. One serious adverse event not considered as causally related to the study vaccination by the study investigator was reported in the dTap-IPVB group.
Conclusion - Non-inferiority of dTap-IPVB to dTap-IPVR was demonstrated. Both vaccines had a clinically acceptable safety and reactogenicity profile when co-administered with MMRV to children 3-4 years old.

Highlights

- We assessed immunogenicity and safety of dTpa-IPV booster vaccine in 3-4 years olds
- The immunogenicity of dTpa-IPV (Boostrix-IPV) was non-inferior to Repevax
- Both vaccines were co-administered with mumps-measles-rubella vaccine
- Both vaccines had clinically acceptable safety and reactogenicity profiles

Abstract

Aim – To evaluate the immunogenicity and safety of a reduced antigen diphtheria-tetanus-acellular pertussis-inactivated poliovirus (dTap-IPV$_B$) vaccine (*Boostrix-IPV*, GSK) as a pre-school booster in 3-4 year old children as compared to dTap-IPV$_R$ (*Repevax*, Sanofi Pasteur), when co-administered with mumps-measles-rubella vaccine (MMRV).

Methods – This phase III, open label, randomised study was conducted in the UK between April 2011 and April 2012. Children due their pre-school dTap-IPV booster vaccination were randomised 2:1 to receive one of two different dTap-IPV vaccines (dTap-IPV$_B$ or dTap-IPV$_R$) with blood sample for immunogenicity assessment just prior and one month after vaccination. Immune responses to diphtheria, tetanus and polio antigens were compared between the study vaccines (inferential comparison). In the absence of an accepted pertussis correlate of protection, the immunogenicity of dTap-IPV$_B$ vaccine against pertussis was compared with historical pertussis efficacy data (inferential comparison). Safety and reactogenicity of both study vaccines were evaluated.

Results – 387 children were randomised and 385 vaccinated: 255 in the dTap-IPV$_B$ group and 130 in the dTap-IPV$_R$ group. Prior to vaccination, ≥76.8% of children had anti-diphtheria and ≥65.5% had anti-tetanus titres above the protection threshold; for pertussis, the pre-vaccination seropositivity rate ranged between 18.1 and 70.6%. Both vaccines were immunogenic with 99.2-100% of children achieving titres above the pre-specified seroprotection /seropositivity thresholds. One serious adverse event not considered as causally related to the study vaccination by the study investigator was reported in the dTap-IPV$_B$ group.

Conclusion – Non-inferiority of dTap-IPV$_B$ to dTap-IPV$_R$ was demonstrated. Both vaccines had a clinically acceptable safety and reactogenicity profile when co-administered with MMRV to children 3-4 years old.

Trial registration: NCT01245049 (ClinicalTrials.gov)

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Keywords: preschool, booster, dTap-IPV, RCT, child, UK

Abbreviations

AE, adverse event; ap, acellular pertussis; ATP, according to protocol; CI, confidence interval; d, diphtheria (low dose); D, diphtheria, (high dose); dTap-IPV, reduced antigen diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine; ELISA, enzyme-linked immunosorbent assays; EMA, European Medicines Agency; El.U/ml, ELISA units per millilitre; FHA, filamentous haemagglutinin; GMC, geometric mean concentration; GMT, geometric mean titre; IPV, inactivated poliovirus; IU/ml, international units per millilitre; m, month; MMR, mumps-measles-rubella vaccine; PRN, pertactin; PT, pertussis toxoid; SAE, serious adverse event; T, tetanus; y, year.

***Title Page**

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Short title: Randomised open-label comparison of two different dTap-IPV vaccines as a pre-school booster in UK children aged 3 and 4 years old.

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Introduction

The timing of primary and booster doses of diphtheria (d), tetanus (T), acellular pertussis (ap) and inactivated poliovirus (IPV) varies widely across Europe[1]. Most countries give two or three doses in the first six months (m) followed by one at 12-18m (termed 2+1 / 3+1 schedules) with a further booster before starting school. However the UK schedule just has three infant doses with no DTaP-IPV booster at 12-18m; at this visit children already receive four injections (*Haemophilus influenzae* type B, pneumococcal conjugate, mumps-measles-rubella [MMR] and meningococcal B). By three to five years of age the protection gained from primary vaccinations in infancy is starting to wane[2] so the pre-school booster is given between three and a half and four years. At this age low dose diphtheria vaccines have been shown to induce adequate immune responses but with the advantage of lower rates of local side effects.[3] dTap-IPV (dTap-IPV_B; *Boostrix-IPV*, GSK) is already used as a pre-school booster in many countries around the world but is licensed only from the age of four. The aim of this study was to generate evidence to support the use of dTap-IPV_B in three to four year olds so it could potentially be used as a pre-school booster vaccine at this age. Thus we aimed to demonstrate that the immunogenicity of dTap-IPV_B is not inferior to that of dTap-IPV_R (*Repevax*, Sanofi-Pasteur), the vaccine in routine use at the time in the UK and which is approved for use in persons from three years of age upwards. In the absence of accepted correlate of protection for pertussis, the immunogenicity of dTap-IPV_B was evaluated by comparison with historical pertussis efficacy data.[4,5]

Methods

Study Design and Setting

We conducted an open-label, randomised, multicentre trial in five paediatric research centres in the UK (Bristol, Exeter, Oxford, Southampton and Taunton) and seven general practices. Ethical approval was obtained from the South West 2 Research Ethics Committee (NHS REC Ref: 10/H0206/43). The

trial was registered with the European Clinical Trials Database (2009-012202-39) and ClinicalTrials.gov (NCT01245049).

Participants

Eligible participants were healthy children between three and less than five years of age who had had their previous vaccines on time as per national immunization program in the UK (three diphtheria, tetanus, pertussis and polio doses primary schedule completed before six months of age and first MMR vaccine before two years of age) but had not already received their routine pre-school dTap-IPV booster. Children were excluded from participating if they had a known allergy to the vaccine components, known immunodeficiency, chronic use of steroids or were concurrently in another clinical trial. Full exclusion criteria are listed in online supplement (Supplementary table 1). Families were recruited either using postal mailings through local Child Health Databases or from their general practices. Vaccination was postponed for any intercurrent febrile illness with axillary temperature ≥37.5°C or other moderate to severe acute illness.

Co-primary objectives were to demonstrate, one month after vaccination, non-inferiority of:

1) The immune responses to diphtheria, tetanus and polio antigens induced by dTap-IPV_B when compared to those induced by dTap-IPV_R
2) The immune response to pertussis antigens induced by dTap-IPV_B when compared to historical data relating to DTaP vaccine (*Infanrix* vaccine, GSK) when administered to infants.

Both study vaccines contained diphtheria (low amounts) and tetanus toxoids, pertussis antigens (low amounts) and three polio strains (vaccine composition is presented in Table 1). However dTap-IPV_B contained three of the five pertussis antigens in dTap-IPV_R at different doses. With no available immunological correlate of protection for pertussis, it was felt that the most clinically relevant comparator would be the historical immunogenicity [4] and efficacy [5] data originally supporting the licensure of this combination of pertussis antigens. The study design and endpoints were

decided in liaison with the European Medicines Agency (EMA) to meet requirements for Paediatric Investigation Plan approval.

