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The total IgM, IgA and IgG antibody responses to pneumococcal polysaccharide vaccination (Pneumovax®23) in a healthy adult population and patients diagnosed with primary immunodeficiencies

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ABSTRACT

Background: Interpretation of the responses to the pneumococcal polysaccharide vaccine (Pneumovax®23, PPV) has proven challenging. In addition, there are few studies documenting the longevity of these responses.
Methods: The age-specific PPV IgM, IgA, IgG and IgG2 concentrations were determined pre, 4–6 weeks and 6 years post-vaccination in the serum of Prevnar®-naïve adults using VaccZyme™ pneumococcal capsular polysaccharide ELISAs.
Results: The median pre-vaccination concentrations were; PPV IgM 53 U/mL (5–95% CI: 16-169 U/mL), IgA 23 U/mL (6-103 U/mL), IgG 41 mg/L (10-184 U/mL) and IgG2 18 mg/L (3-95 U/mL). 4–6 weeks post-vaccination there was a median 6-fold (5–95% CI: 2–24) increase in PPV IgM (median 315 U/mL (5–95% CI: 60-1133 U/mL), 18-fold (4–74) increase in IgA (369 U/mL (78-1802 U/mL)), 9-fold (2–19) increase in IgG (375 mg/L (77–1238 mg/L)) and 8-fold (1–20) increase in IgG2 (141 mg/L (25–573 mg/L)). This was significant for all isotypes in all age ranges ($p < 0.0001$). Six years post-vaccination median PPV concentrations were; IgM 54 U/mL (17–128), IgA 85 U/mL (19–279), IgG 148 mg/L (30–997) and IgG2 57 mg/L (9–437). The median concentrations for all ages 6 years post-vaccination were significantly elevated compared to the pre-vaccination titres for PPV IgA, IgG and IgG2 isotypes only. The PPV IgM and IgA responses were influenced by age. At 6 years post vaccination, in individuals with normal PPV IgG, 34 individuals had PPV IgM and/or IgA concentrations below the lower limit of the healthy adult ranges. We also used the healthy adult reference ranges developed in this study to assess a cohort of primary immunodeficiency (PID) patients.
Conclusion: These ranges will help to provide a framework for assessment and definition of normal response to PPV, which will facilitate clinical interpretation of a deficient polysaccharide response in those suspected of antibody deficiency.

1. Introduction

Interpretation of the pneumococcal polysaccharide vaccine (PPV, Pneumovax®23) antibody concentrations and antibody longevity post-vaccination has proven challenging and to date there are few studies reporting the responses in a healthy adult population. The definition of a normal response, and the development of normal concentration ranges for PPV IgG antibodies have been problematic as immunisation with the protein-conjugate vaccine (Prevnar®) complicates interpretation [1]. In addition, responses can differ greatly for the individual 23 serotypes and may also vary with age [2]. Since the IgM, IgA, IgG and IgG2 responses to PPV are important tools for aiding in the diagnosis and monitoring of individuals with a compromised adaptive immune system [1,3–7], and given that the responses can be variable in heterogeneous immunodeficiencies it is essential that concentration ranges and responses in healthy populations are established and defined.

Measurement of pneumococcal antibodies can be achieved with measurement of a cumulative antibody response to all 23 serotypes, or with the measurement of individual serotype-specific antibodies [8–13]. Measurement of total pneumococcal antibodies in response to PPV may have some advantages over serotype

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analysis as there are standardized commercial assays available that are widely used. Interpretation may be simpler and it has been proposed that such a measurement may be a useful screening tool for patients being evaluated for a humoral immunodeficiency, reflexing to serotype-specific analysis when needed [1,14]. In addition to measurement of the IgG isotype, measurement of pneumococcal IgM, IgA and IgG2 can be achieved by commercially available ELISA kits [4,15–17].

In the present study, we aimed to define the PPV IgM, IgA, IgG and IgG2 concentration ranges and responses to PPV pre-vaccination and at 4–6 weeks and 6 years post-vaccination in 100 Prevnar-naïve adults.

