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Response to pneumococcal polysaccharide vaccination in patients with chronic and allergic aspergillosis

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ABSTRACT

Introduction: Pneumococcal infection causes significant morbidity in patients with underlying lung disease, and vaccination has been associated with reduced disease rates. Response to vaccination has not been studied in chronic lung conditions characterised by ongoing infection or inflammation like chronic pulmonary aspergillosis (CPA).
Methods: In a prospective observational study, consecutive patients with CPA, allergic aspergillosis and bronchiectasis attending a national referral centre received pneumococcal 23-valent polysaccharide vaccine (PPV-23) and had pre- and post-vaccination antibody concentrations quantified as part of routine clinical care. Serotype-specific pneumococcal IgG antibodies were quantified for 12 serotypes using a multiplex microsphere assay. A protective response was defined as a level of >1.3 μg/mL or a ≥ fourfold rise in concentration for ≥70% of serotypes, pre to post-vaccination. C-reactive protein, Immunoglobulins and mannose binding lectin (MBL) levels were measured and correlated to vaccine response.
Results: A total of 318 patients were enrolled. In vaccine-naïve patients ($n = 127$), the lowest pre-vaccination levels were seen with serotypes 1 and 4 and the highest with serotype 19A. A protective response post-vaccination was seen in 50% of patients. The poorest responses were observed with serotypes 1, 3 and 4. Levels of C-reactive protein did not affect efficacy. Profound MBL deficiency was found in 28.8%; there were no significant differences in response to vaccination in patients with or without MBL deficiency. Post-vaccination serotype-specific concentrations waned gradually, however they were still elevated compared to pre-vaccination after 2–5 years.
Conclusions: Patients with chronic and allergic aspergillosis exhibited a poor response to PPV-23 vaccination compared to healthy adults. An alternative vaccination strategy or delay of vaccination until their underlying condition is better controlled, e.g. after treatment with antifungals may result in better response.

1. Introduction

Streptococcus pneumoniae infection causes substantial morbidity and mortality globally. It is a major cause of serious illness, disability and death in the extremes of age and those with underlying medical conditions or immune compromise [1]. Mortality of community-acquired pneumonia (CAP) requiring hospital admission in the UK ranges between 5.7% and 14%, increasing to higher than 30% when intensive care admission is required [2,3]. *S. pneumoniae* is a particularly important pathogen in patients with chronic obstructive pulmonary disease (COPD), as it may be responsible for up to a third of infective exacerbations, and can be isolated from sputum in at least a third of patients [4].

There are more than 94 *S. pneumoniae* serotypes with different serotypes causing disease of varying severity. Weinberger et al. reported that patients with infections caused by serotypes

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3, 6A, 6B, 9N and 19F had a significantly higher risk of dying than those infected with serotypes 1, 7F and 8, and that serotype 3 (a heavily encapsulated serotype) had a higher case–fatality ratio than serotypes 5 and 14 [5]. Vaccine efficacy for serotype 3 following pneumococcal 23-valent polysaccharide (PPV-23) vaccination in the elderly has been reported as being poor, possibly due to its increased resistance to opsonophagocytosis [6].

Pneumococcal vaccination is recommended in patients with chronic pulmonary conditions and has been shown to reduce the rates of invasive pneumococcal disease (IPD) [7]. Studies of effectiveness of PPV-23 in this group of patients have yielded inconclusive results [8–10]. Moreover, immunity may wane more rapidly in COPD patients [11,12]. Patients with asthma are also at risk for IPD, but it is not clear if they respond better that COPD patients. Concomitant infection may blunt the response to vaccination, and vaccination is usually deferred after acute infections are treated. There are no data on the response to vaccination in patients with chronic pulmonary conditions characterised by chronic infection or inflammation, such as chronic pulmonary aspergillosis (CPA), allergic broncho-pulmonary aspergillosis (ABPA) or bronchiectasis.

