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BMJ Open OPTIMUM study protocol: an adaptive randomised controlled trial of a mixed whole-cell/acellular pertussis vaccine schedule

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ABSTRACT

Introduction Combination vaccines containing whole-cell pertussis antigens were phased out from the Australian national immunisation programme between 1997 and 1999 and replaced by the less reactogenic acellular pertussis (aP) antigens. In a large case-control study of Australian children born during the transition period, those with allergist diagnosed IgE-mediated food allergy were less likely to have received whole-cell vaccine in early infancy than matched population controls (OR: 0.77 (95% CI, 0.62 to 0.95)). We hypothesise that a single dose of whole-cell vaccine in early infancy is protective against IgE-mediated food allergy.

Methods and analysis This adaptive double-blind randomised controlled trial is investigating whether a mixed whole-cell/aP vaccine schedule prevents allergic disease in the first year of life. The primary outcome is IgE-mediated food allergy by 12 months of age. Secondary outcomes include new onset of atopic dermatitis by 6 or 12 months of age; sensitisation to at least one allergen by 12 months of age; seroconversion in anti-pertussis toxin IgG titres after vaccination with aP booster at 18 months of age; and solicited systemic and local adverse events following immunisation with pertussis-containing vaccines. Analyses will be performed using a Bayesian group sequential design.

Ethics and dissemination This study has been approved by the Child and Adolescent Health Service Human Research Ethics Committee, Perth, Western Australia (RGS 00019). The investigators will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki and with the International Conference on Harmonisation Guidelines for Good Clinical Practice. Individual consent will be requested. Parents will be reimbursed reasonable travel and parking costs to attend the study visits. The dissemination of these research findings will follow the National Health and Medical Research Council of Australia Open Access Policy. **Trial registration number** ACTRN12617000065392p.

INTRODUCTION

In comparison with those from other countries, Australian children have one of the

Strengths and limitations of this study

- The trial is powered to detect a meaningful reduction in food allergy by 12 months, a clinically important outcome.
- The trial uses a Bayesian group sequential design with prespecified stopping rules; compared with alternative trial designs, this approach may be more efficient and more likely to yield a conclusive answer to the research question.
- This trial will not only provide safety and clinical efficacy data it may also offer mechanistic insights into the non-specific effects of vaccination on the developing immune system.
- As this trial is being conducted in a setting with very high coverage for maternal pertussis vaccination, we will not be able to examine the impact of maternally derived antibodies on infant immune responses to priming with pertussis and non-pertussis vaccine antigens.

highest prevalences of IgE-mediated food allergy in the first year of life¹ and experience high rates of hospital-coded food-related anaphylaxis before 4 years of age.²

The development of oral tolerance to food allergens is likely to be food and dose-dependent, may have specific optimal windows of exposure and may be influenced by the integrity of the epithelial skin barrier.³ The timing of introduction of peanuts for the primary and secondary prevention of IgE-mediated peanut allergy was examined in the Learning Early about Peanut Allergy (LEAP) trial.⁴ This showed that the introduction of peanuts between 4 and 11 months old decreased the risk of IgE-mediated peanut allergy by 80% at 5 years old in children with a history of severe atopic dermatitis, egg allergy or both, compared with children who avoided

all dietary peanut for 5 years.⁴ Meta-analysis suggests benefit from the early introduction of both, peanut and egg for the prevention of food allergy.⁵ This has informed infant feeding guidelines and since 2016 the Australasian Society of Clinical Immunology and Allergy, among other expert groups, has supported their introduction in the first year of life.⁶ This advice has been extended to complementary feeding with dairy and wheat products,⁶ although it remains uncertain whether this approach will decrease the prevalence of all IgE-mediated food allergy.

Pertussis-containing vaccines

The widespread use of whole-cell pertussis (wP)-containing vaccines through the WHO Extended Program of Immunisation commenced in 1974.⁷ These wP formulations were initially provided as combination vaccines with diphtheria and tetanus toxoids but now wP-containing vaccines are mainly manufactured as multicomponent formulations that also include *Haemophilus influenzae* type b (Hib) and hepatitis B (HB) antigens (DTwP-Hib-HB).