2. Materials and Methods

2.1. Volunteer inclusion criteria

Healthy subjects were eligible to participate in the study if they met all of the following inclusion criteria: male or female adults aged 18 years or older on the date of vaccination or after physician evaluation, able to return for 2 follow-up visits (4–6 weeks and 6 years post-vaccination) and willing to comply with study guidelines and requirements. Additionally, these healthy adult donors were screened to determine lack of recurrent infections and inflammation at the time of vaccination, and were free of pneumococcal infection in the period 4 weeks to 6 year post-vaccination.

2.2. Exclusion criteria

Subjects were ineligible to participate in this study if they met any of the following exclusion criteria:

(1) Previous vaccination with any licensed or experimental pneumococcal vaccine prior to commencement of the study.
(2) Contraindication for vaccination with PPV.
(3) History of severe adverse reactions associated with a vaccine or vaccine component.
(4) Pregnancy or plans to be pregnant within 3 months of starting the study.
(5) If the patient was ever diagnosed with an immune deficiency or immune suppression, defined as presence of one or more of the following conditions:
    (a) Previous or current diagnosis of an immunodeficiency (primary or secondary).
    (b) Previous or current diagnosis of autoimmune disease
    (c) Previous or current diagnosis of malignancies
    (d) Previous or current diagnosis of diabetes.
    (e) Current diagnosis of active infection such as pneumonia, otitis media, HIV or other significant viral infection etc.
    (f) Previous or current diagnosis of renal disease such as nephritis or nephrotic syndrome.
    (g) Previous or current diagnosis of protein-losing enteropathy.
(6) On any form of systemic, and sustained immunosuppression.

2.3. Healthy adult volunteer sample selection

100 normal healthy adult volunteers were initially recruited into the study between 2008 and 2010, with 77 of these meeting the above defined inclusion and exclusion criteria (40 males and 37 females; median age 44 years, range 22–66). All individuals were vaccinated with Pneumovax®23 (25ug per serotype/0.5 mL) at the Mayo Clinic, Rochester, Minnesota, USA and were required to complete a health-related questionnaire. Samples were collected pre-vaccination, 4–6 weeks post-vaccination and 6 years post-vaccination and stored at −80 °C.

Samples were available from 67 individuals for all three time points and from 77 individuals for the pre-vaccination and 4–6 weeks post-vaccination time points only.

2.4. Primary immunodeficiency (PID) patients

Data were obtained from 102 patients (median age 41 years, range 18–74) diagnosed with primary antibody deficiency at the Mayo Clinic, Rochester, Minnesota, USA (Common Variable Immunodeficiency, (CVID) n = 37; CVID with granulomatous lymphocytic interstitial lung disease (GLILD) n = 21; unclassified PID n = 39; X-linked agammaglobulinemia (XLA), n = 5). All patients were vaccinated with PPV and samples taken within 2 years of vaccination.

2.5. Ethics

Sample collection was approved by the Mayo Clinic Institutional Review Board with external collaboration with The Binding Site Group. All participants provided written informed consent.

2.6. Measurement of PPV antigen-specific antibodies

Commercially available ELISA kits (VaccZyme™ pneumococcal capsular polysaccharide ELISAs, The Binding Site Group Limited, UK) were used to measure PPV IgM, IgA, IgG and IgG2 according to the manufacturer's instructions. All four ELISAs employ the use of C-polysaccharide absorption to improve the specificity of pneumococcal antibody detection. The data obtained was stratified by age. Median values and 5–95% confidence intervals (5–95% CI) were calculated to establish the healthy adult concentration ranges for each age group. Cut-offs used in this study were the lower limit of the normal range (LLNR) and the median values (see Table 1). The LLNR was determined by calculating the 5th percentile of the PPV IgG, IgG2, IgM and IgA antibody concentrations in the 77 healthy volunteers 4–6 weeks post-vaccination.