Mannose-binding lectin (MBL) is a multimeric protein involved in the innate immune response. It activates the complement system for opsonisation, allowing recognition and ingestion of the pathogen by phagocytes. Circulating MBL is the product of the co-dominant MBL2 gene, and deficiency is coded by multiple genetic variants. MBL deficiency has been linked with a wide range of disorders, including recurrent pneumonia [13–15], worse respiratory function in those with chronic fungal disease and cystic fibrosis [16] and increased risk of death due to pneumococcal infection [15]. It is relatively common in patients with chronic lung disorders.

As no data exist on the efficacy of PPV-23 in patients with chronic respiratory infections, our aim was to establish whether patients with these conditions achieve a protective response following PPV-23 vaccination and whether MBL deficiency affects that response.

2. Methods

Consecutive patients seen in the pulmonary aspergillosis clinic of the National Aspergillosis Centre (NAC), University Hospital South Manchester (UHSM) from October 2005 to November 2011 were prospectively enrolled. Pneumococcal serology and vaccinations were performed as part of routine clinical care. Age, sex, and concomitant steroid use were documented.

2.1. Definitions

Patients attending the NAC have a range of respiratory conditions. The groups studied included those with CPA, ABPA, severe asthma with fungal sensitisation (SAFS) and bronchiectasis. CPA was defined as the presence of at least one pulmonary cavity on thoracic imaging, with or without aspergilloma with symptoms for more than 3 months (such as weight loss, fatigue, cough, haemoptysis and breathlessness), and positive *Aspergillus* serology (precipitating and/or IgG antibody) and/or positive cultures/histology for *Aspergillus* species [17]. ABPA is defined as asthma (of any severity) or sputum plug production, with elevated total IgE (>500 IU/mL, usually >1000 IU/mL), eosinophilia, positive *Aspergillus*- specific IgG or IgE or *Aspergillus* skin prick test [18]. SAFS is defined as severe asthma (British Thoracic Society/Scottish Intercollegiate Guidelines Network 2014), total IgE <1000 IU/mL (to exclude ABPA), sensitisation to one or more fungi by skin prick test or RAST test (specific IgE > 0.4 IU/mL), and negative *Aspergillus* precipitins (IgG) [19].

2.2. Pneumococcal serology and vaccination

Serotype-specific pneumococcal IgG antibodies were quantified for 12 serotypes using a multiplex microsphere assay as previously described [20]. A level of ≥0.35 μg/mL was taken to indicate a protective level per serotype pre-vaccination [21]. Patients with levels of <0.35 μg/mL to six or more serotypes were classified as having non-protective serology and were given PPV-23 (Pneumovax, Sanofi Pasteur, MSD), if they had never received this vaccine or >5 years had lapsed since the previous vaccination. Vaccine was administered intramuscularly over the deltoid area and no concomitant vaccines were administered. Vaccine history was obtained from the patient or, if unknown, from the primary care provider and serology was repeated to assess response to PPV-23 at the next routine clinic visit up to 3 months post-vaccination. Adequate response to vaccination was defined as a level of >1.3 μg/mL or a ≥ four-fold rise for ≥70% of serotypes (or 9 of 12) within 3 months post-vaccination [22].

C-reactive protein, immunoglobulin levels (IgG, IgA, IgM) and MBL levels were tested at baseline. Immunoglobulins were measured by immunonephelometry on a Siemens BNII analyser (Siemens, Frimley, UK). Serum MBL concentrations were determined by enzyme-linked immunosorbent assay (ELISA) (MBL Oligomer ELISA Kit, BioPorto Diagnostics A/S, DK) with a reported detection range of 0.5–4 mg/L. The study was registered with the Trust audit department. Ethical approval was not required as this was a service evaluation in unselected clinic patients.

2.3. Statistical analysis

Comparisons between the four disease groups for demographics, serotype response, immunoglobulin and MBL levels were carried out using Chi-square, ANOVA and Kruskal-Wallis tests as appropriate. Immunoglobulin values were log transformed prior to analysis to obtain a reasonable approximation to a normal distribution. Wilcoxon signed rank tests were performed to compare pre- and post-vaccination serology. An assessment as to whether some serotypes elicited a protective response more frequently was made using Cochrane's *Q*-test. Spearman correlations were used to investigate the associations between immunoglobulin and MBL levels.