wP formulations contain killed *Bordetella pertussis* organisms. While they are inexpensive and still used in most countries, fever, irritability and other inflammatory manifestations (reactogenicity) driven by the cell wall components, as well as earlier (subsequently disproved) concerns about rare neurologic reactions, led to the development of aP vaccines in the late 1970s. aP-containing vaccines first replaced wP-containing schedules in Japan from 1981,⁸ followed by other high-income countries from the mid-1990s.⁹ Whereas aP formulations are better tolerated than wP,^{10 11} the reactogenicity of wP-only primary vaccine courses appears to be attenuated if given in an accelerated fashion and when the first dose is administered before the age of 3 months.¹² Although no significant differences have been observed in the total number of serious adverse events (SAEs) within 60 days and within 6 months of either type of pertussis-containing vaccine,^{13 14} a lower risk of convulsions (RR: 0.47 (95% CI: 0.31 to 0.73)) and hypotonic hyporesponsive episodes (RR: 0.26 (95% CI: 0.08 to 0.81)) has been reported in aP compared with wP vaccinees.¹¹

In Australia, the change-over to primary immunisation with aP-containing formulations occurred between 1997 and 1999. Among Australian children who completed a three-dose primary course of pertussis vaccines during the period of transition, those primed with a first dose of wP (followed by doses of either aP or wP) appeared to have lower risk of pertussis in adolescence than those who were primed with aP-containing vaccines only.¹⁵

While aP vaccines induce a T helper 2 (Th₂)-predominant phenotype, pathogen-associated molecular patterns within wP appear to elicit Th₁/Th₁₇ downstream polarisation.¹⁶ These differential immune phenotypes have been shown to persist into adulthood, despite repeated aP booster doses.¹⁷

Boosted IgE responses specific to coadministered tetanus and diphtheria toxoids have been reported in infants primed with aP doses only but not in infants

primed with wP or mixed wP/aP schedules.^{18 19} IgE mediated sensitisation to egg and milk antigens,^{19 20} as well as the induction of type 2 cytokines to beta-lactoglobulin have also been described in aP-only primed infants. The clinical importance of these findings are yet to be determined.

Rationale for the trial

In the first year of life, there occurs a natural shift from an inherently skewed Th₂ microenvironment in neonates, towards Th₁₇ and then Th₁ immune responses. This phase of the ontogeny of early life immunity coincides with the postnatal development of oral tolerance and represents a biologically plausible opportunity for targeting prevention of IgE-mediated food allergy.

An initial ecological analysis of publicly available hospitalisation data suggested that in Australia, the phasing out of wP in favour of aP-only regimes for scheduled doses at 2, 4 and 6 months old coincided with an apparent rise in the incidence of admissions to hospital coded as food-associated anaphylaxis among young children. A case-control study subsequently found that children primed with a first dose of wP were less likely to be diagnosed with IgE-mediated food allergy than age-matched children primed with aP only (OR: 0.77 (95% CI, 0.62 to 0.95)).²¹

We therefore hypothesise that priming with a first dose of wP helps to induce an allergy protective immunophenotype in susceptible individuals, while still being safe and well tolerated. The biological plausibility of this off-target effect is supported by the known pro-Th₁/Th₁₇ immunomodulating properties of some cellular components within wP formulations, which may help to balance the early life Th₂-biased adaptive immune responses. This may in turn reduce the susceptibility to IgE-mediated food allergy in those individuals who are more prone to maintain a Th₂-biased responses into later infancy.

Although the rationale for our study is supported by both immunological and clinical observational data from Australia,^{19 21} we note that a Swedish trial of children primed with DTwP versus DTaP in the early 1990s found no overall protection against IgE-mediated food allergy or food sensitisation.²² In that trial, food allergy was ascertained by parent-reported symptoms coupled with demonstration of IgE antibodies to the food of interest; skin prick testing only included milk and egg white antigens at the age of 7 months, and only egg white at 2.5 years of age; and no breakdown in skin prick positivity by food or type of food allergy was provided.²² Similarly, no association between the type of pertussis-containing vaccine and development of IgE-mediated food allergy was found in a birth cohort of the Isle of Wight.²³ In post hoc analyses of trial data from a cohort of Australian children, recipients of a first dose of wP did not appear to have a lower risk of parent-reported asthma, atopic rhinitis or atopic dermatitis, at the ages of 5, 8 and 11.5 years, compared with those who received a first dose of aP.²⁴ In the same cohort, children primed with at least