Study Procedures

After initial contact and eligibility checking, the study comprised two visits. At the first, written informed consent was obtained from the parent/legal guardian. Children were then randomised using GSK's central Internet Randomisation system (SBIR) (using a block size of six and a minimisation procedure accounting for centre) and allocated to receive either dTap-IPV_B (lots AC39B034B, AC39B026A, AC39B032A1) or dTap-IPV_R (lots DEXTA397AZ, DEXTA419AZ) in a 2:1 ratio as their pre-school dTap-IPV booster with both groups also receiving a dose of MMR booster (*Priorix*, GSK, Lots AMJRB892AZ, AMJRC160AZ, AD01B679C, AD01B801A, AD01B733B). After randomisation, the study was open label with both investigator and child's parents aware of their allocation. A blood sample (2.5mls) was drawn before vaccination. Vaccines were given intramuscularly dTap-IPV into the left deltoid, MMR into right deltoid, using 25mm 23G needles, respectively. Solicited local and general symptoms occurring within four days following vaccination were recorded in diary cards as were other (unsolicited) adverse events (AEs) occurring within 30 days of vaccination. Information on serious adverse events (SAEs) occurring at any time-point during the study was also collected. The second and final study visit was 30 days (range: 21–48 days) after the first visit and comprised a second blood sample and collection of diary cards.

Laboratory Assays

All assays were performed at the laboratories of GSK Biologicals (Rixensart, Belgium) with laboratory staff blinded to the participant group. Antibodies against diphtheria toxoid (anti-diphtheria), tetanus toxoid (anti-tetanus) and pertussis components (pertussis toxoid [PT], filamentous haemagglutinin [FHA] and pertactin [PRN]) were measured by enzyme-linked immunosorbent assays (ELISA) developed in-house. Specific IgG antibodies to measles, mumps and rubella were measured using commercially available ELISAs following the manufacturers' instructions (Dade Behring, Germany).

For both anti-diphtheria and tetanus thresholds for correlates of clinical protection were defined as 0.1 international units per millilitre (IU/ml), three times the lower quantification limit of the assays as previously demonstrated [6,7]. With no established serological correlates of protection for pertussis antigens [8–10], measles [11], mumps [12] or rubella, the thresholds for serological responses (positive: greater than or equal) were arbitrarily defined as the lower limits of the assays: 5 El.U/ml (all pertussis antigens), 150 mIU/ml, 231 U/ml and 4 IU/ml, respectively. Seroconversion was defined as seropositivity in the relevant assay in participants seronegative before vaccination. Antibody titres against poliovirus types 1, 2 and 3 were determined by the manufacturer's in-house virus micro-neutralisation test standardized according to WHO guidance [13] and were expressed as the reciprocal of the dilution resulting in 50% inhibition. Polio antibody titres greater than or equal to 1:8 dilution were considered seropositive and protective [14].

Statistics

Analysis of Immunogenicity

The protocol pre-defined standard non-inferiority criteria [15]. For diphtheria and tetanus responses - the upper 95% confidence interval (CI) limit of the (dTap-IPV_R group minus dTap-IPV_B group) difference between the percentage of participants in the two groups with post-vaccine antibody concentrations above the pre-defined protective threshold was to be less than 10%; for poliovirus types 1, 2 and 3 - the upper 95% CI limit of the ratio of geometric mean titres (GMTs) (dTap-IPV_R group divided by dTap-IPV_B group) was to be less than or equal to two and for pertussis antigens - the upper 95% CI limit of the ratio of geometric mean concentrations (GMCs) (historic DTaP data [4,5] divided by dTap-IPV_B group in this study) was to be less than or equal to 1.5.

Secondary objectives were to describe the immunogenicity of both study vaccines in terms of seroprotection/seropositivity rates and GMCs/GMTs for all antigens, prior to and one month after booster vaccination; the percentage of participants with booster response to the pertussis and polio antigens; to describe the immune responses to the MMR vaccine in terms of seroconversion rates

against mumps, measles and rubella, one month after booster vaccination; and to assess the safety and reactogenicity of the study vaccines in terms of solicited symptoms, unsolicited AEs and SAEs.

The primary analysis was based on the cohort of participants who completed the study according to protocol (ATP) for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated participants with serological results excluded from this ATP cohort was 5% or more, a second analysis of the total vaccinated cohort was to be performed to complement the ATP analysis.

Given the absence of serologic correlates of protection against pertussis, an immuno-bridging approach was used to assess immune responses to pertussis antigens, by extrapolating the efficacy of a vaccine against pertussis as demonstrated in infants to an older age group, as previously described.[16]

Safety

Safety and reactogenicity of the study vaccines were assessed in terms of solicited symptoms (local and general), unsolicited symptoms and SAEs. The intensity of solicited symptoms was graded as mild, moderate or severe (defined in Supplementary Table 2) and assessment of causality by vaccination was assessed by investigators. Additionally, p values for the difference in proportion of participants reporting the solicited symptom, and solicited and unsolicited symptoms combined, were computed post-hoc using the continuity adjusted chi-square method. However, the results should be interpreted with caution since there was no adjustment for multiplicity.

Sample size

It was calculated that 230 participants in the dTap-IPV_B group and 115 in the dTap-IPV_R group (a total of 345) would provide at least 90% overall power to reach conclusions on all the co-primary objectives simultaneously (with Bonferroni adjustment). Assuming a dropout rate of 10%, a total of 384 participants (256 participants in dTap-IPV_B group and 128 in dTap-IPV_R group) was chosen to ensure that a sufficient number of evaluable participants was available for inclusion in the per

protocol cohort for analysis of immunogenicity. Statistical analysis was done by GSK with independent statistical verification carried out by KJC statistics (www.kjcstatistics.com).

Results

The study ran from April 2011 to April 2012. 387 children were enrolled and 385 were vaccinated: 255 in dTap-IPV_B arm, 130 in dTap-IPV_R group (Figure 1). There were no significant differences in baseline characteristics in the ATP immunogenicity cohort: in both groups mean age at vaccination was 3.1 years with an equal proportion of genders and similar heritage (Table 2). The ATP immunogenicity cohort comprised 76.5%/73.8% (dTap-IPV_B/dTap-IPV_R, respectively) of the total vaccinated cohort mainly due to missing serological data through difficulties in obtaining blood samples. As per protocol, an additional total vaccinated cohort immunogenicity analysis was performed but found no significant difference in primary or secondary outcomes – results are provided as an online appendix (Supplementary Table 3-Table 5).

Immunogenicity results

For the study's primary inferential analyses; at 30 days post booster vaccination the non-inferiority criteria for the upper bounds of the 95% CI of differences between comparator vaccines were met for all component antigens (*i.e.*, seroprotection levels for diphtheria and tetanus, and GMCs ratio for polio and pertussis antigens) (Table 3).

For the secondary analyses the pre booster titres (Table 4) showed that prior to boosting for all antigens a high proportion of children in both groups had antibody levels below the defined seroprotection / seropositivity thresholds; with 16.7-34.5% for diphtheria and tetanus and 30.4-40.6% for polio. For pertussis 29.4-81.9% of participants had IgG titres below the pre-determined optimal serological thresholds. For all antigens, 30 days post dTap-IPV booster vaccination the proportions of seroprotected / seropositive children had risen to >99% indicating adequate serological response. Comparing antibody GMC / GMT between the two study vaccines at one month post dTap-IPV vaccination (Table 4), marginally higher point estimates for diphtheria, tetanus,

Polio3 and PRN after dTap-IPV_R vaccination, and marginally higher point estimates for the Polio1, Polio2, PT and FHA after dTap-IPV_B vaccination were observed.