2.7. Statistical analysis

Index of Individuality (II) was calculated using the following formula (CV_I/CV_G) where CV_I is the within subject biological variation and CV_G the between subject biological variation. Shapiro-Wilks, Kruskal-Wallis, Fishers exact test, and Mann Whitney U tests were performed using Graphpad Prism software. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Total PPV responses in a healthy adult population

The PPV IgM, IgA, IgG and IgG2 concentrations pre-vaccination, and in response to PPV vaccination in the healthy adult population 4–6 weeks and 6 years post-vaccination are shown in Table 1. The LLNR was determined from the 4–6 week post-vaccination concentrations (PPV IgG 77 mg/L, PPV IgG2 25 mg/L, PPV IgA 78 U/mL and PPV IgM 60 U/mL). The increase in concentrations between pre- and 4–6 weeks post-vaccination were significant for all immunoglobulins. The median concentrations of PPV IgA, IgG and IgG2 but not IgM were significantly higher than the pre-vaccination concentration at 6 years post-vaccination. The Indices of Individuality (II) for PPV IgM, IgA, IgG and IgG2 are shown in Supplementary Table 1. IgA had the largest II and IgG2 the lowest, with the II for all specific responses to PPV > 1.0.

Table 1
The PPV IgM, IgA, IgG and IgG2 concentrations pre vaccination, at 4–6 weeks and 6 years post PPV-vaccination in a healthy adult population.

	Pre-vaccination	Adult median antibody concentrations and fold increase in concentrations pre/post-vaccination (5–95% CI)					
		4–6 weeks post-vaccination			6 years post-vaccination		
	Median Concentration (5–95% CI)	Median Concentration (5–95% CI)	P value†	Fold Increase (5–95% CI)	Median Concentration (5–95% CI)	P value†	Fold Increase (5–95% CI)
Sample number	77	77			67		
PPV IgM (U/mL)	53 (16–169)	315 (60–1133)	<0.0001	6 (2–24)	54 (17–128)	0.85	1 (1–2)
PPV IgA (U/mL)	23 (6–103)	369 (78–1802)	<0.0001	18 (4–74)	85 (19–279)	<0.0001	3 (1–19)
PPV IgG (mg/L)	41 (10–184)	375 (77–1238)	<0.0001	9 (2–19)	148 (30–997)	<0.0001	4 (1–12)
PPV IgG2 (mg/L)	18 (3–95)	141 (25–573)	<0.0001	8 (1–20)	57 (9–437)	<0.0001	4 (1–11)

† P value is for the appropriate post vaccination concentration relative to the pre vaccination concentration.

3.2. Age-specific pneumococcal responses in a normal adult population

The age-specific responses to PPV are shown in Fig. 1 and Tables 2 and 3. The median increase in concentration between pre- and 4–6 weeks post-vaccination were significant for all ages and all immunoglobulins ($p < 0.0001–0.0002$). The median concentrations of PPV IgA, IgG and IgG2 were significantly higher at 6 years post-vaccination than at pre-vaccination for all ages ($p = 0.0002–0.04$) but not for PPV IgM ($p = 0.1–0.8$).

The IgM and IgA responses were influenced by age. The IgM concentrations at pre-vaccination and 4–6 weeks post-vaccination ($p = 0.002$ and $p = 0.0003$ respectively) and the IgA concentrations 4–6 weeks post-vaccination ($p = 0.005$) decreased with increasing age. Age did not influence the IgG or IgG2 response.

3.3. Correlation of pneumococcal responses in a healthy adult population

Correlations between the total immunoglobulins and PPV responses are shown in Supplementary Table 2. The median concentrations highly correlated between PPV IgG and PPV IgA ($p = 0.001$ and $p = 0.006$, Supplementary Table 3, respectively) but not between PPV IgM and PPV IgA ($p = 0.13$ and $p = 0.06$) or between PPV IgM and PPV IgG ($p = 0.19$ and 0.11) (Supplementary Table 3).

3.4. Longitudinal assessment of PPV IgA and IgM in individuals with normal PPV IgG post-vaccination

PPV IgM, IgA and IgG2 responses were assessed in individuals with PPV IgG greater than the LLNR (>77 mg/L) post-vaccination (Fig. 2). At 4–6 weeks post vaccination, 74/77 individuals had PPV IgG > 77 mg/L. In those individuals 2, 1 and 2 individuals had PPV IgM, IgA and IgG2 concentrations < LLNR. At 6 years post-vaccination, 51/67 individuals had PPV IgG > 77 mg/L. Of these 27, 18 and 0 had PPV IgM, IgA and IgG2 concentrations < LLNR. A total of 34 individuals had PPV IgG concentrations above the LLNR but PPV IgM and/or IgA concentrations below the LLNR 6 years post-vaccination.