The conventional two-sided 5% significance level was employed and the statistical software package SPSS version 20 was used throughout.

3. Results

Patient characteristics are shown in Table 1. No patients had HIV or any condition requiring immunosuppressive medications like malignancy or transplant.

3.1. Vaccine Naïve

One hundred twenty-seven (39.9%) patients seen in the clinic had never received pneumococcal vaccination. Data on all 12

Table 1
Patient demographics for the 4 underlying disease groups. CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitisation.

	n	Male (%)	Age in years (range)
CPA	156	91 (58.3)	60.4 (19–87)
ABPA	82	40 (48.8)	58.5 (29–77)
Asthma/SAFS	43	14 (32.6)	48.7 (18–68)
Bronchiectasis	36	13 (36.1)	57.6 (25–85)

serotypes were available for 124 patients; of these, 70 (56.5%) had a level of 0.35 μg/mL or higher for more than 6 serotypes. Patients with ABPA more often had a protective level for more than 6 serotypes (69.0%) compared to patients with CPA (56.1%), SAFS (50.0%) and bronchiectasis (42.9%), although this did not reach statistical significance ($p = 0.35$). The mean number of serotypes with antibody levels above 0.35 μg/mL was 6.7 for CPA, 7.3 for ABPA, 6.6 for SAFS and 5.8 for bronchiectasis ($p = 0.47$).

In all groups, the lowest levels were seen against serotypes 1 and 4 and the highest against serotype 19A (Table 2). There were no differences between the patient groups in terms of individual serotype antibody levels, although asthmatics (ABPA and SAFS) had slightly higher anti-serotype 3 antibody level (Table 2).

3.2. Post-vaccination

Fifty-five patients had pre- and post-vaccination antibody concentrations available, and 40 had concentrations available within 3 months of vaccination. Of these, 20 (50.0%) patients had an adequate response. Among different diagnoses, response rates were: 10/21 (47.6%) for CPA, 3/5 (60.0%) for ABPA, 3/7 (42.9%) for SAFS and 4/7 (57.1%) for bronchiectasis ($p = 0.91$). Table 3 shows serotype-specific antibody concentrations pre- and post-vaccination for all 55 patients. Serotype 19A, followed by 14, 19F and 18C were the commonest serotypes the patients had been exposed to and already had immunity, and serotype 4, followed by 1 and 3, were the least. Mean (SD) age for responders was 53.3 (9.8) vs. 53.9 (12.6) for non-responders ($p = 0.30$).

Overall, the poorest responses were observed for serotype 4, followed by 1 and 3 (Table 3). The mean (SD) CRP level for non-responders was 23.0 (30.3) vs. 29.8 (38.3) for responders ($p = 0.72$). History of concurrent steroid use was available for 21 patients only; therefore, steroid use could not be assessed as a factor influencing vaccination effectiveness.

Among 49 patients who had serology available 3 months-2 years post-PPV-23, 38 (77.6%) had a level of ≥0.35 μg/mL for more than 6 serotypes, a percentage significantly higher compared to pre-vaccination ($p = 0.014$). The mean number of serotypes with levels above 0.35 μg/mL was 8.8 for CPA, 9.1 for ABPA, 8.0 for SAFS and 8.8 for bronchiectasis (p, NS). For the 58 patients with levels available between 2 and 5 years post-vaccination, 42 (72.4%) had a level of ≥0.35 μg/mL for more than 6 serotypes. This retained marginal

Table 2
Frequency of antibody levels ≥0.35 μg/mL to 12 pneumococcal serotypes in vaccine-naïve patients, by patient group (only 124 patients had serotypes 3, 7F and 19A tested). CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitisation. *p* values indicate difference in percentage of protective levels for each serotype between patient groups. $p < 0.05$ is considered significant.