Prior to boosting, evidence of antibodies persistence for the MMR vaccine (Table 4) was observed for at least 89.7% of children meeting the immunological criteria for measles, mumps or rubella in each group. One month after the MMR booster dose all children had antibody titres above the defined immunological criteria with no significant differences in GMTs between groups.

Safety Results

In the four day post vaccination period, 216/255 (84.7%; dTap-IPV_B) and 108/130 (83.1%; dTap-IPV_R) (p=0.79) of participants reported at least one solicited symptom or unsolicited AE. For both vaccines redness and pain were the most commonly reported. Severe (grade 3) symptoms were reported by a maximum of 11.0% (redness in the dTap-IPV_B group) and 18.4% (redness in the dTap-IPV_R group) (p=0.08) of participants (Table 5).

During the 31-day (Days 0-30) post vaccination unsolicited reporting period, 88/255 (34.5%; dTap-IPV_B) and 36/130 (27.7%; dTap-IPV_R) (p=0.22) of participants reported at least one AE of which 4.7% and 4.6% (p=1.0) respectively were considered to be severe.

Diarrhoea and vomiting, reported for 9/255 (3.5%) participants were the most frequently reported unsolicited AE in the dTap-IPV_B group while rash, reported for 6/130 (4.6%) participants was the most frequently reported unsolicited AE in the dTap-IPV_R group.

One SAE was reported during the whole clinical study duration; . pneumonia requiring hospitalisation reported for one participant in the dTap-IPV_B arm. This was felt not to be causally related to vaccination by the investigator. No study participants withdrew from the study due to an AE or SAE.

Discussion

This study compares the immunogenicity and AEs of two alternative dTap-IPV vaccines for use as a pre-school booster in the UK vaccine schedule. According to the primary outcomes, the study vaccine response was non-inferior to its comparator at one month post-vaccination – both vaccines boosting serological responses above accepted thresholds. There were no significant differences in solicited or unsolicited local reactions between the two vaccines, with mild redness and pain reported in 49.8-58.4% of cases.

In this study which followed the UK infant schedule in use at that time, we found that by the age of three and a half years, almost a third of children had antibody levels that had waned below desired levels for at least one vaccine component (Table 4) – reinforcing the requirement for a pre-school booster. This is in line with a previous study showing serological evidence of protection from UK primary course DTaP had substantially waned by the age of three to -four years [17].

For diphtheria, although post-booster all children had antibody levels above threshold, GMCs were marginally higher for dTap-IPV$_R$ than dTap-IPV$_B$ but still 80-fold above the level considered protective. Due to the long half–life of these antibodies, this degree of boosting above the protective threshold has been shown to remain clinically effective for ten years, based on a mathematical model [18].

With no agreed immunological correlate of protection against pertussis, it was not appropriate to simply compare the antibody response between the two study vaccines because dTap-IPV$_R$ contains two additional pertussis antigens. Accordingly, our pre-defined primary analysis was to compare the immune responses to the booster dose of dTap-IPV$_B$ given in this study against historical immunogenicity data from the original study that demonstrated clinical effectiveness for this combination of antigens. This primary analysis showed non-inferiority. In a secondary analysis we compared the GMCs for the antigens common to both vaccines. All titres were significantly boosted but, as might be expected, with minor difference between the vaccines. GMCs for PT and FHA were

higher for dTap-IPV$_B$ than dTap-IPV$_R$, while the reverse was true for PRN. Clearly both vaccines used as boosters can provide a serological response. However even with adequate pertussis vaccine responses, data from the US have shown rapid waning of clinical protection (27% per year after the fifth dose of pertussis vaccine) [19] leading the US to introduce an adolescent booster dose for pertussis[20].Further investigations would need to be done to determine if the additional pertussis antigen contained in dTap-IPV$_R$ resulted in any significant difference in the rate of waning between the vaccines.

The limitation of this study is that whilst randomised, because of the difference in the visual aspects of the study vaccines, the study was designed to be open label. This meant that for AE recording the parents were not blinded to the study arm – despite this there were no significant differences between AE outcomes. Since the study the UK infant vaccine schedule has changed with the introduction of the rotavirus and meningococcal B immunisation programmes. In response to rising rates of neonatal pertussis, in 2012 the UK introduced maternal dTap vaccination at 28-32 weeks gestation. This has been highly successful with significant reduction in the number of cases.[21] However there is some evidence that increased maternal titres may adversely affect early infant vaccine responses,[22, 23] increasing the importance of an effective the pre-school booster.

In conclusion, we found dTap-IPV$_B$ to be non-inferior to dTap-IPV$_R$ with all children making an equivalent immune response after boosting indicative of protection being afforded at the same level as demonstrated now in the population as monitored by national surveillance systems. There were minor differences between vaccines for individual antigens but these are unlikely to be of any clinical significance.

Trademark statement

Boostrix-IPV, *Infanrix* and *Priorix* are trademarks of the GSK group of companies. *Repevax* is a trade mark of Sanofi-Pasteur.

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Declaration of interest

R Marlow declares receiving conference travel expenses from GSK group of companies in 2014.

A Finn received grants paid to his institution from Novartis (Novartis Vaccines Division was subsequently acquired by the GSK group of companies), GSK group of companies and Sanofi Pasteur MSD for studies outside the submitted work. Owing to his membership on the Joint Committee on Vaccination and Immunisation for the United Kingdom Department of Health, Adam Finn no longer gives lectures or undertakes advisory work for industry, either paid or unpaid.

M Snape reports grants from GSK group of companies, Novartis, Johnson and Johnson, MedImmune where he acted as investigator for clinical vaccine studies; speaker fees from Novartis; and consultancy fees from MedImmune.

A J Pollard reports previous grants from Pfizer and Okairos in the past 36 months. His department received unrestricted educational grants from Pfizer/GSK/Astra Zeneca in July 2016 and

Gilead/MSD/GSK/Astra Zeneca in June 2017 for a course on Infection and Immunity in Children. A J Pollard is chair of the UK Department of Health's (DH) Joint Committee on Vaccination and Immunization (JCVI) and the scientific advisory group on vaccines for the European Medicines Agency and is a member of the WHO's SAGE; the views presented in this manuscript do not necessarily represent the views of DH JCVI, EMA or WHO.

S N Faust reports grants from GSK group of companies; S N Faust has been advisory board member to vaccine and antimicrobial manufacturers (GSK, AstraZeneca, Pfizer, Novartis, Sanofi, Cubist Pharmaceuticals, Actelion Pharmaceuticals, Astellas, Merck).

M Snape, A Pollard, S N Faust and R Tomlinson declare that all honoraria and fees were paid to the employing institution and no personal fee or honoraria of any kind were received at any time.

S Kuriyakose and N Mesaros declare they are employed by the GSK group of companies; N Mesaros holds shares in the GSK group of companies. HH Han was a GSK employee at the time the study was conducted; she is now employee of Takeda Pharmaceuticals.

R Tomlinson declares receipt of recruitment fees from GSK; all honoraria were paid to the employing institution (Royal Devon & Exeter NHS Trust) and no personal fee or honoraria of any kind were received at any time.