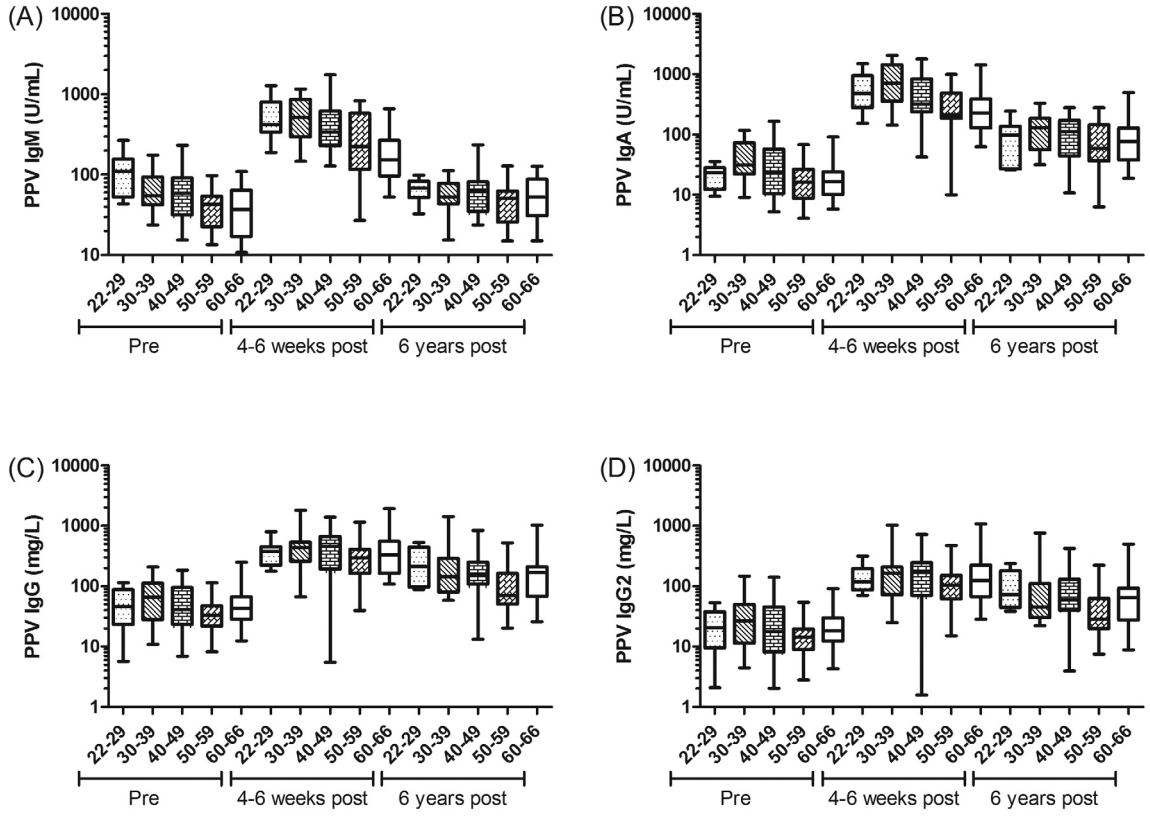

Fig. 1. Age-stratified concentrations of PPV (A) IgM, (B) IgA, (C) IgG and (D) IgG2. Specific antibody concentrations were defined in a healthy adult population vaccinated with PPV at pre-vaccination and 4–6 weeks and 6 years post-PPV. Box and Whisker plots show median concentrations, interquartile range and minimum/maximum values.

Table 2
The age specific PPV IgM, IgA, IgG and IgG2 concentrations pre-vaccination and 4–6 weeks and 6 years post PPV-vaccination in a healthy adult population.