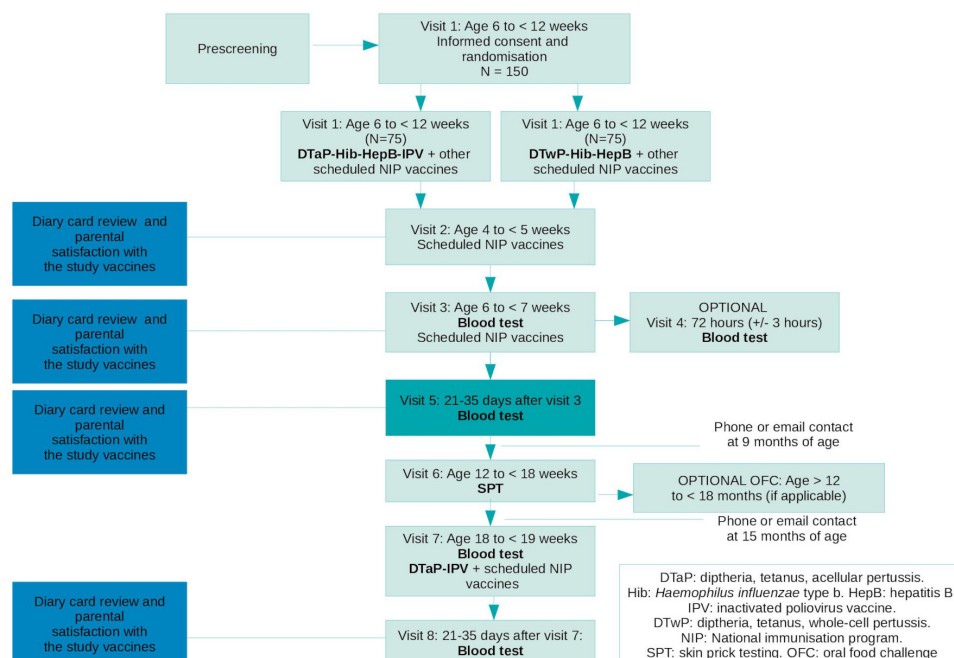


Figure 1 Trial flowchart. Stage 1. DTaP, diptheria, tetanus, acellular pertussis; DTwP, diptheria, tetanus, whole-cell pertussis; Hib, *Haemophilus influenzae* type b; HepB, hepatitis B; IPV, inactivated poliovirus vaccine; NIP, National immunisation program; OFC, oral food challenge; SPT, skin prick testing.

one dose of wP had an apparent higher risk of peanut IgE-mediated sensitisation across the above-mentioned ages compared with recipients of aP-only doses.²⁴ Neither study was adequately powered to exclude a clinically important difference in their chosen endpoints.

Here we describe the protocol of the Optimising Immunisation Using Mixed Schedules (OPTIMUM) study, an adaptive clinical trial to investigate the effect of wP for the prevention of IgE-mediated food allergy.

METHODS AND ANALYSIS

Design

OPTIMUM is an investigator-initiated phase IV, two-stage, multisite, parallel, double-blind, adaptive, randomised controlled trial of a single dose of wP given at the age of 6 to <12 weeks, followed by aP at 4 and 6 months, versus three aP doses only, for the prevention of IgE-mediated food allergy. The procedures for enrolment, intervention and the selection of primary and secondary endpoints are based on the principles of pragmatic Bayesian sequential trial design. The trial flowcharts (figures 1 and 2) and the timeline of the study visits (tables 1 and 2) are presented below.

Objectives

The primary objective is to determine whether, compared with the Australian standard of care of three priming doses of aP, a mixed wP/aP schedule (first dose of wP followed by doses of aP) protects against the development of IgE-mediated food allergy.

Study settings

OPTIMUM is being conducted at the Perth Children's Hospital in Perth (PCH), Western Australia. Recruitment for stage 1 started in January 2018, with 150th participant randomised in January 2020. Stage 2 will also include sites in Sydney and Melbourne.

Patient and public involvement

Patients and consumers were involved in the design and conduct of this research. The proposed project was presented to a consumer reference committee prior to submission of the grant and following the award of funding. A consumer representative sits on the study steering committee.

Outcomes

The primary endpoint is IgE-mediated food allergy by the age of 12 months and confirmed, where necessary, before 18 months. For the purpose of this trial, the study participant will be considered to have reached the primary endpoint if there is evidence of sensitisation to a food on skin prick test, and either:

1. Unequivocal IgE-mediated food allergy, defined as (1) a positive oral food challenge or (2) clinician-diagnosed food anaphylaxis, with symptoms affecting at least 2 of the following: skin, gastrointestinal tract, respiratory tract, cardiovascular system, or
2. Highly probable IgE-mediated food allergy, defined as a history of food allergic reaction consistent with PRACTALL criteria.²⁵

Secondary endpoints include (1) parent-reported clinician-diagnosed new onset of atopic dermatitis by 6