Authors´ contributions

R Marlow, A Finn, A J Pollard, S N Faust, M Snape, S Kuriyakose were involved in the conception and design of the study; R Marlow , A Finn, A J Pollard, M Snape, S N Faust, R Tomlinson, S Kuriyakose, N Mesaros and HH Han were involved in data acquisition, analysis or interpretation. R Marlow produced the first draft of the manuscript, all authors revised the work critically, approved the final version to be published and take full accountability for all aspects of the work.

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335 **Figures**

336 **Figure 1 - Participant flow chart**

337 Footnote: ATP, according to protocol; dTap-IPV_B, reduced diphtheria-tetanus-acellular pertussis-
338 polio vaccine (*Boostrix-IPV*); dTap-IPV_R, reduced diphtheria-tetanus-acellular pertussis-polio vaccine
339 (*Repevax*)

Introduction

The timing of primary and booster doses of diphtheria (d), tetanus (T), acellular pertussis (ap) and inactivated poliovirus (IPV) varies widely across Europe[1]. Most countries give two or three doses in the first six months (m) followed by one at 12-18m (termed 2+1 / 3+1 schedules) with a further booster before starting school. However the UK schedule just has three infant doses with no DTaP-IPV booster at 12-18m; at this visit children already receive four ~~vaccines~~injections (*Haemophilus influenzae* type B~~-~~, pneumococcal conjugate, mumps-measles-rubella [MMR] and meningococcal B). By ~~3-5~~three to five years ~~(y)~~ of age the protection gained from primary vaccinations in infancy is starting to wane[2] so the pre-school booster is given between ~~3.5-4y.~~three and a half and four years. At this age low dose diphtheria vaccines have been shown to ~~give~~induce adequate immune ~~response~~responses but with the advantage of lower rates of local side effects.[3] dTap-IPV (dTap-IPV_B; *Boostrix-IPV*, GSK) is already used as a pre-school booster in many countries around the world but is licensed only from the age of ~~4y.~~four. The aim of this study was to generate evidence to support the use of dTap-IPV_B in ~~3-4y~~three to four year olds so it could potentially be used as a pre-school booster vaccine at this age. Thus we aimed to demonstrate that the immunogenicity of dTap-IPV_B is not inferior to that of dTap-IPV_R (*Repevax*, Sanofi-Pasteur), the vaccine in routine use at the time in the UK and which is approved for use in persons from ~~3~~three years of age ~~onwards.~~upwards. In the absence of accepted correlate of protection for pertussis, the immunogenicity of dTap-IPV_B was evaluated ~~as compared~~by comparison with historical pertussis efficacy data.[4,5]

Methods

Study Design and Setting

We conducted an open-label, randomised, multicentre trial in ~~5~~five paediatric research centres in the UK (Bristol, Exeter, Oxford, Southampton and Taunton) and ~~7~~seven general practices. Ethical approval was obtained from the South West 2 Research Ethics Committee (NHS REC Ref:

10/H0206/43). The trial was registered with the European Clinical Trials Database (2009-012202-39) and ClinicalTrials.gov (NCT01245049).

Participants

Eligible participants were healthy children between ~~3~~three and less than ~~5y~~five years of age who had had their previous vaccines on time as per national immunization program in the UK (~~3~~three diphtheria, tetanus, pertussis and polio doses primary schedule completed before ~~6~~six months of age and first MMR vaccine before ~~2y~~two years of age) but had not already received their routine pre-school dTap-IPV booster ~~dose~~. Children were excluded from participating if they had a known allergy to the vaccine components, known immunodeficiency, chronic use of steroids or were concurrently in another clinical trial. Full exclusion criteria are listed in online supplement (Supplementary table 1). Families were recruited either using postal mailings through local Child Health Databases or from their general practices. Vaccination was postponed for any intercurrent febrile illness with axillary temperature ≥37.5°C or other moderate to severe acute illness.

Co-primary objectives were to demonstrate, ~~1~~one month after vaccination, non-inferiority of:

1) The immune responses to diphtheria, tetanus and polio antigens induced by dTap-IPV_B when compared to those induced by dTap-IPV_R
2) The immune response to pertussis antigens induced by dTap-IPV_B when compared to historical data relating to DTaP vaccine (*Infanrix* vaccine, GSK) when administered to infants.

Both study vaccines contained diphtheria (low ~~dose~~amounts) and tetanus toxoids, pertussis antigens (low ~~dose~~amounts) and three polio strains (vaccine composition is presented in Table 1). However dTap-IPV_B contained three of the five pertussis antigens in dTap-IPV_R at different doses. With no available immunological correlate of protection for pertussis, it was felt that the most clinically relevant comparator would be the historical immunogenicity [4] and efficacy [5] data originally supporting the licensure of this combination of pertussis antigens. The study design and endpoints

were decided in liaison with the European Medicines Agency (EMA) to meet requirements for Paediatric Investigation Plan approval.

Study Procedures

After initial contact and eligibility checking, the study comprised ~~of~~ two visits. At the first, written informed consent was obtained from the parent/legal guardian. Children were then randomised using GSK's central Internet Randomisation system (SBIR) (using a block size of ~~6~~six and a minimisation procedure accounting for centre) and allocated to receive either dTap-IPV_B (lots AC39B034B, AC39B026A, AC39B032A1) or dTap-IPV_R (lots DEXTA397AZ, DEXTA419AZ) in a 2:1 ratio as their pre-school dTap-IPV booster with both groups also receiving a dose of MMR booster (*Priorix*, GSK, Lots AMJRB892AZ, AMJRC160AZ, AD01B679C, AD01B801A, AD01B733B). After randomisation, the study was open label with both investigator and child's parents aware of their allocation. A blood sample (2.5mls) was drawn before vaccination. Vaccines were given intramuscularly dTap-IPV into the left deltoid, ~~-~~MMR into right deltoid, using 25mm 23G needles~~.~~, respectively. Solicited local and general symptoms occurring within 4four days following vaccination were recorded in diary cards as were other (unsolicited) adverse events (AEs) occurring within 30 days of vaccination. Information on serious adverse events (SAEs) occurring at any time-point during the study was also collected. The second and final study visit was 30 days (range: 21–48 days) after the first visit and comprised a second blood sample and collection of diary cards.

Laboratory Assays

All assays were performed at the laboratories of GSK Biologicals (Rixensart, Belgium) with laboratory staff blinded to the participant ~~groups.~~group. Antibodies against diphtheria toxoid (anti-diphtheria), tetanus toxoid (anti-tetanus) and pertussis components (pertussis toxoid [PT], filamentous haemagglutinin [FHA] and pertactin [PRN]) were measured by enzyme-linked immunosorbent assays (ELISA) developed in-house. Specific IgG antibodies to measles, mumps and rubella were measured using commercially available ELISAs following the manufacturers' instructions (Dade Behring,

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Germany). For both anti-diphtheria and tetanus thresholds for correlates of clinical protection were defined as 0.1 international units per millilitre (IU/ml), three times the lower quantification limit of the assays as previously demonstrated [6,7]. With no established serological correlates of protection for pertussis antigens [8–10], measles [11], mumps [12] or rubella, the thresholds for serological responses (positive: greater than or equal) were arbitrarily defined as the lower limits of the assays: 5 El.U/ml (all pertussis antigens), 150 mIU/ml, 231 U/ml and 4 IU/ml, respectively. Seroconversion was defined as seropositivity in the relevant assay in participants seronegative before vaccination. Antibody titres against poliovirus types 1, 2 and 3 were determined by the manufacturer's in-house virus micro-neutralisation test standardized according to WHO guidance [13] and were expressed as the reciprocal of the dilution resulting in 50% inhibition. Polio antibody titres greater than or equal to 1:8 dilution were considered seropositive and protective [14].

