

SUPPLEMENTARY FILES;**APPENDIX 1: DEFINITIONS**

PCV7-serotype CAP	CAP due to serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F)	
PCV13non7-serotype CAP	CAP due to serotypes included in PCV13, excluding serotypes also included in PCV7 (serotypes 1, 3, 5, 6A/C, 7F/A, 19A)	
PPV23non13-serotype CAP	CAP due to serotypes included in PPV23, excluding serotypes also included in PCV13 (serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F)	
Non-vaccine-serotype CAP	CAP due to a) any non-PCV13-, non-PPV23-serotype and b) untyped pneumococcal cases – blood culture or BINAX UAD positive without subsequent serotype identification, or Bio-plex24 assay positive for cell wall polysaccharide only	
Clinical risk factors for pneumococcal disease	Chronic respiratory disease	Includes chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis
	Chronic heart disease	Includes ischaemic heart disease requiring medication or regular follow-up, congenital heart disease, hypertension with cardiac complications, and chronic heart failure
	Chronic kidney disease	Includes nephrotic syndrome, chronic kidney disease stages 4 and 5, end stage renal failure, and renal transplant
	Chronic liver disease	Includes cirrhosis, biliary atresia, and chronic hepatitis
	Immunosuppression	Includes those who are immunocompromised by disease such as asplenia or splenic dysfunction, haematological disease including malignancy, solid organ or bone-marrow transplant, immunodeficiency, HIV, or treatment with immunosuppressive therapies but not steroids
	Diabetes mellitus requiring therapy	
	Individuals with cochlear implants	
	Individuals with cerebrospinal fluid (CSF) leaks	
Pneumococcal clinical risk group	adults 16–64 years with ≥1 one or more clinical risk factors for pneumococcal disease as identified in the Green Book or age ≥65 years	

APPENDIX 2: Target serotypes for human-Monoclonal Antibodies (h-MAAb), associated cross-reactivity, Bio-plex24 immunoassay reporting, and final serotype designation;

h-MAAb target	Serotype(s) with which h-MAb cross-reacts	Bio-plex24 result	Final serotype designation
1	n/a	1	1
2	n/a	2	2
3	n/a	3	3
4	n/a	4	4
5	n/a	5	5
6A	6B, 6C, 6D	6A/C	6C
6B	6A, 6D	6B/D	6B
7F	7A	7F/A	7F
8	n/a	8	8
9N	9L, 18A, 43, 47A	9N	9N
9V	9A, 9L	9A/V	9V
10A	10B, 10C, 10F, 33C, 39	Group 10 or 33C or 39	10A
11A	11C, 11D, 11E, 16A, 16F, 18A, 18B, 18C	11A/C/E or Group 16	11A
12F	12B, 22A, 44	12F or 44 or 22A	12F
14	9L, 9N	14	14
15B	15A, 15C, 15F, 11D, 12B, 18A	Group 15	15A
17F	n/a	17F	17F
18C	18A, 18B, 18F	18B/C/F	18C
19A	19F, 9A, 9L, 9V, 18B, 18C	19A	19A
19F	19A, 19B, 19C	Group 19	19F
20	n/a	20	20
22F	6C, 6D, 20	22F	22F
23F	32A, 32F	23F or Group 32	23F
33F	33A, 33B, 33D	33A/B/D/F	33F

h-MAAb: human monoclonal antibody; **Bold** indicates final serotype designation based on predominant serotype identified in national invasive pneumococcal disease surveillance data.

For 16 of 24 targeted serotypes, the h-MAAb exhibit cross reactivity for non-targeted pneumococcal serotypes. When a h-MAAb cross reacts with another targeted serotype this can be taken into consideration for interpretation of results. Consequentially, definitive serotype designations can be achieved for 13 serotypes, with serogroup combinations reported for the remaining 11 targeted serotypes. For serogroup combinations, a final serotype designation has been achieved based on the predominant serotype derived from corresponding national invasive pneumococcal disease surveillance data.