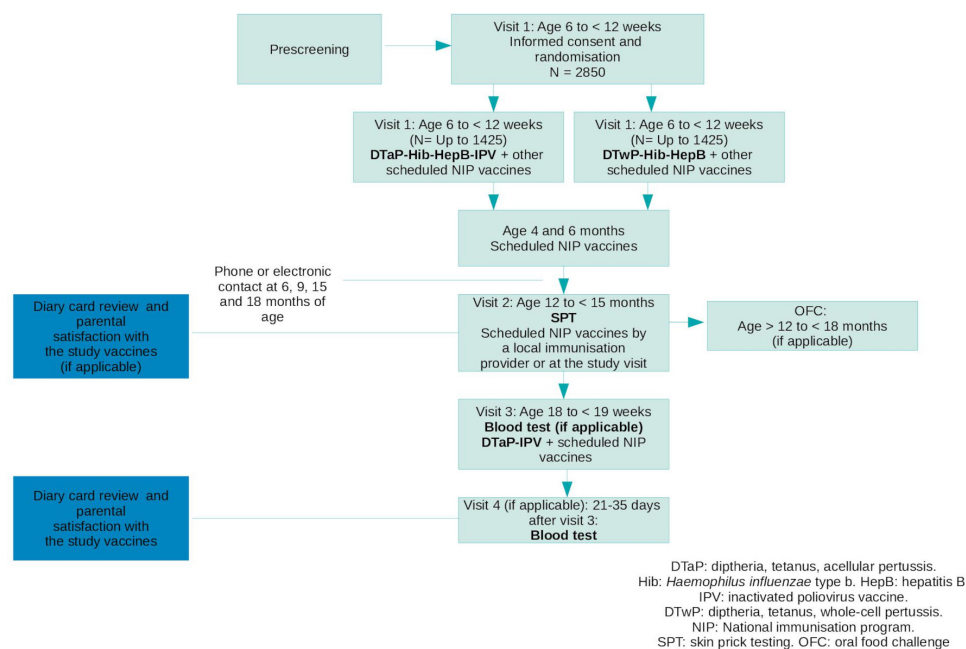


Figure 2 Trial flowchart. Stage 2. DTaP, diphtheria, tetanus, acellular pertussis; DTwP, diphtheria, tetanus, whole-cell pertussis; Hib, *Haemophilus influenzae* type b; HepB, hepatitis B; IPV, inactivated poliovirus vaccine; NIP, National immunisation program; OFC, oral food challenge; SPT, skin prick testing.

or 12 months of age with a positive skin prick test to any allergen by 12 months of age (a weal measuring 1 mm greater than the negative control); (2) a fourfold or greater rise in pertussis toxin-specific IgG 21–35 days after a booster dose of aP at 18 months of age; (3) sensitisation to at least one allergen by 12 months of age, defined as a skin prick test with a weal measuring (a) 1 or (b) 3 mm greater than the negative control; (4) solicited local and systemic adverse events following immunisation with pertussis-containing vaccines and (5) vaccination experience reported as either unsatisfactory or very unsatisfactory on a 5-point Likert scale.

Additional stage 1-specific secondary endpoints are described in [table 3](#).

Participants

In Perth, Western Australia, the identification of potentially eligible study participants is carried out by trained staff during the antenatal and immediate postnatal periods in Saint John of God (SJOG) Subiaco and SJOG Mount Lawley hospitals, as well as through expressions of interest received via SJOG Murdoch Hospital and via email. Similar procedures will be implemented for the enrolment of study participants in Sydney and Melbourne.

Healthy infants aged 6 to <12 weeks old and born ≥ 32 weeks' gestation are eligible for enrolment. Additional eligibility criteria include: (1) parent with capacity to understand the information sheet, consent form and study-related procedures; (2) access to a telephone; (3) permission for other parties involved in the child's treatment and the Australian Immunisation Register (AIR) to be notified of their participation in this trial; (4) consent for the study staff to access the child's immunisation history from AIR and/or local provider and (5) consent

to obtain medical information from the child's healthcare provider, pathology or medical records from enrolment until 1 month after the 18-month vaccines. Exclusion criteria are (1) history of pre-existing IgE-mediated food allergy and/or (2) pertussis infection; (3) receipt of any prior vaccine except for a single birth dose of HB vaccine within the first 7 days of life; (4) contraindication or allergy to any vaccine or vaccine components; (5) contraindication to paracetamol; (6) receipt or planned receipt of other investigational medicinal products until the final study visit; (7) receipt or planned receipt of any non-routine vaccines within 14 days after the first dose of pertussis-containing vaccine; (8) receipt of more than 2 weeks of immunosuppressants or immune modifying drugs; (9) serious chronic illness including severe congenital anomalies affecting heart, brain and/or lungs; (10) history of any neurologic disorders or seizures; (11) administration of immunoglobulins and/or any blood products since birth or planned administration during the study period; (12) planned travel to any country that remains at risk of a poliomyelitis transmission at any time before 19 months of age.