Serotype	% of patients with adequate levels (≥0.35 μg/mL)					4 group comparison chi-square test
	All patients ($n = 127$)	CPA ($n = 57$)	ABPA ($n = 29$)	SAFS ($n = 25$)	Bronchiectasis ($n = 16$)	
1	26	25	31	24	25	$p = 0.92$
4	16	12	24	12	19	$p = 0.49$
5	53	53	59	48	50	$p = 0.88$
6B	52	51	55	56	44	$p = 0.86$
9V	50	51	62	48	25	$p = 0.12$
14	76	75	90	72	62	$p = 0.18$
18C	70	67	72	80	62	$p = 0.57$
19F	73	79	69	76	56	$p = 0.30$
23F	61	65	59	56	56	$p = 0.84$
3	41	35	48	58	21	$p = 0.08$
7F	69	75	72	54	64	$p = 0.27$
19A	80	79	86	75	79	$p = 0.77$

Table 3
Serotype-specific antibody concentrations pre- and post-vaccination in 55 patients with chronic lung conditions (CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitisation). Numbers indicate mean value (range), *p* values indicate significance of rise in antibody titre for each serotype post-vaccination. $p < 0.05$ is considered significant.

Serotype	CPA $n = 24$		*p*	ABPA $n = 8$		*p*	SAFS $n = 11$		*p*	Bronchiectasis $n = 12$		*P*
	Pre	Post		Pre	Post		Pre	Post		Pre	Post	
1	0.10 (0.1–281)	0.54 (0.01–308)	0.001	0.21 (0.05–12.1)	1.18 (0.05–152)	0.021	0.14 (0.05–0.24)	0.89 (0.08–3.5)	0.005	0.20 (0.05–2.64)	1.52 (0.01–18.1)	0.015
4	0.09 (0.01–0.45)	0.22 (0.01–14.5)	0.001	0.19 (0.05–0.30)	0.26 (0.04–14.1)	0.26	0.06 (0.01–0.37)	0.50 (0.04–12.8)	0.007	0.13 (0.01–0.36)	0.21 (0.01–1.74)	0.017
5	0.22 (0.01–6.0)	2.25 (0.01–99)	0.001	0.25 (0.05–4.2)	1.95 (0.05–229)	0.025	0.15 (0.05–0.94)	9.98 (0.29–12.8)	0.003	0.40 (0.04–1.55)	5.70 (0.04–28)	0.003
6B	0.22 (0.01–11.7)	1.03 (0.05–91)	0.001	0.16 (0.05–2.2)	1.11 (0.05–2.96)	0.13	0.10 (0.01–9.8)	1.80 (0.05–382)	0.005	0.19 (0.01–6.22)	3.30 (0.20–17.1)	0.002
9V	0.16 (0.01–0.92)	1.74 (0.01–29)	0.001	0.33 (0.09–0.96)	1.56 (0.05–30)	0.018	0.17 (0.02–2.14)	0.75 (0.09–13.4)	0.004	0.12 (0.01–4.83)	1.70 (0.46–33)	0.002
14	0.35 (0.05–54)	5.96 (0.05–265)	0.003	2.25 (0.05–7.9)	13.3 (0.47–125)	0.012	1.69 (0.17–27)	8.77 (0.01–486)	0.021	0.52 (0.01–33)	8.06 0.12–36)	0.028
18C	0.54 (0.01–13.7)	5.90 (0.01–88)	0.001	0.18 (0.05–1.73)	3.63 (0.05–17.0)	0.017	0.79 (0.08–8.0)	11.60 (0.83–94)	0.003	1.22 (0.04–6.02)	2.92 (0.20–83)	0.008
19F	0.78 (0.01–38)	3.90 (0.09–68)	0.001	0.40 (0.05–7.9)	1.14 (0.05–24)	0.40	0.48 (0.05–12.7)	0.88 (0.05–92)	0.009	0.67 (0.05–5.47)	2.82 (0.15–54)	0.010
23F	0.26 (0.01–45)	1.12 (0.01–32)	0.001	0.89 (0.05–35)	0.85 (0.05–41)	0.18	0.16 (0.01–1.85)	2.96 (0.16–15.1)	0.003	0.39 (0.01–3.38)	3.12 (0.01–91)	0.010
3	0.15 (0.01–8.4)	0.37 (0.05–45)	0.003	0.94 (0.02–10.1)	0.41 (0.05–44)	0.31	0.32 (0.05–1.08)	0.60 (0.05–33)	0.074	0.14 (0.04–4.43)	3.16 (0.07–45)	0.028
7F	0.46 (0.05–3.0)	1.74 (0.05–183)	0.001	0.70 (0.05–2.5)	5.61 (0.24–164)	0.012	0.23 (0.04–4.2)	0.82 (0.05–23)	0.008	0.34 (0.02–1.09)	1.12 (0.09–41)	0.008
19A	1.72 (0.01–19.1)	4.62 (0.01–687)	0.014	0.66 (0.05–19.5)	11 (0.05–606)	0.56	1.02 (0.03–6.9)	2.62 (0.04–456)	0.037	1.40 (0.08–17)	4.76 (0.17–98)	0.06

