Potential clinical efficacy of the 10-valent pneumococcal-Protein D conjugate vaccine in children with chronic suppurative lung diseases: a double-blind randomised controlled trial

Combating *H. influenzae* **R**elated **R**espiratory **P**athology

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Background

- Chronic suppurative lung diseases (CSLD) in children are important causes of morbidity and recurrent acute exacerbations are associated with long term lung function decline.[1]
- Non-typeable *H. influenzae* (NTHi) and *S. pneumoniae* are commonly isolated from the lower airways of both children and adults with CSLD.[2]
- The potential clinical impact of a non-typeable *Haemophilus influenzae* (NTHi) vaccine in children with CSLD has not been investigated.
- We aimed to determine the clinical efficacy of the 10-valent pneumococcal-Protein D conjugate vaccine (10vPHiD-CV) in children aged 18-months to <18-years with CSLD (Immunogenicity data are presented in Poster xxx).

Primary clinical objective

- Determine the efficacy of 10vPHiD-CV in reducing the incidence of acute exacerbations in the 12-months following the 2nd dose of study vaccine.

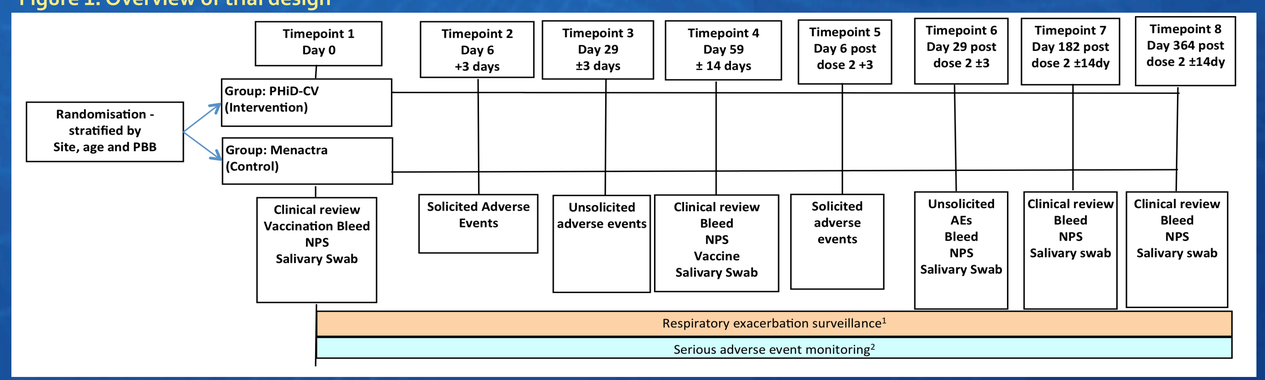
Secondary clinical objectives

- Determine the efficacy of 10vPHiD-CV in reducing the incidence of any parent/carer-reported respiratory symptoms in the 12 months following the second dose of study vaccine.
- Determine the efficacy of 10vPHiD-CV in reducing antibiotic use in the 12 months following the second dose of study vaccine.

Methods

- Multi-centre, parallel group (1:1 allocation), double-blind, randomised controlled trial.[3]
- Children received 2 doses, 2-months apart of 10vPHiD-CV or meningococcal-ACYW$_{135}$ conjugate vaccine (Figure 1).
- Inclusion/exclusion criteria are listed in Box 1; a glossary of terms is provided in Box 2.
- Children underwent active fortnightly surveillance for acute exacerbations, respiratory symptoms and antibiotic use for 12-months post the second dose of vaccine.
- In intention-to-treat analyses, incidence rate ratios (IRRs) were calculated with child-weeks at risk commencing 14-days post the second vaccine dose.
- Child time at risk was calculated in weeks for exacerbations and antibiotic use and fortnights were the denominator for parent/carer reported respiratory symptoms.
- Subanalyses were performed to determine the incidence of clinical endpoints following the first dose of vaccine.