Statistics

Analysis of Immunogenicity

The protocol pre-defined standard non-inferiority criteria [15]. For diphtheria and tetanus responses - the upper 95% confidence interval (CI) limit of the (dTap-IPV$_R$ group minus dTap-IPV$_B$ group) difference between the percentage of participants in the two groups with post-vaccine antibody concentrations above the pre-defined protective threshold was to be less than 10%; for poliovirus types 1, 2 and 3 - the upper 95% CI limit of the ratio of geometric mean titres (GMTs) (dTap-IPV$_R$ group divided by dTap-IPV$_B$ group) was to be less than or equal to ~~2~~two and for pertussis antigens - the upper 95% CI limit of the ratio of geometric mean concentrations (GMCs) (historic DTaP data [4,5] divided by dTap-IPV$_B$ group in this study) was to be less than or equal to 1.5.

Secondary objectives were to describe the immunogenicity of both study vaccines in terms of seroprotection/seropositivity rates and GMCs/GMTs for all antigens, prior to and one month after booster vaccination; the percentage of participants with booster response to the pertussis and polio antigens; to describe the immune responses to the MMR vaccine in terms of seroconversion rates

against mumps, measles and rubella, one month after booster vaccination; and to assess the safety and reactogenicity of the study vaccines in terms of solicited symptoms, unsolicited ~~adverse events~~AEs and SAEs.

The primary analysis was based on the cohort of participants who completed the study according to protocol (ATP) for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated participants with serological results excluded from this ATP cohort was 5% or more, a second analysis of the total vaccinated cohort was to be performed to complement the ATP analysis.

Given the absence of serologic correlates of protection against pertussis, an immuno-bridging approach was used to assess immune responses to pertussis antigens, by extrapolating the efficacy of a vaccine against pertussis as demonstrated in infants to an older age group, as previously described.[16]

Safety

Safety and reactogenicity of the study vaccines were assessed in terms of solicited symptoms (local and general), unsolicited symptoms and SAEs. The intensity of solicited symptoms was graded as mild, moderate or severe (defined in Supplementary Table 2) and assessment of causality by vaccination was assessed by investigators. Additionally, p values for the difference in proportion of participants reporting the solicited symptom, and solicited and unsolicited symptoms combined, were computed post-hoc using the continuity adjusted chi-square method. However, the results should be interpreted with caution since there was no adjustment for multiplicity.

Sample size

It was calculated that 230 participants in the dTap-IPV_B group and 115 in the dTap-IPV_R group (a total of 345) would provide at least 90% overall power to reach conclusions on all the co-primary objectives simultaneously (with Bonferroni adjustment). Assuming a dropout rate of 10%, a total of 384 participants (256 participants in dTap-IPV_B group and 128 in dTap-IPV_R group) was chosen to

ensure that a sufficient number of evaluable participants ~~were~~was available for inclusion in the per protocol cohort for analysis of immunogenicity. Statistical analysis was done by GSK with independent statistical verification carried out by KJC statistics (www.kjcstatistics.com).

Results

The study ran from April 2011 to April 2012. 387 children were enrolled and 385 were vaccinated: 255 in dTap-IPV_B arm, 130 in dTap-IPV_R group (Figure 1). There were no significant differences in baseline characteristics in the ATP immunogenicity cohort: in both groups mean age at vaccination was 3.1 years with an equal proportion of genders and similar heritage (Table 2). ~~89.0% of participants were Caucasian.~~ The ATP immunogenicity cohort comprised 76.5%/73.8% (dTap-IPV_B /dTap-IPV_R, respectively) of the total vaccinated cohort mainly due to missing serological data through difficulties in obtaining blood samples. As per protocol, an additional total vaccinated cohort immunogenicity analysis was performed but found no significant difference in primary or secondary outcomes – results are provided as an online appendix (Supplementary Table 3 ~~Table5~~Table 5).

Immunogenicity results

For the study's primary inferential analyses; at 30 days post booster vaccination the non-inferiority criteria for the upper bounds of the 95% CI of differences between comparator vaccines were met for all component antigens (*i.e.*, seroprotection levels for diphtheria and tetanus, and GMCs ratio for polio and pertussis antigens) (Table 3).

For the secondary analyses the pre booster titres (Table 4) showed that prior to boosting for all antigens a high proportion of children in both groups had antibody levels below the defined seroprotection / seropositivity thresholds; with 16.7-34.5% for diphtheria and tetanus and 30.4-40.6% for polio. For pertussis 29.4-81.9% of participants had IgG titres below the pre-determined optimal serological thresholds. For all antigens, 30 days post dTap-IPV booster vaccination the proportions of seroprotected / seropositive children had risen to >99% indicating adequate serological response. Comparing antibody GMC / GMT between the two study vaccines at one

month post dTap-IPV vaccination (Table 4), marginally higher point estimates for diphtheria, tetanus, Polio3 and PRN after dTap-IPV_R vaccination, and marginally higher point estimates for the Polio1, Polio2, PT and FHA after dTap-IPV_B vaccination were observed.

Prior to boosting, evidence of antibodies persistence for the MMR vaccine (Table 4) was observed for at least 89.7% of children meeting the immunological criteria for measles, mumps or rubella in each group. One month after the MMR booster dose all children had antibody titres above the defined immunological criteria with no significant differences in GMTs between groups.

Safety Results

In the ~~4~~four day post vaccination period, 216/255 (84.7%; dTap-IPV_B) and 108/130 (83.1%; dTap-IPV_R) (p=0.79) of participants reported at least one solicited symptom or unsolicited ~~adverse event.~~AE. For both vaccines redness and pain were the most commonly reported. Severe (grade 3) symptoms were reported by a maximum of 11.0% (redness in the dTap-IPV_B group) and 18.4% (redness in the dTap-IPV_R group) (p=0.08) of participants (Table 5).

During the 31-day (Days 0-30) post vaccination unsolicited reporting period, 88/255 (34.5%; dTap-IPV_B) and 36/130 (27.7%; dTap-IPV_R) (p=0.22) of participants reported at least one ~~adverse event~~AE of which 4.7% and 4.6% (p=1.0) respectively were considered to be severe.

Diarrhoea and vomiting, reported for 9/255 (3.5%) participants were the most frequently reported unsolicited AE in the dTap-IPV_B group while rash, reported for 6/130 (4.6%) participants was the most frequently reported unsolicited AE in the dTap-IPV_R group.

One SAE was reported during the whole clinical study duration; ~~*i.e.*~~ pneumonia requiring hospitalisation reported for one participant in the dTap-IPV_B arm. This was felt not to be causally related to vaccination by the investigator. No study participants withdrew from the study due to an ~~adverse event or serious adverse event~~AE or SAE.

Discussion

This study compares the immunogenicity and ~~adverse events~~AEs of two alternative dTap-IPV vaccines for use as a pre-school booster in the UK vaccine schedule. According to the primary outcomes, the ~~vaccines were~~study vaccine response was non-inferior to its comparator at one month post-vaccination – both vaccines boosting serological responses above accepted thresholds. There were no significant differences in solicited or unsolicited ~~side effects~~local reactions between the two vaccines, with mild redness and pain reported in 49.8-58.4% of cases.

