Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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ARTICLE INFO

Article history:
Received 8 October 2017
Received in revised form 7 March 2018
Accepted 9 March 2018
Available online xxxx

Keywords:
Preschool booster
dTap-IPV
RCT
Child
UK

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

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.

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https://doi.org/10.1016/j.vaccine.2018.03.021
0264-410X/

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)

1. 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 12–18 m (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 12–18 m; 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].

2. Methods

2.1. 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).

2.2. 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.

2.3. 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 (2.5 mls) was drawn before vaccination. Vaccines were given intramuscularly dTap-IPV into the left deltoid, MMR into right deltoid, using 25 mm 23 G 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.

2.4. 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]

Please cite this article in press as: Marlow R et al. 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. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.03.021