Figure 1. Overview of trial design



Box 1. Trial eligibility criteria

Inclusion Criteria	Exclusion Criteria
• Child aged ≥ 18 months and < 18 years with CSLD, bronchiectasis or recurrent PBB (Box 2)	• Chronic lung condition, including cystic fibrosis, other than those under investigation in this study
• At least 2 respiratory exacerbations within the 18-months prior to enrolment	• Prior vaccination with PHiD-CV vaccine; contraindication to PHiD-CV and/or quadrivalent (ACYW$_{135}$) meningococcal conjugate vaccine
• Age-appropriately immunised with PCV7 and/or PCV13	• Known hypersensitivity to any component of the vaccines, including latex
• A prior dose of Pneumovax 23 was permitted. At least 2-months post the dose of non-study pneumococcal vaccine was required prior to enrolment	• Confirmed or suspected immunosuppressive condition or immunodeficiency disorder that may be expected to interfere with immune response to vaccination
• If vaccinated with a meningococcal C conjugate vaccine, a period of at least 6 months post vaccination was required prior to enrolment.	• Current (or within 90 days prior to receiving study vaccine) or planned (during the active study period) immunosuppressive therapy, including systemic corticosteroids (≥14 days). Inhaled steroids were allowed
• Negative urine pregnancy test if post-menarcheal female	• Administration of immunoglobulins and/or blood products within 90 days prior to receiving study vaccine, or planned administration of such products during the study period
• Provision of written informed consent from parent/guardian (assent from child as per local HREC requirements)	• Active participation in a clinical trial of another investigational drug/vaccine or interventional therapy
• Parent/child willing and able to meet the requirements of the protocol	• Acute disease at the time of enrolment. Acute disease was defined as a moderate or severe illness with or without fever (axillary temperature ≥ 38.0°C) at the time of enrolment. A temperature greater than or equal to this cut-off warrants deferral of the vaccination pending recovery of the participant
• Not planning to move from the study area in the 14 months post enrolment	• Other medical/psychosocial condition that the investigators considered warranted exclusion from the trial to prevent potential harm/risk to the subject or may adversely affect study outcomes

Box 2: Glossary of study definitions

Term	Definition
Chronic suppurative lung disease (CSLD)	A clinical syndrome where there are signs/symptoms indicating chronic endobronchial suppuration with or without HRCT evidence of radiological bronchiectasis. This includes chronic wet or productive cough and either failure of cough to respond to oral antibiotics or presence of additional respiratory symptoms or signs (eg. clubbing, chest wall deformity or crackles)
Bronchiectasis	Features of CSLD plus confirmed bronchiectasis by chest HRCT scan in last 5 years
Recurrent protracted bacterial bronchitis (PBB)	The presence of isolated chronic (>4 weeks) of wet/moist cough that resolves with antibiotics in the absence of pointers suggestive of an alternative specific cause of cough. 3 prior episodes defined recurrent PBB.
Respiratory exacerbation	An increase in sputum volume or purulence or ≥ 3-days of change in cough (>20% increase in cough score or type [dry to wet]). A cough must have been wet to be considered an exacerbation. The 'baseline-state' for each child was established at enrolment, prior to any exacerbations. This consisted of a combination of symptoms [daily cough (yes/no), cough quality (wet/dry/none), cough score averaged over 2 days and signs [sputum colour (if any present), crackles on chest auscultation].
Respiratory symptoms under surveillance	cough, sputum production, sputum colour, rhinorrhoea, fever, wheeze, shortness of breath, tachypnoea, dyspnoea, stridor, headache, sore throat, earache.

Results

- The required sample size of 206 children was not achieved given recruitment difficulties.
- 879 children were screened and 62 enrolled; 481 (55%) were ineligible, 257 (29%) refused & 79 (9%) were not enrolled for other reasons. One child was unblinded & withdrawn following a serious adverse event unrelated to study vaccine & excluded from the analysis.
- The mean age of enrolled children 7.0-years (95%CI 6.0, 7.9); 53.5% were male (Table 1). There were no differences in gender and age between children who were and were not enrolled.
- Baseline characteristics are provided in Table 1 and incidence rates of clinical endpoints are presented in Table 2.