	Age stratified median antibody concentrations (5–95% CI)														
	Pre-vaccination				4–6 weeks post-vaccination					6 years post-vaccination					
Age ranges (years)	22–29	30–39	40–49	50–59	60–66	22–29	30–39	40–49	50–59	60–66	22–29	30–39	40–49	50–59	60–66
Sample number	11	18	17	15	16	11	18	17	15	16	7	16	15	13	16
PPV IgM (U/mL)	109 (43–268)	55 (24–175)	59 (16–233)	43 (14–98)	37 (11–109)	418 (189–1275)	519 (146–1158)	340 (129–1756)	223 (27–830)	153 (53–660)	68 (33–99)	53 (16–113)	61 (24–234)	50 (15–128)	52 (15–128)
PPV IgA (U/mL)	23 (9–36)	31 (9–118)	23 (5–165)	16 (4–68)	17 (6–92	477 (153–1496)	711 (141–2059)	318 (43–1793)	211 (10–996)	224 (63–1431)	97 (26–244)	131 (31–331)	113 (11–279)	59 (6–279)	76 (19–496)
PPV IgG (mg/L)	46 (6–115)	65 (11–208)	41 (7–184)	33 (8–114)	43 (12–250	379 (178–807)	439 (66–1817)	459 (5–1396)	294 (40–1148)	332 (108–1931)	213 (89–535)	142 (58–1433)	153 (13–846)	70 (20–528)	169 (26–1029)
PPV IgG2 (mg/L)	21 (2–54)	27 (4–147)	18 (2–141)	14 (3–54)	18 (4–92)	118 (70–319)	166 (25–1029)	169 (2–724)	103 (15–474)	123 (29–1077)	73 (38–237)	45 (22–769)	60 (4–423)	28 (8–223)	64 (9–501)

3.5. Use of healthy adult reference ranges to assess a cohort of PID patients

We used the reference ranges to compare the pneumococcal responses in 102 patients diagnosed with a PID (Fig. 3). The percentage of non-responders were high for PPV IgM and IgA but lower for PPV IgG and IgG2 (78% vs 88% vs 63% vs 49%, $P < 0.0001$).

4. Discussion

Current guidelines recommend measurement of PPV IgG only for the assessment of polysaccharide antibody production in individuals suspected of antibody deficiency. The IgG responses to PPV are complicated due to the success of Prevnar. Additionally, knowledge of antibody decrease post-vaccination per unit time in a healthy adult population is lacking. Such information is required to set the threshold for interpretation of the antibody response to PPV. In the present study, we report age-specific concentration reference ranges and responses for PPV IgM, IgA, IgG and IgG2 pre-vaccination, 4–6 weeks post-vaccination and 6 years post-vaccination in a population of healthy adults.

Recent data suggests that additional measurement of PPV IgM and IgA may provide identification of those individuals who have a persistent antibody deficiency, as well as those most at risk of infection [4,5,7,18,19] suggesting the utility and value of a multi-isotypic approach to defining a deficient antibody response. The purpose of this study was to assess the antibody response to PPV in a healthy adult age-defined population at 4–6 weeks and 6 years post vaccination. The pre-vaccination concentrations for all four immunoglobulins were comparable, where reported, to previous publications [13,16,20]. However, Cavaliere et al. reported that the pre-vaccination PPV IgM and IgA concentrations in several CVID patients were lower than the LLNR reported in this study (PPV IgM 35 U/mL vs 60 U/mL, PPV IgA 46.7 U/mL vs 78 U/mL respectively) [4]. In addition, Chua et al. and Janssen et al. [1,15] also reported several antibody deficiency patients with a post-vaccination PPV IgG concentration < 40 mg/L. Their results together with data presented in this study suggest pre-vaccination concentrations below the LLNR may be a useful baseline screen for identifying an antigen-specific antibody deficiency.