Table 4
Immunoglobulin (mg/L) and MBL (mg/L) levels in the 4 patient groups. CPA, chronic pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitisation. MBL, mannose binding lectin. p values indicate difference in levels among the different patient groups. $p < 0.05$ is considered significant.

		N	Mean	Range
IgG values	CPA	144	13.0	3.3 to 35.2
	ABPA	80	9.9	5.2 to 30.5
	SAFS/asthma	36	8.6	1.2 to 19.1
	Bronchiectasis	30	10.7	7.4 to 18.2
			$p < 0.001$	
IgA values	CPA	147	3.0	1.0 to 10.0
	ABPA	81	2.4	0.4 to 9.2
	SAFS/asthma	36	2.1	0.7 to 4.7
	Bronchiectasis	31	2.3	0.7 to 6.4
			$p < 0.001$	
IgM values	CPA	146	0.9	0.2 to 3.7
	ABPA	81	0.8	0.2 to 4.0
	SAFS/asthma	36	1.0	0.5 to 2.7
	Bronchiectasis	29	0.8	0.4 to 1.5
			$p = 0.22$	
		N	Median	Range
MBL values	CPA	149	1.9	<0.05 to >4.0
	ABPA	78	1.3	<0.05 to >4.0
	SAFS/asthma	29	1.2	<0.05 to 3.9
	Bronchiectasis	8	0.5	<0.05 to >4.0
			$p = 0.03$	

significance compared to pre-vaccination ($p = 0.05$). The mean number of serotypes with levels above the 0.35 μg/mL cut-off was 7.9 for CPA, 9.0 for ABPA, 8.3 for SAFS and 8.3 for bronchiectasis (p, NS). Twenty patients received a second dose of PPV-23 if more than 5 years had elapsed from a previous dose, and had levels checked within 3 months; only 7 (35.0%) had an adequate response.

3.3. Immunoglobulin and MBL levels

Patients with CPA had statistically higher levels of IgG and IgA but not IgM, likely consistent with chronic ongoing inflammatory response (Table 4). We identified 7 patients with hypogammaglobinaemia (IgG <6.0 mg/L; 3 with CPA, 3 with SAFS and 1 with ABPA) and no patients with selective IgA deficiency. None of the patients with hypogammaglobinaemia had a protective response to the vaccine. Profound MBL deficiency (<0.5 mg/L) was found in 76/264 (28.8%) patients. Of the 55 patients with pre- and post-vaccination serotype levels, 39 had MBL data. Of these, 15 (38.5%) were MBL-deficient. Six of the 15 MBL-deficient patients (40.0%) had an adequate response compared to 11/24 (45.8%) of those with adequate MBL levels ($p = 0.72$). MBL deficiency was more common in bronchiectasis, although data was available for only 8 patients with this condition (Table 4). Higher MBL levels were associated with higher IgG (Spearman correlation rho = 0.22; $p = 0.004$) and IgA (rho = 0.15; $p = 0.05$) levels.

4. Discussion

This study reports the response rates to PPV-23 in patients with chronic or allergic aspergillosis. The proportion of poor responders is higher than that reported in previous studies of healthy adults or patients with other chronic lung diseases, although such studies suffer from lack of standardisation [23–25]. The poor response may be attributed to the ongoing inflammation observed in chronic infections; however, this was not reflected in the inflammatory markers (CRP).