Temporary exclusion criteria for vaccination visits include (1) fever; (2) acute moderate or severe illness without fever; and (3) for visits 2, 3 and 7 (stage 1 only) receipt of any vaccination within the preceding 14 days.

Study procedures

Baseline assessment

Participants are enrolled by a medical officer. On the day of the first study visit, written consent is obtained, and eligibility confirmed prior to randomisation. Demographics and other baseline data are recorded ([table 4](#)). A detailed history of all food exposure is also taken.

Table 1 Stage 1: Schedule of enrolment, interventions and assessments

Procedures	Recruitment and prescreening	Visit 1 (6 weeks to <12)	Visit 2 (4 to <5 months)	Visit 3 (6 to <7 months)	Visit 4 (72±3 hours after visit 3; optional)	Visit 5 (21–35 days after visit 3)	9 months phone or electronic contact	Visit 6 (12 months to <18 months)	Oral food challenge (≥12 to <18 months)	15 months phone or electronic contact	Visit 7 (18 months to <19 months)	Visit 8 (21–35 days after visit 7)
Study information and permission to contact	X											
Informed consent		X							X			
Eligibility assessment	X	X	X	X	X	X		X	X	X	X	X
Demographics	X											
Medical history	X								X			
Randomisation	X											
Prevaccination assessment	X	X	X	X				X*		X		
Administration of the IMP (wP) or comparator (aP)	X											
National immunisation programme (NIP) vaccines	X	X	X	X				X†		X		
Food exposure and atopic dermatitis questionnaire	X	X	X	X		X	X	X		X	X	X
Oral food challenge (if applicable)									X			
Skin prick test								X				
Administration of the catch-up vaccine (DTaP-IPV)										X		
Blood collection				X	X	X	X				X	X
Assessment of elimination criteria		X	X	X	X	X	X	X	X	X	X	X

*Only if NIP vaccines will be given at study site.

†On parental request. Alternatively, NIP vaccines can be given by a local immunisation provider.

DTaP, diphtheria, tetanus, acellular pertussis; IPV, inactivated poliovirus vaccine; wP, whole-cell pertussis.

Table 2 Stage 2: Schedule of enrolment, interventions and assessments

Procedures	Recruitment and prescreening	Visit 1 (6 to<12 weeks)	6 and 9 months		12 months phone or electronic contact	Visit 2 (12 to<15 months)	Oral food challenge (≥12 to<18 months)	15 months phone or electronic contact	18 months phone or electronic contact	Visit 3 (18 to<19 months)	Visit 4 (21- 35 days after visit 3)
			phone or electronic contact	phone or electronic contact							
Study information and permission to contact	X										
Informed consent	X						X				
Eligibility assessment	X				X		X			X	
Demographics	X										
Medical history	X						X				
Randomisation	X										
Pre vaccination assessment	X				X(*)					X	
Administration of the IMP (wP) or comparator (aP)	X										
National immunisation programme (NIP) vaccines	X					X(†)				X	
Skin prick test						X					
Food exposure and atopic dermatitis questionnaire			X	X	X			X		X	
Oral food challenge (if applicable)							X				
Administration of the catch-up vaccine (DTaP-IPV)										X	
Blood collection (if applicable)										X	
Assessment of elimination criteria	X				X					X	X

*Only if NIP vaccines are given at the study site.

†On parental request. NIP vaccines can be given by a local immunisation provider.

DTaP, diphtheria, tetanus, acellular pertussis; IPV, inactivated poliovirus vaccine; wP, whole-cell pertussis.

Table 3 Stage 1-specific immunological endpoints

Immunological endpoints	Description
Atopic immunophenotype	The change in the log titres of total IgE and tetanus toxoid, egg white and whole egg-specific IgE immediately prior the third dose of pertussis-containing vaccine and 21–35 days postvaccination
Vaccine immune responses	Seropositive IgG titres against pertussis toxin, filamentous haemagglutinin and pertactin-specific IgG at 7 months of age
	A fourfold or greater rise in filamentous haemagglutinin and pertactin-specific IgG from 18 to 19 months of age
	Seroprotective IgG titres against all 13-valent pneumococcal vaccine capsular polysaccharides, polyribosylribitol phosphate capsular polysaccharide of Hib and tetanus toxoid at 7 and 19 months of age

Hib, *Haemophilus influenzae* type b.

Because fever and irritability are common following immunisation with wP,^{10 11} a prophylactic dose of oral paracetamol (15 mg/kg) is administered immediately before or up to 30 min after vaccination, and the caregiver advised to administer further doses 6 and 12 hours later.