In this study which followed the UK infant schedule in use at that time, we found that by the age of ~~3.5~~three and a half years, almost a third of children had antibody levels ~~of immunity~~ that had waned below desired levels for at least one vaccine component (Table 4) – reinforcing the requirement for a pre-school booster. This is in line with a previous ~~studies~~study showing serological evidence of protection from UK primary course DTaP ~~has~~had substantially waned by the age of ~~3-4yrs~~three to four years [~~16~~17].

For diphtheria, although post-booster all children had antibody levels above threshold, GMCs were marginally higher for dTap-IPV$_R$ than dTap-IPV$_B$ but still 80-fold above the level considered protective. Due to the long half–life of these antibodies, this degree of boosting above the protective threshold has been shown to remain clinically effective for ten years, based on a mathematical model [~~17~~18].

With no agreed immunological correlate of protection against pertussis, it was not appropriate to simply compare the antibody response between the two study vaccines because dTap-IPV$_R$ contains two additional pertussis antigens. Accordingly, our pre-defined primary analysis was to compare the immune responses to the booster dose of dTap-IPV$_B$ given in this study against historical immunogenicity data from the original study that demonstrated clinical effectiveness for this combination of antigens. This primary analysis showed non-inferiority. In a secondary analysis we compared the GMCs for the antigens common to both vaccines. All titres were significantly boosted

but, as might be expected, with minor difference between the vaccines. GMCs for PT and FHA were higher for dTap-IPV$_B$ than dTap-IPV$_R$, while the reverse was true for PRN. Clearly both vaccines used as boosters can provide ~~clinical protection.~~a serological response. However even with adequate pertussis vaccine responses, data from the ~~USA~~US have shown rapid waning of clinical protection (27% per year after the ~~5th~~fifth dose of pertussis vaccine) [~~18~~19] leading ~~to~~ the ~~introduction of~~US to introduce an adolescent booster dose for pertussis [~~19~~20].Further investigations would need to be done to determine if the additional pertussis antigen contained in dTap-IPV$_R$ resulted in any significant difference in the rate of waning between the vaccines.

The limitation of this study is that whilst randomised, because of the difference in the visual aspects of the study vaccines, the study was designed to be open label. This meant that for ~~adverse event~~AE recording the parents were not blinded to the study arm – despite this there were no significant differences between AE outcomes. Since the study the UK infant vaccine schedule has changed with the introduction of the rotavirus and meningococcal B immunisation programmes. In response to rising rates of neonatal pertussis, in 2012 the UK introduced maternal dTap vaccination at 28-32 weeks gestation. This has been highly successful with significant reduction in the number of cases.[~~20~~21] However there is some evidence that increased maternal titres may adversely affect early infant vaccine responses,[~~21,~~22, 23] increasing the importance of an effective the pre-school booster.

In conclusion, we found dTap-IPV$_B$ to be non-inferior to dTap-IPV$_R$ with all children ~~protected after boosting.~~making an equivalent immune response after boosting indicative of protection being afforded at the same level as demonstrated now in the population as monitored by national surveillance systems. There were minor differences between vaccines for individual antigens but these are unlikely to be of any clinical significance.

Trademark statement

Boostrix-IPV, *Infanrix* and *Priorix* are trademarks of the GSK group of companies. *Repevax* is a trade mark of Sanofi-Pasteur.

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Declaration of interest

R Marlow declares receiving conference travel expenses from GSK group of companies in 2014.

A Finn received grants paid to his institution from Novartis (Novartis Vaccines Division was subsequently acquired by the GSK group of companies), GSK group of companies and Sanofi Pasteur MSD for studies outside the submitted work. Owing to his membership on the Joint Committee on Vaccination and Immunisation for the United Kingdom Department of Health, Adam Finn no longer gives lectures or undertakes advisory work for industry, either paid or unpaid.

M Snape reports grants from GSK group of companies, Novartis, Johnson and Johnson, MedImmune where he acted as investigator for clinical vaccine studies; speaker fees from Novartis; and consultancy fees from MedImmune.

A J Pollard reports previous grants from Pfizer and Okairos in the past 36 months. His department received unrestricted educational grants from Pfizer/GSK/Astra Zeneca in July 2016 and Gilead/MSD/GSK/Astra Zeneca in June 2017 for a course on Infection and Immunity in Children. A J Pollard is chair of the UK Department of Health's (DH) Joint Committee on Vaccination and Immunization (JCVI) and the scientific advisory group on vaccines for the European Medicines Agency and is a member of the WHO's SAGE; the views presented in this manuscript do not necessarily represent the views of DH JCVI, EMA or WHO.

S N Faust reports grants from GSK group of companies; S N Faust has been advisory board member to vaccine and antimicrobial manufacturers (GSK, AstraZeneca, Pfizer, Novartis, Sanofi, Cubist Pharmaceuticals, Actelion Pharmaceuticals, Astellas, Merck).

M Snape, A Pollard, S N Faust and R Tomlinson declare that all honoraria and fees were paid to the employing institution and no personal fee or honoraria of any kind were received at any time.

S Kuriyakose and N Mesaros declare they are employed by the GSK group of companies; N Mesaros holds shares in the GSK group of companies. HH Han was a GSK employee at the time the study was conducted; she is now employee of Takeda Pharmaceuticals.

R Tomlinson declares receipt of recruitment fees from GSK; all honoraria were paid to the employing institution (Royal Devon & Exeter NHS Trust) and no personal fee or honoraria of any kind were received at any time.

Authors´ contributions

R Marlow, A Finn, A J Pollard, S N Faust, M Snape, S Kuriyakose were involved in the conception and design of the study; R Marlow , A Finn, A J Pollard, M Snape, S N Faust, R Tomlinson, S Kuriyakose, N Mesaros and HH Han were involved in data acquisition, analysis or interpretation. R Marlow

264 produced the first draft of the manuscript, all authors revised the work critically, approved the final

265 version to be published and take full accountability for all aspects of the work.

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Figures

Figure 1 - Participant flow chart

Footnote: ATP, according to protocol; dTap-IPV$_B$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (*Boostrix-IPV*); dTap-IPV$_R$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (*Repevax*)

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Table_1

Table 1 – Comparison of vaccine components

Vaccine	Diphtheria toxoid (IU)	Tetanus toxoid (IU)	Pertussis antigens (µg)				Polio antigens (D-antigen units)			Adjuvant
			PT	FHA	PRN	Fimbriae 2/3	1	2	3	
dTap-IPV$_R$	≥2	20	2.5	5	3	5	40	8	32	Aluminium phosphate: 0.33 mg Al^{3+}
dTap-IPV$_B$	≥2	20	8	8	2.5	-	40	8	32	Aluminium hydroxide and phosphate: 0.5 mg Al^{3+}
DTaP	30	40	25	25	8	-	-	-	-	Aluminium hydroxide: 0.5 mg Al^{3+}

Footnote: IU, international units; PT, pertussis toxoid; FHA, filamentous haemagglutinin; PRN, pertactin; dTap-IPV$_B$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (Boostrix); dTap-IPV$_R$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (Repevax); DTaP, diphtheria-tetanus-acellular pertussis vaccine (Infanrix)

Table 2 – Demographic characteristics (ATP cohort for immunogenicity)

	dTap-IPV$_B$ group (N = 195)	**dTap-IPV$_R$ group** (N = 96)
Age (years) at vaccination		
Mean (SD)	3.1 (0.2)	3.1 (0.2)
Range (min–max)	3-4	3-4
Female/male, %	48.7/51.3	53.1/46.9
Heritage, n (%)		
African / African American	1 (0.5)	3 (3.1)
Asian – Central / South Asian	3 (1.5)	4 (4.2)
Asian – South East Asian	2 (1.0)	0 (0)
White – Arabic / North African	1 (0.5)	0 (0)
White – Caucasian / European	175 (89.7)	84 (87.5)
Other	13 (6.7)	5 (5.2)

Footnote: ATP, according to protocol; N, number of participants in each group; n, number of participants in a given category; SD, standard deviation; min, minimum; max, maximum; dTap-IPV$_B$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (Boostrix-IPV); dTap-IPV$_R$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (Repevax).