Table 1. Baseline characteristics of CHiRRP children

Child characteristic	PHiD-CV n = 31	MenACYW135 n = 30	p value
Age group			
< 6 years	15 (48.4%)	12 (40.0%)	0.510
≥ 6 years	16 (51.6%)	18 (60.0%)	
Gender			
Male	18 (58.1%)	14 (46.7%)	0.373
Female	13 (41.9%)	16 (53.3%)	
Respiratory diagnosis			
PBB	14 (45.2%)	18 (59.7%)	0.529
CSLD	9 (29.0%)	7 (23.3%)	
Bronchiectasis	8 (25.8%)	5 (16.7%)	
Age appropriately immunised with PCV7			
Yes	29 (93.6%)	24 (80.0%)	0.141
Not applicable	1 (3.3%)	6 (20.0%)	
Unknown	1 (3.1%)	0 (0.0%)	
Age appropriately immunised with PCV13			
Yes	8 (25.8%)	9 (30.0%)	0.121
Not applicable	20 (64.5%)	19 (63.3%)	
Unknown	3 (9.7%)	2 (6.7%)	
Prior 23-valent pneumococcal polysaccharide vaccine			
Yes	10 (32.3%)	4 (13.3%)	0.068
Unknown	2 (6.5%)	2 (6.7%)	
Mean # parent reported respiratory exacerbations in past 18 months (95%CI)	7.7 (6.1 – 9.4)	8.2 (6.1 – 10.2)	0.725

Table 2: Incidence rates (IR) / child time at risk and Incidence Rate Ratios (IRR) for clinical endpoints

Endpoint	PHiD-CV N = 31	MenACYW135 N = 30		
	n/time at risk (IR)	n/time at risk (IR)	IRR (95%CI)	P-value
Exacerbations post dose 2	71 / 1698 weeks (4.2 / 100 weeks)	73 / 1549 week (4.7 / 100 weeks)	0.88 (0.64 – 1.23)	0.237
Exacerbations post dose 1	106 / 1877 weeks (5.6 / 100 weeks)	106 / 1637 weeks (6.5 / 100 weeks)	0.87 (0.67 – 1.14)	0.160
Fortnights with respiratory symptoms post dose 2	213/849 fortnights (25/100 fortnights)	260 / 775 fortnights (36/100 fortnights)	0.75 (0.62 – 0.90)	0.002
Fortnights with respiratory symptoms post dose 1	266 / 939 fortnights (28/100 fortnights)	320 / 818 fortnights (39/100 fortnights)	0.72 (0.62 – 0.85)	<0.001
Antibiotic courses < 14 days post dose 2	77 / 1692 weeks (4.5/100 weeks)	94 / 1528 weeks (6.2/100 weeks)	0.74 (0.55 – 0.99)	0.025
Antibiotic courses < 14 days post dose 1	109 / 2094 weeks (5.2/100 weeks)	123 / 1961 weeks (6.3/100 weeks)	0.83 (0.64 – 1.07)	0.078
Antibiotic courses < 28 days post dose 2	92 / 1657 weeks (5.5/100 weeks)	102 / 1515 weeks (6.7 / 100 weeks)	0.82 (0.62 – 1.09)	0.091
Antibiotic courses < 28 days post dose 1	127/2051 weeks (6.2/100 weeks)	133/1938 weeks (6.9/100 weeks)	0.90 (0.71 – 1.15)	0.204
Antibiotics of any duration post dose 2	92 / 1647 weeks (6.8 / 100 weeks)	102 / 1505 weeks (5.6 / 100 weeks)	0.82 (0.62 – 1.09)	0.086
Antibiotics of any duration post dose 1	127 / 2035 weeks (6.9 / 100 weeks)	133 / 1926 weeks (6.2 / 100 weeks)	0.90 (0.71 – 1.15)	0.207

Discussion

- We have identified a potentially important role for the 10vPHiD-CV in the clinical management of children with CSLD.
- While the sample size was inadequate for the primary endpoint, children who received 10vPHiD-CV required less courses of antibiotics and experienced less time with respiratory symptoms than those in the control group.
- Our clinical data are supported by the mucosal and systemic antibody responses to vaccine presented in Poster xx.
- Larger trials, involving multiple recruitment sites, are now required to confirm our findings.

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