SUPPLEMENTARY TABLE 1: Clinical features and comparative analysis of PCV13- versus non-PCV13-serotype CAP

	PCV13	Non-PCV13	OR (95%CI)	p value	aOR (95%CI)	p value
Patients	325	658				
Demographics						
Age, years	72.6 (62.1-82.2)	66.6 (50.3-78.6)		<0.001	1.02 (1.01-1.03)	<0.001
16-49 years	40 (12.3)	162 (24.6)	Reference			
50-64 years	66 (20.3)	145 (22.0)	1.84 (1.17-2.91)			
65-74 years	85 (26.2)	138 (21.0)	2.49 (1.59-3.91)			
75-84 years	75 (23.1)	129 (18.8)	2.35 (1.49-3.72)			
≥85 years	59 (18.2)	84 (12.8)	2.84 (1.73-4.66)	<0.001*		
Male	169 (52.0)	315 (47.9)	1.17 (0.90-1.53)	0.241		
Care Home Resident	5 (1.5)	24 (3.7)	0.41 (0.16-1.09)	0.066	0.28 (0.10-0.75)	0.012
PPV23 vaccination ^a	128 (42.0)	188 (28.6)	1.63 (1.22-2.17)	<0.001		
Comorbid disease						
Smoking status ^a						
Never smoker	92 (29.2)	172 (26.9)	Reference			
Ex-smoker	142 (45.1)	260 (40.7)	1.02 (0.74-1.41)			
Current smoker	81 (25.7)	207 (32.4)	0.73 (0.51-1.05)	0.087*		
Alcohol excess	11 (3.4)	29 (4.4)	0.76 (0.37-1.54)	0.445	0.96 (0.46-1.99)	0.915
Malignancy	22 (6.8)	64 (9.7)	0.67 (0.40-1.11)	0.121	0.52 (0.31-0.90)	0.019
Liver disease	5 (1.5)	17 (2.6)	0.59 (0.22-1.61)	0.298	0.67 (0.24-1.89)	0.447
Kidney disease	35 (10.8)	38 (5.8)	1.97 (1.22-3.19)	0.005	1.71 (1.02-2.86)	0.041
Chronic heart disease	53 (16.3)	79 (12.0)	1.43 (0.98-2.08)	0.063	1.07 (0.72-1.60)	0.732
Congestive cardiac failure	24 (7.4)	33 (5.0)	1.51 (0.88-2.60)	0.135		
Ischaemic heart disease	35 (10.8)	55 (8.4)	1.32 (0.85-2.07)	0.218		
Chronic lung disease (excluding asthma)	98 (30.2)	170 (25.8)	1.24 (0.92-1.66)	0.153	1.04 (0.77-1.42)	0.782
COPD	84 (25.8)	155 (23.6)	1.13 (0.83-1.54)	0.431		
Asthma	30 (9.2)	79 (12.0)	0.75 (0.48-1.16)	0.193		
Diabetes Mellitus	49 (15.1)	96 (14.6)	1.04 (0.72-1.51)	0.84	0.90 (0.61-1.33)	0.601
Cerebrovascular disease	29 (8.9)	48 (7.3)	1.25 (0.77-2.02)	0.372	1.05 (0.63-1.74)	0.863
Cognitive impairment	8 (2.5)	24 (3.6)	0.67 (0.30-1.50)	0.325		
Immunocompromise	17 (5.2)	25 (3.8)	1.40 (0.74-2.63)	0.297	1.87 (0.95-3.70)	0.072
Study Year						
6	60 (18.5)	107 (16.3)	Reference			
7	54 (16.6)	129 (19.6)	0.75 (0.48-1.17)			
8	47 (14.5)	104 (15.8)	0.81 (0.50-1.29)			
9	78 (24.0)	143 (21.7)	0.97 (0.64-1.48)			
10	86 (26.5)	175 (26.6)	0.88 (0.58-1.32)	0.952*		
Disease Severity						
CURB-65 0-1	117 (36.0)	330 (50.2)	Reference			
CURB-65 2	108 (33.2)	184 (28.0)	1.66 (1.20-2.28)			
CURB-65 ≥3	100 (30.8)	144 (21.9)	1.96 (1.40-2.74)	<0.001*		
Outcomes						
Critical Care admission	32 (9.8)	70 (10.6)	0.92 (0.59-1.43)	0.702		
30-day mortality	20 (6.2)	33 (5.0)	1.24 (0.70-2.20)	0.457		

Data are presented as n (%) or median (interquartile range). PPV23: 23-valent pneumococcal polysaccharide vaccine; COPD: chronic obstructive pulmonary disease; CURB-65: confusion, urea >7mmol.L⁻¹, respiratory rate > 30 breaths.min⁻¹, blood pressure <90mmHg [systolic] <60mmHg [diastolic], age ≥65years. Odds ratio (OR) and p values compare PCV13 serotype disease to non-PCV13 serotype disease. aOR – adjusted for age, residential care status, active malignancy, liver disease, chronic alcohol excess, cerebrovascular disease, diabetes mellitus, chronic lung disease, chronic heart disease, immunosuppression and chronic kidney disease. Bold values indicate p value <0.05. ^a – PPV23 vaccine status and smoking status unavailable for 67 and 29 patients respectively, # - p value for trend