Table 4 Enrolment questionnaire

Baseline data	Information collected
Demographics and infant's medical history	Gender, date of birth, place of residence, number and order of siblings, infant's and parental ethnicity, parental country of birth and education, combined income, infant's medical history and concomitant medications
Birth history	Maternal gravidity and parity, intrapartum antibiotics, delivery type, Apgar score at 1 and 5 min, gestational age at delivery, weight, length and head circumference at birth, neonatal systemic antibiotics, hepatitis B vaccine at birth
Maternal immunisation history confirmed on AIR or through vaccination providers	Pertussis-containing vaccine given in the preceding pregnancy and within the last 5 years; seasonal influenza vaccination during the preceding pregnancy
Family history of atopic diseases	Parental-reported, clinician-confirmed history of asthma, atopic dermatitis, food allergy or allergic rhinoconjunctivitis in first-degree relatives
Physical examination	General appearance, skin assessment, objective SCORAD (SCORing Atopic Dermatitis, only for stage 2), temperature, weight, length, head circumference

AIR, Australian Immunisation Register.

Randomisation and blinding

Eligible participants are randomised 1:1 to receive a 0.5 mL dose of the WHO-prequalified pentavalent formulation of DTaP-HB-Hib (PENTABIO PT Bio Farma, study vaccine),²⁶ or else a hexavalent formulation of DTaP-HB-Hib plus inactivated poliovirus vaccine (IPV) (INFANRIX HEXA, GlaxoSmithKline, comparator vaccine),²⁷ as the first dose of the pertussis vaccination schedule between 6 and <12 weeks of age. This is given via intramuscular injection into the anterolateral aspect of the right thigh. Other scheduled 6-week doses are coadministered per Australia's national immunisation programme.²⁸

Randomisation is by computer-generated allocation sequence prepared by the trial statistician and based on randomly permuted blocks of size 6, 8 or 10. The randomisation codes are password-protected and held by the trial statistician. The allocation sequence is concealed from all blinded research staff in a non-transparent envelope until completion of the study.

An unblinded pharmacist or research nurse obtains the next contiguous allocation and prepares the study or comparator vaccine into a clear 1 mL ready to administer syringe, labelled with the study participant's number and their identifiers. The syringes are covered to prevent unblinding. At enrolment, vaccines may be administered by either a blinded or an unblinded nurse. If unblinded, this nurse has no further involvement in the follow-up of the participant. Parents and all other research staff remain blinded until the study completion.

To maintain blinding while ensuring all participants receive at least three priming doses of IPV, a dose of DTaP-IPV (INFANRIX IPV, GlaxoSmithKline, catch-up vaccine),²⁹ in lieu of DTaP, is administered to all participants at the age of 18 months.

The blinding process may be broken under compelling medical or safety circumstances. Code breaks will be authorised by the coordinating principal investigator and will be communicated directly to the parents and/or medical team by the trial statistician.

Follow-up

Participants are reviewed in clinic by a research nurse. Where applicable, routine vaccinations are administered (figures 1 and 2 and tables 1 and 2). Questionnaires capture food exposure, supplementation with vitamins, probiotics, fish oils or others, clinical diagnoses of atopic dermatitis and IgE-mediated food allergy, pet ownership and childcare attendance. A memory aid is supplied for parents to record the onset of new medical events, manifestations of allergic diseases and exposure to foods for the duration of the study.

Laboratory testing

Venous bloods samples are obtained for the following analyses.

Plasma IgE studies

Total, tetanus toxoid and food allergen-specific IgE is measured in plasma at the age of 6, 7 and 19 months (stage 1 only), using ImmunoCAP total and specific IgE assays (Thermo Fisher Scientific/Phadia, Uppsala, Sweden). These data will be used to calculate a fold change in the logarithm of IgE in each child from before their routine 6-month vaccines to approximately 1-month postvaccination. IgE levels ≥ 0.35 kU/L are considered positive.

Vaccine antibody responses

Vaccine antigen-specific IgG titres are measured immediately before and 21–35 days after the 6-month (stage 1 only) and 18-month vaccine doses. These antibody levels are measured using a multiplex fluorescent bead assay.³⁰

For stage 1, sera will be tested for IgG against *B. pertussis* antigens (pertussis toxin, filamentous haemagglutinin, pertactin, fimbriae agglutinogens 2–3), tetanus toxoid, capsular polysaccharide of Hib (Hib-PRP) and each of the 13-valent pneumococcal vaccine serotypes. For stage 2, sera will only be tested for pertussis toxin-specific IgG in the first 300 study participants enrolled at PCH.

The putative protective thresholds for pertussis toxin and filamentous haemagglutinin-specific IgG are set at ≥ 5 IU/mL, seroprotective IgG titres for tetanus toxoid at ≥ 0.1 IU/mL,³¹ Hib-PRP at ≥ 1.0 μ g/mL³² and for all 13-valent pneumococcal vaccine serotypes at ≥ 0.35 μ g/mL.^{33 34}

We will measure the geometric mean titres of IgG antibodies to pertussis toxin at 1 month after an 18-month aP booster dose.