Studies of vaccine programmes of individuals with chronic infections such as malaria and hepatitis in developing countries have shown that they are less likely to develop protective immunity from vaccines for unrelated illnesses. The underlying mechanisms for that impairment are unclear [26]. Studies have revealed that humoral immunity is affected by chronic infections. Polysaccharide antigens as in the PPV-23 vaccine stimulate B-lymphocytes. Altered chemokine production due to chronic infections may affect B-cell migration and the formation of germinal centres where B cells differentiate and proliferate. Additionally, altered cytokine production by chronic infections can significantly affect the differentiation and survival of plasma cells, resulting in defective antibody responses [27]. Studies on hepatitis and HIV patients have identified abnormal B-cell subpopulations, such as exhausted or anergic B cells, not only HIV- or Hepatitis C-specific B cells [28,29]. Blood dendritic cells and splenic marginal zone macrophages trap polysaccharide antigens before transferring them to marginal zone B cells that produce protective antibodies [30–32]. Chronic infections may also lead to altered antigen-presenting cell function.

Post-vaccination antibody concentrations waned gradually, however they were still significantly elevated compared to pre-vaccination after 2–5 years. There was no difference in the rate of decline in patients with CPA or ABPA/asthma. As expected, revaccination with PPV-23 five or more years later did not result in improved response compared to primary vaccination. Previous data has shown that a comparable response can be achieved with repeat vaccination [33].

A significant number of patients seen in clinic for the first time had never been vaccinated with PPV-23 despite relevant recommendations for patients with chronic lung disease. Uptake of PPV-23 may be suboptimal; efforts should focus on vaccinating patients with chronic lung disease both in primary care and specialist clinics.

MBL deficiency has been noted more frequently in patients with CPA than in normal controls and may increase susceptibility to Aspergillus disease [34]. MBL deficiency also results in susceptibility to other infections, such as IPD. Therefore, vaccination may be recommended for MBL-deficient individuals. We found that MBL deficient patients responded to PPV-23 at least as well as MBL-sufficient patients, and our findings agree with those of van Kessel et al. [35].

A major limitation of our study is the lack of outcome data, such as hospitalisation for pneumonia, infective exacerbations, or mortality. There have been several randomised controlled trials (RCT) on the efficacy of PPV-23 in patients with chronic lung disease. Results have been conflicting; a meta-analysis of 7 RCTs found a trend but no statistically significant reduction in pneumonia (OR 0.72), frequency of infective exacerbations (OR 0.58) and all-cause mortality (OR 0.94) [36]. Therefore, PPV-23 may reduce overall morbidity, however no definite benefit in measurable outcomes has been observed. The conclusion of the meta-analysis was that a larger study is required in order to demonstrate effectiveness of the vaccine. With the relatively small numbers of patients included in our study, we would likely not be able to demonstrate a significant benefit on outcomes with PPV-23.

In addition, patients with chronic lung disease have been known to have higher pneumococcal serotype antibody levels compared to the general population, perhaps because of more frequent pneumococcal infections [12,25]. This may make comparisons with post-vaccine serology difficult to interpret and may underestimate vaccine response. This may be partially overcome in our study as we vaccinated only patients with non-protective titres for at least 6 serotypes.

Another limitation of the study is the use of the cut-off of 1.3 μg/mL or a 4-fold rise in titres as evidence of adequate response to pneumococcal vaccination. Although recommended in guidelines, this cut-off has not been validated and there is no consensus on the most appropriate cut-off [22]. History of steroid use was

not available for most patients; therefore, no conclusions could be reached on the effect of steroids on vaccine effectiveness.

In conclusion, patients with chronic aspergillosis respond poorly to pneumococcal polysaccharide vaccination. Postponing vaccination until the chronic condition is under better control, i.e. after treatment with antifungals in our patients, may result in a better serological response to vaccination and better protection. Alternatively, use of conjugate vaccine before PPV-23 may offer better protection, in a regimen similar to that recommended for the immunocompromised [7]. This needs further study, as T-cell dependent responses are also probably affected by chronic infection [37].

Conflict of interest statement

All authors report no conflicts of interest.

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