SUPPLEMENTARY TABLE 2: Clinical features and comparative analysis of those with PPV23- versus non-PPV23-serotype CAP

	PPV23	Non-PPV23	OR (95%CI)	p value	aOR (95%CI)	p value
Patients	732	316				
Demographics						
Age, years (IQR)	69·3 (54·2-80·1)	69·1 (53·1-80·6)		0·953	1·00 (0·99-1·01)	0·761
16-49 years	149 (20·4)	62 (19·6)	Reference			
50-64 years	153 (20·9)	69 (21·8)	0·92 (0·61-1·39)			
65-74 years	169 (23·1)	68 (21·5)	1·03 (0·69-1·56)			
75-84 years	156 (21·3)	65 (20·6)	0·99 (1·66-1·51)			
≥85 years	105 (14·3)	52 (16·5)	0·84 (0·54-1·31)	0·658 [#]		
Male	346 (47·4)	156 (49·4)	0·92 (0·71-1·20)	0·558		
Care Home Resident	23 (3·2)	11 (3·5)	0·90 (0·43-1·88)	0·785	0·86 (0·41-1·82)	0·701
PPV23 vaccination ^a	236 (34·5)	105 (36·5)	0·92 (0·69-1·22)	0·55		
Comorbid disease						
Smoking status ^a						
Never smoker	199 (28·2)	87 (27·9)	Reference			
Ex-smoker	298 (42·3)	129 (41·4)	1·01 (0·73-1·40)			
Current smoker	208 (29·5)	96 (30·8)	0·95 (0·67-1·34)	0·756		
Alcohol excess	26 (3·6)	15 (4·8)	0·74 (0·39-1·42)	0·36	0·76 (0·39-1·49)	0·419
Malignancy	55 (7·5)	35 (11·1)	0·65 (0·42-1·02)	0·06	0·63 (0·40-1·02)	0·058
Liver disease	15 (2·1)	8 (2·5)	0·81 (0·34-1·92)	0·625	0·85 (0·35-2·10)	0·729
Kidney disease	62 (8·5)	18 (5·7)	1·53 (0·89-2·64)	0·121	1·63 (0·93-2·88)	0·090
Chronic heart disease	90 (12·3)	49 (15·5)	0·76 (0·52-1·11)	0·16	0·71 (0·48-1·05)	0·086
Congestive cardiac failure	36 (4·9)	25 (7·9)	0·60 (0·35-1·02)	0·058		
Ischaemic heart disease	67 (9·2)	30 (9·5)	0·96 (0·61-1·51)	0·861		
Chronic lung disease (excluding asthma)	194 (26·5)	73 (31·5)	0·79 (0·57-1·08)	0·141	0·95 (0·70-1·30)	0·770
COPD	172 (23·5)	80 (25·3)	0·91 (0·67-1·23)	0·527		
Asthma	87 (11·9)	33 (10·4)	1·16 (0·76-1·77)	0·501		
Diabetes Mellitus	111 (16·2)	47 (14·9)	1·02 (0·71-1·48)	0·904	0·99 (0·68-1·45)	0·958
Cerebrovascular disease	55 (7·5)	25 (7·9)	0·95 (0·58-1·55)	0·824	0·92 (0·55-1·53)	0·742
Cognitive impairment	24 (3·3)	11 (3·5)	0·94 (0·45-1·94)	0·867		
Immunocompromise	30 (4·1)	15 (4·8)	0·86 (0·45-1·62)	0·635	0·97 (0·50-1·90)	0·937
Disease Severity						
CURB65 0-1	316 (43·2)	155 (49·1)	Reference			
CURB65 2	225 (30·7)	87 (27·5)	1·27 (0·93-1·74)			
CURB65 ≥3	191 (26·1)	74 (23·4)	1·27 (0·91-1·76)	0·119 [#]		
Study Year						
6	126 (17·2)	50 (15·8)	Reference			
7	142 (19·4)	56 (17·7)	1·00 (0·64-1·58)			
8	113 (15·4)	45 (14·2)	1·00 (0·62-1·61)			
9	172 (23·5)	67 (21·2)	1·02 (0·66-1·57)			
10	179 (24·5)	98 (31·0)	0·72 (0·48-1·09)	0·117 [#]		
Outcomes						
Critical Care admission	73 (10·0)	33 (10·4)	0·95 (0·62-1·47)	0·817		
30-day mortality	44 (6·0)	10 (3·2)	1·96 (0·97-3·95)	0·056		