Skin prick testing and oral food challenge

Participants are skin prick tested following the Australasian Society of Clinical Immunology and Allergy guidelines.³⁵

The allergen panel (Immunotek, Madrid, Spain) includes cow's milk, hen's egg, peanut, cashew, house dust mite (*Dermatophagoides pteronyssinus*), cat, rye grass (*Lolium perenne*), a positive control (10 mg/mL histamine) and negative control (saline). Tests are performed using conventional single prick lancets (Entaco, distributed by Stallergenes) on the infant's forearm or back, as indicated by the study site-specific standard operating procedure. At the discretion of the site principal investigator, skin prick testing can be performed before the age of 12 months to confirm IgE-mediated sensitisation in children suspected of having an IgE-mediated food reaction. In this case, the allergen panel will be decided by the site principal investigator and the test will be repeated as per study protocol at the 12 months' study visit.

Food allergen skin prick tests >1 mm will be used to select infants for oral food challenge(s). The latter will be performed at the study site between 12 and 18 months of age, following modifications of the Australasian Society of Clinical Immunology and Allergy protocols, with internationally standardised scoring and stopping criteria.²⁵

Additional studies

For both stages, parental consent is requested for a fraction of the bloods to be used for future mechanistic studies. For stage 1, additional consent is requested for transcriptomic analysis and immunophenotyping of whole blood and cryopreserved mononuclear cells immediately before and 72 hours after the third dose of pertussis-containing vaccine to enable research into the effects of wP/aP priming on cellular immune functions.

Data collection

Case report forms and relevant source documentation are maintained for every trial participant enrolled in the study, either in paper or in electronic form. For stage 1, all case report forms are paper-based; for stage 2, case report forms and source documents may be paper or electronic based. Any paper records are stored under locked, confidential conditions. Data is entered onto a password-protected electronic database built in Medrio EDC for stage 1 and REDCap (Research Electronic Data Capture System) for stage 2. Automatic edit checks are created to ensure the data entered is consistent and correct. Study-related documentation will be archived until the youngest participant reaches 25 years old; or until 15 years after the end of the trial/publication (whichever is later); or as required by local guidelines.

Statistical analysis

The number and proportion of participants with IgE-mediated food allergy by 12–18 months of age will be summarised by treatment group, as well as the number of inconclusive results. The primary analysis will use independent beta-binomial models with uniform priors for the primary endpoint in each study arm. The null hypothesis that a first dose of DTwP-HB-Hib provides no reduction in IgE-mediated food allergy by 12 months of age compared with DTaP-HB-Hib will be rejected at the final analysis if the posterior probability of a reduction exceeds 0.95, that is,

$$\Pr(\theta_1 < \theta_0 | D) > 0.95$$

where θ_1 is the probability of IgE-mediated food allergy by 12 months of age when given a first dose of DTwP-HB-Hib and θ_0 when given DTaP-HB-Hib, and D is the data at the final analysis. The parameter posteriors and their difference will be summarised by their means and highest density intervals.

Secondary analyses of the primary endpoint will assume a logistic regression model to investigate covariate adjustment and post hoc investigation of subgroup effects. None of these subgroup analyses are prespecified and will be noted as post hoc when reporting.

Interim analyses

This trial allows interim analyses to be undertaken at prespecified sample sizes to decide whether the trial should be stopped early for futility or expected success. The decisions are made in accordance with prespecified

stopping rules based on the data available at the time of the interim analysis. Due to the delay in observing the primary endpoint, the stopping rules will be based on predictive probabilities of detecting treatment effect rather than posterior probabilities of the effect itself.

Interim analyses will begin after 200 subjects have complete data on the primary endpoint. Subsequent interim analyses will occur every further 200 subjects with complete primary endpoint data until either a stopping rule is met or enrolment is close to completion. If all subjects are enrolled up to the maximum sample size prior to a stopping rule being met, then no more interim analyses will be undertaken.

The predictive probability of success is calculated by imputing future data according to the model posterior predictive distribution given the data observed so far and calculating the expected trial outcome if future data were to be observed. That is,

$$PPoS_k = E[Pr(1 <_0 | D_k, \tilde{D}_k) > 0.95 | D_k]$$

is the predictive probability that the null hypothesis would be rejected at the posterior probability threshold 0.95 if additional data, $\tilde{D}_k$ were observed given the current data D_k . If the predictive probability of success at the currently enrolled sample size exceeds 0.95, then enrolment will cease for expected success. If the predictive probability of success at the maximum planned sample size is less than 0.05 then enrolment will cease for futility. In either case, follow-up of participants already enrolled will continue to completion of their scheduled follow-up, and a final analysis will be undertaken as in the previous section.