Table 3 – Responses to vaccination and calculation of criteria for non-inferiority (inferential analyses)

	Vaccine Antigen	Control* data	(N)	dTap-IPV$_B$ group data	(N)		Criteria for non-inferiority
						Control group minus dTap-IPV$_B$ group % (95% CI)	
Group response rate (%)	Diphtheria	100	(90)	99.4	(177)	0.56% (-3.55; **3.14**)	
	Tetanus	100	(90)	98.3	(176)	1.70% (-2.43; **4.90**)	UL<10%
						Control group / dTap-IPV$_B$ group	
GMTs	Polio 1	1983.1	(63)	2175.6	(131)	0.91 (0.65; **1.28**)	
	Polio 2	2168.7	(61)	2796.9	(100)	0.78 (0.54; **1.12**)	UL<2
	Polio 3	4522.5	(68)	3468.8	(126)	1.30 (0.93; **1.84**)	
						DTaP-APV039 / dTap-IPV$_B$ group	
GMCs (El.U/ml)	PT	45.7	(2884)	69.8	(203)	0.65 (0.59; **0.72**)	
	FHA	83.6	(685)	362.1	(204)	0.23 (0.20; **0.27**)	UL<1.5
	PRN	112.3	(631)	148.6	(204)	0.76 (0.64; **0.89**)	

Footnote: The group difference in booster response to the diphtheria and tetanus antigens and the adjusted GMT ratios between groups for the poliovirus types 1, 2 and 3 antigens, one month post-booster vaccinations are based on the according-to-protocol cohorts. The GMC ratios between groups for the anti-PT, anti-FHA and anti-PRN antigens one month post-booster vaccination is based on the total vaccinated cohort. *Control data represent the data from the dTap-IPV$_R$ group for diphtheria, tetanus and polio types 1, 2 and 3 antigens, and from the DTaP-APV039 study for the pertussis antigens (PT, FHA and PRN). Bold values represent that the statistical criterion for non-inferiority was met.

CI, confidence interval; GMC, geometric mean concentration; GMT, geometric mean titre adjusted for baseline titre; El.U/ml, Enzyme-Linked Immunosorbent Assay units per millilitre; UL, upper limit of the 95% confidence interval; N, number of participants with pre- and post-vaccination results available; PT, pertussis toxoid; FHA, filamentous haemagglutinin; PRN, pertactin; dTap-IPV$_B$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (Boostrix-IPV); dTap-IPV$_R$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (Repevax); DTaP, diphtheria-tetanus-acellular pertussis vaccine (Infanrix)

Table 4 – According to protocol pre-post vaccination serology results as proportion above serological threshold and pre-post vaccination geometric mean concentrations / titres (descriptive analyses)

Vaccine antigen			dTap-IPV$_B$ group		dTap-IPV$_R$ group	
			Pre (95%CI)	Post (95%CI)	Pre (95%CI)	Post (95%CI)
Diphtheria		(% ≥ 0.1 IU/ml)	76.8 (69.9-82.8)	100 (98.1-100)	83.3 (74.0-90.4)	100 (96.2-100)
		(GMC IU/ml)	0.228 (0.194-0.267)	8.113 (7.259-9.068)	0.259 (0.209-0.320)	11.948 (10.003-14.271)
Tetanus		(% ≥ 0.1 IU/ml)	65.5 (58.0-72.5)	100 (98.1-100)	70.0 (59.4-79.2)	100 (96.2-100)
		(GMC IU/ml)	0.209 (0.173-0.253)	6.787 (5.961-7.727)	0.241 (0.184-0.315)	9.194 (7.565-11.175)
Pertussis	PT	(% ≥ 5 El.U/ml)	18.1 (12.7-24.7)	100 (98.1-100)	20.0 (12.3-29.8)	100 (96.2-100)
		(GMC El.U/ml)	3.4 (3.0-3.9)	70.1 (62.2-79.0)	3.2 (2.9-3.6)	47.8 (39.9-57.3)
	FHA	(% ≥ 5 El.U/ml)	64.4 (56.8-71.5)	100 (98.1-100)	70.6 (59.7-80.0)	100 (96.2-100)
		(GMC El.U/ml)	12.9 (10.0-16.6)	358.3 (312.5-410.8)	10.7 (7.9-14.5)	164.8 (138.5-196.1)
	PRN	(% ≥ 5 El.U/ml)	34.9 (27.8-42.4)	99.5 (97.2-100)	40.7 (30.5-51.5)	100 (96.2-100)
		(GMC El.U/ml)	4.3 (3.8-5.0)	151.4 (127.5-179.6)	4.3 (3.7-5.0)	209.8 (168.5-261.3)
Polio	1	(%≥ 8 ED_{50})	59.4 (51.3-67.1)	99.4 (96.5-100)	63.6 (51.9-74.3)	100 (95.2-100)
		(GMT ED_{50})	12.8 (10.6-15.5)	2183.3 (1812.4-2630.1)	13.2 (10.2-17.1)	1876.1 (1472.8-2389.7)
	2	(%≥ 8 ED_{50})	68.6 (60.7-75.7)	99.2 (95.6-100)	69.6 (58.2-79.5)	100 (94.9-100)
		(GMT ED_{50})	15.5 (12.8-18.8)	2693.1 (2176.3-3332.5)	14.6 (11.3-18.8)	2203.8 (1681.0-2889.4)
	3	(%≥ 8 ED_{50})	64.1 (56.0-71.6)	99.4 (96.5-100)	59.5 (47.9-70.4)	100 (95.5-100)
		(GMT ED_{50})	15.4 (12.7-18.8)	3762.4 (3080.9-4594.6)	14.5 (10.4-20.1)	4185.1 (3318.3-5278.3)
Measles		(% ≥ 150 mIU/ml)	97.5 (93.7-99.3)	100 (97.3-100)	97.4 (90.8-99.7)	100 (94.7-100)
		GMC mIU/mL	2644.0 (2261.3-3091.6)	3817.7 (3422.3-4258.8)	2702.6 (2146.0-3403.6)	3798.0 (3262.6-4421.1)
Mumps		% ≥ 231 U/ml	89.7 (83.9-94.0)	100 (97.3-100)	90.8 (81.9-96.2)	100 (94.7-100)
		GMC U/mL	1035.3 (869.8-1232.3)	6801.9 (6155.0-7516.8)	971.7 (752.1-1255.5)	6219.4 (5365.8-7208.8)
Rubella		% ≥ 4 IU/ml	100 (97.7-100)	100 (97.3-100)	100 (95.3-100)	100 (94.7-100)
		GMC IU/mL	66.5 (59.1-74.8)	134.3 (120.7-149.4)	72.6 (59.8-88.1)	130.3 (111.7-152.0)

Footnote: CI, confidence interval; GMC, geometric mean concentration; GMT, geometric mean titre; El.U/ml, Enzyme-Linked Immunosorbent Assay units per millilitre; IU/ml, international units per millilitre; ED_{50}, median effective dose; mIU/ml, milli-international units per millilitre; MMR, mumps-measles-rubella; N, number of participants with available results; PT, pertussis toxoid; FHA, filamentous haemagglutinin; PRN, pertactin; U/ml, units per millilitre; dTap-IPV$_B$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (Boostrix-IPV); dTap-IPV$_R$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (Repevax); pre, pre-booster vaccination blood sampling; post, post-booster vaccination blood sampling

Table 5 – Solicited local and general symptom rates for each vaccine in first 4 days after vaccination as both percentage and absolute number of participants.