Data are presented as n (%) or median (interquartile range). PPV23: 23-valent pneumococcal polysaccharide vaccine; COPD: chronic obstructive pulmonary disease; CURB-65: confusion, urea >7mmol.L⁻¹, respiratory rate > 30 breaths.min⁻¹, blood pressure <90mmHg [systolic] <60mmHg [diastolic], age ≥65years. Odds ratio (OR) and p values compare PPV23 serotype disease to non-PPV23 serotype disease. aOR – adjusted for age, residential care status, active malignancy, liver disease, chronic alcohol excess, cerebrovascular disease, diabetes mellitus, chronic lung disease, chronic heart disease, immunosuppression and chronic kidney disease. Bold values indicate p value <0.05. ^a – PPV23 vaccine status and smoking status unavailable for 68 and 29 patients respectively, # - p value for trend

SUPPLEMENTARY TABLE 3: Sensitivity analysis examining the clinical features of those with PCV13-versus non-PCV13-serotype CAP, excluding serotype 3.

	PCV13	Non-PCV13	OR (95% CI)	P value
16-64 years, no clinical risk factor	35 (23.3)	208 (31.6)	0.81 (0.52-1.29)	0.38
16-64 years, ≥1 risk factor	24 (16.0)	99 (15.1)	1.16 (0.70-1.91)	0.573
≥65 years, no clinical risk factor	32 (21.3)	137 (20.8)	0.89 (0.56-1.43)	0.641
≥65 years, ≥1 risk factor	59 (39.3)	214 (32.5)	1.17 (0.78-1.77)	0.438
Pneumococcal clinical risk group*	115 (76.7)	450 (68.4)	1.23 (0.77-1.94)	0.38
Number of risk factors				
0	67 (44.7)	345 (52.4)	Reference	
1	58 (38.7)	212 (32.2)	1.30 (0.86-1.98)	
2	21 (14.0)	81 (12.3)	1.24 (0.69-2.22)	
>3	4 (2.7)	20 (3.0)	0.79 (0.22-2.78)	0.576

Data are presented as n (%). Bold values indicate p value <0.05. Clinical risk factors include; chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression (splenic dysfunction, haematological disease including malignancy, solid organ or bone-marrow transplant, immunodeficiency, HIV, or treatment with immunosuppressive therapies but not steroids), diabetes mellitus requiring therapy, splenic dysfunction, and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants.

*: age ≥65years or age 16-64years with ≥1 risk factor, #: p value for trend

SUPPLEMENTARY TABLE 4: Sensitivity analysis examining the clinical features of those with PPV23-versus non-PPC23-serotype CAP, excluding serotype 3.

	PPV23	Non-PPV23	OR (95% CI)	P value
16-64 years, no clinical risk factor	182 (34.3)	70 (22.1)	1.83 (1.33-2.52)	<0.001
16-64 years, ≥1 risk factor	68 (12.8)	61 (19.3)	0.61 (0.42-0.90)	0.011
≥65 years, no clinical risk factor	105 (19.8)	70 (22.2)	0.87 (0.62-1.22)	0.409
≥65 years, ≥1 risk factor	176 (33.2)	115 (36.4)	0.87 (0.65-1.16)	0.336
Pneumococcal clinical risk group*	349 (65.7)	246 (77.9)	0.55 (0.40-0.75)	<0.001
Number of risk factors				
0	287 (54.1)	140 (44.3)	Reference	
1	158 (29.8)	129 (40.8)	0.60 (0.44-0.81)	
2	61 (12.6)	41 (13.0)	0.80 (0.51-1.24)	
>3	19 (3.6)	6 (1.9)	1.54 (0.60-3.65)	0.005

Data are presented as n (%). Bold values indicate p value <0.05. Clinical risk factors include; chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression (splenic dysfunction, haematological disease including malignancy, solid organ or bone-marrow transplant, immunodeficiency, HIV, or treatment with immunosuppressive therapies but not steroids), diabetes mellitus requiring therapy, splenic dysfunction, and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants.

*: age ≥65years or age 16-64years with ≥1 risk factor, #: p value for trend