These decision thresholds were selected on the basis of a thorough trial simulation study.

Sample size

A maximum sample size of 3000 participants (1500 per arm) is planned; 150 participants in stage 1 and up to 2850 in stage 2. In accordance with trial simulations of the above design, we estimate the trial will have 85% power to detect a reduction in IgE-mediated food allergy by 12 months of age from 10% to 7% while controlling the probability of type I error at no more than 5%.

The sample size for this study is adaptive, therefore the actual trial sample size may be less than 3000 participants. Based on simulation studies undertaken for the trial design, the actual sample size is likely to be at least 1000 participants and very unlikely to be fewer than 500 participants given the expected accrual rates and timing of the first interim analysis. We estimated a 69% probability of stopping early for futility if the null was true, and in the scenario above (reduction from 10% to 7% in the primary endpoint), we estimated 59% probability of stopping early for expected success.

Safety reporting and trial oversight

Solicited and unsolicited adverse events following immunisation are collected on diary cards in the 7 days after

administration of pertussis-containing vaccines. Solicited local adverse events include injection site pain, erythema, induration and swelling; the solicited systemic adverse events recorded are fever $\geq 38^\circ\text{C}$ (axillary), drowsiness, irritability, anorexia, vomiting, diarrhoea and restlessness. The definition and intensity grading for fever, diarrhoea and local reactions (except for immunisation site pain) follows the Brighton Collaboration guidelines.^{36–40} For other solicited adverse events, intensity grading scales based on impact on daily activities are used (grade 0 or absent; grade 1 if easily tolerated; grade 2, sufficiently discomforting to interfere with normal everyday activities and grade 3, if prevents normal everyday activities or requires significant medical intervention).

The following are considered adverse events of specific interest (AESI) and will be captured throughout the study: (1) vaccine failure including (but not limited to) laboratory confirmed or suspected: vaccine homotypic meningococcal disease, vaccine serotype invasive pneumococcal disease, invasive Hib and pertussis and (2) hypotonic hyporesponsive episode as defined by the Brighton Collaboration Working Group.⁴¹ Any new illness that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation and results in persistent or significant disability/incapacity is reported by the coordinating principal investigator to the sponsor as an SAE. SAEs deemed related to the study vaccines or procedures will be captured throughout the entire study period; if unrelated, they are only reported from visit 1 to 6 months postrandomisation. The relationship of SAEs and AESIs to the trial vaccines is determined by a study physician.

An independent data safety and monitoring committee meets at least twice a year to monitor the overall conduct of the trial including adherence to stopping rules, safety-related endpoints and other outcome measures. Site-specific monitoring visits take place after the enrolment of the first 50 study participants. Subsequent visits are scheduled by the project manager or as per the coordinating principal investigator and the data safety and monitoring committee request.

Ethics and dissemination

This study has been approved by the Child and Adolescent Health Service Human Research Ethics Committee, Perth, Western Australia (RGS 00019). The trial is conducted in accordance with the principles of the Declaration of Helsinki and with the International Conference on Harmonisation Guidelines for Good Clinical Practice. Individual consent is required for participation. Parents will be reimbursed reasonable travel and parking costs to attend the study visits. The dissemination of these research findings will follow the National Health and Medical Research Council Open Access Policy.

Final considerations

A successful trial is likely to reinforce the WHO position statement of preferentially using wP rather than aP-only

regimes in countries with wP-based primary courses⁴²; however, hurdles for the implementation of a mixed wP/aP schedule are anticipated in other settings where regulatory barriers will need to be addressed and additional strategies to gain the confidence of consumers and stakeholders will be needed.

EARLIER PROTOCOL VERSIONS

The present manuscript is based on version 11 of the study protocol. Following the award of Australian NHMRC funding for stage 2 of this project, a series of protocol amendments have been submitted and approved before any analyses and while all the investigators (including the trial statistician) remained blinded. The major amendment (protocol version 8, 106 study participants enrolled) and subsequent refinements (versions 9 to 11) are summarised as follows:

Inclusion/exclusion criteria: revised eligibility criteria allow for the enrolment of moderate to late preterm infants and infants with pre-existing atopic dermatitis (the latter have the highest risk of developing the primary outcome).³

Primary endpoint definition: the original primary endpoint was a composite outcome of either clinician-confirmed IgE-mediated food allergy or atopic dermatitis by the age of 18 months. This has been modified as described in the outcome section of this manuscript.

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