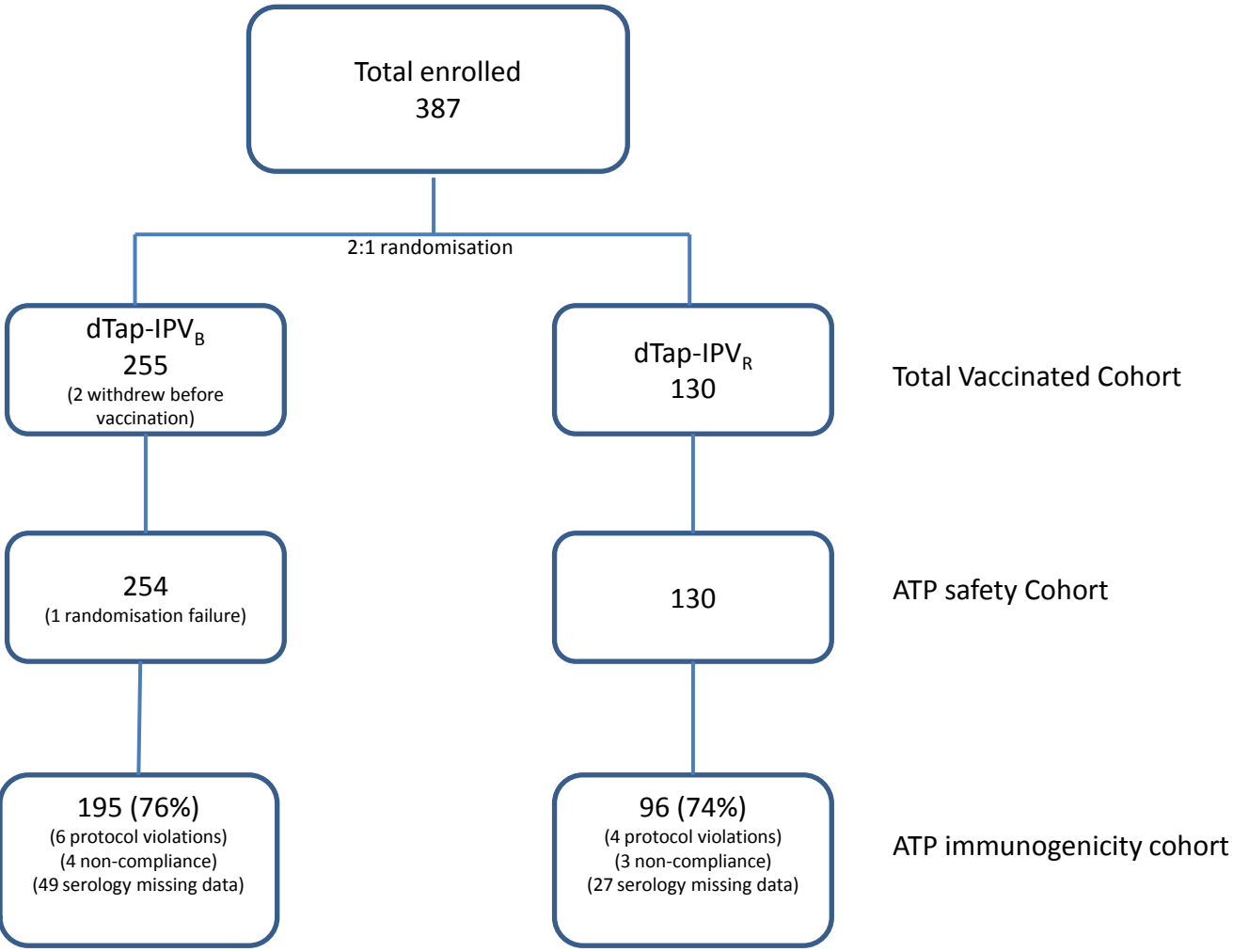
	All reactions			Severe (Grade 3) reactions		
	dTap-IPV$_B$ group (N=255)	**dTap-IPV$_R$ group (N=125)**	**p**	**dTap-IPV$_B$ group (N=255)**	**dTap-IPV$_R$ group (N=125)**	**p**
Pain, % (n)	49.8 (127)	56.0 (70)	0.30	1.2 (3)	4.8 (6)	0.07
Redness, % (n)	57.3 (146)	58.4 (73)	0.92	11.0 (28)	18.4 (23)	0.07
Swelling, % (n)	36.1 (92)	42.4 (53)	0.28	7.1 (18)	13.6 (17)	0.06
Irritability, % (n)	42.0 (107)	39.2 (49)	0.69	1.6 (4)	0.8 (1)	0.89
Drowsiness, % (n)	30.2 (77)	31.2 (39)	0.94	1.6 (4)	0.8 (1)	0.89
Loss of appetite, % (n)	26.3 (67)	24 (30)	0.72	2.4 (6)	2.4 (3)	1.00
Fever, % (n)	7.1 (18)	7.2 (9)	1.00	1.6 (4)	0.8 (1)	0.89

Footnote: Number in brackets represents the number of cases.

N, number of participants with available results; n, number of participants reporting the symptom; dTap-IPV$_B$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (Boostrix-IPV); dTap-IPV$_R$, reduced diphtheria-tetanus-acellular pertussis-polio vaccine (Repevax). p values or the difference in proportion of participants reporting the solicited symptom, and solicited and unsolicited symptoms combined, were computed using the continuity adjusted chi-square method. However, the results should be interpreted with caution since there was no adjustment for multiplicity.

Severe (Grade 3) reactions were defined as: Pain (Cried when limb was moved/spontaneously painful), Swelling / Redness (>20mm in diameter), Irritability (Crying that could not be comforted/prevented normal activity), Drowsiness (Drowsiness that prevented normal activity), Loss of appetite (Did not eat at all), Fever (axillary temperature >39.0°C).

Figure_1


Total enrolled
387
2:1 randomisation
dTap-IPV$_B$
255
(2 withdrew before vaccination)
dTap-IPV$_R$
130
Total Vaccinated Cohort
254
(1 randomisation failure)
130
ATP safety Cohort
195 (76%)
(6 protocol violations)
(4 non-compliance)
(49 serology missing data)
96 (74%)
(4 protocol violations)
(3 non-compliance)
(27 serology missing data)
ATP immunogenicity cohort

Consort checklist

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