Adult age-specific reference ranges for the increase in concentration from pre- to post-vaccination, and the final concentrations post-vaccination for all PPV immunoglobulins were developed. There was at least a two-fold increase in PPV IgG concentration post-vaccination, which is supportive of previous studies suggesting a 2–4 fold increase for the assessment of antibody deficiency [6,21]. Post-vaccination antibody concentration is a correlate of protection as it is statistically associated with vaccine-induced protection [22,23]. Achievement of a post-vaccination antibody concentration is important irrespective of magnitude of response, and for IgG, the LLNR or correlate of protection in the normal adult population was 77 mg/L. This is higher than previously defined by Chua et al. (50 mg/L determined from the geometric mean of two studies of healthy unvaccinated adults) [15].

The reference ranges developed in this study were used to assess a cohort of PID patients. The percentage of non-responders was higher for PPV IgM and IgA compared to PPV IgG and IgG2. The responders for PPV IgM and IgA were almost exclusively in individuals diagnosed with PIDs other than CVID and XLA. This association could not be statistically validated due to small numbers in some patient groups, but it would be interesting to explore this association further in a larger population. Responders for PPV IgG and IgG2 were a mixture representing all four groups of PID patients. It is important to note, that this was a retrospective analysis, and did not account for the fact that several patients in each

Table 3
The age specific fold increases in concentrations from pre-vaccination to 4–6 weeks and 6 years post PPV-vaccination for PPV IgM, IgA, IgG and IgG2 in a normal healthy adult population.

	Median fold increase in concentrations pre/post vaccination (5–95% CI)									
	4–6 weeks post-vaccination					6 years post-vaccination				
Age ranges (years)	22–29	30–39	40–49	50–59	60–66	22–29	30–39	40–49	50–59	60–66
Sample number	11	18	17	15	16	7	16	15	13	16
PPV IgM (U/mL)	3 (2–25)	8 (2–23)	6 (1–35)	5 (2–23)	4 (1–39)	0.8 (0.3–2)	0.9 (0.6–2)	0.9 (0.7–2)	1 (0.7–2)	1 (0.9–4)
PPV IgA (U/mL)	21 (15–65)	19 (3–86)	15 (4–177)	20 (1–67)	14 (3–73)	4 (2–7)	3 (0.9–20)	2 (1–18)	3 (0.7–17)	4 (1–21)
PPV IgG (mg/L)	9 (2–51)	8 (0.7–17)	11 (0.5–22)	10 (1–22)	8 (2–19)	4 (2–11)	4 (1–10)	3 (0.8–23)	2 (0.6–12)	3 (0.9–38)
PPV IgG2 (mg/L)	10 (2–51)	7 (0.8–17)	10 (0.5–28)	9 (1–17)	8 (2–20)	4 (2–11)	4 (0.9–8)	3 (0.8–25)	2 (0.6–10)	3 (0.9–43)

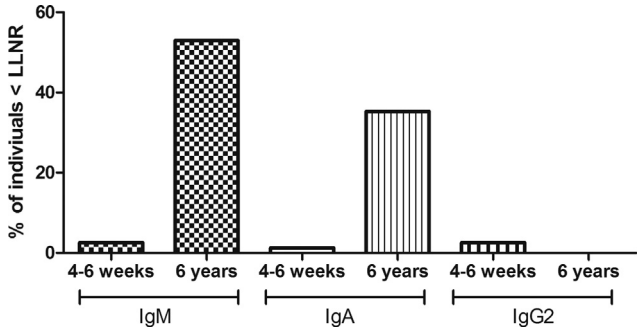

Fig. 2. Percentage of healthy individuals with normal PPV IgG that had low concentrations of PPV IgG2, IgM or IgA at 4–6 weeks and 6 years post-vaccination. In individuals with normal PPV IgG (>77 mg/L), the percentage of individuals with antibody concentrations below the LLNR for PPV IgG2, IgM or IgA was calculated at 4–6 weeks and 6 years post-vaccination.

group may have received immunoglobulin replacement, which can confound interpretation of the antibody data.

Previous studies have reported influence of age on the response to pneumococcal vaccination. Park and Nahm, and Ademokun et al. [24,25] reported that older adults (>65 years) had lower PPV IgM and IgA in response to PPV compared to younger adults. In addition, adults (>55 years of age) vaccinated with PPV failed to demonstrate a decrease in the risk of pneumonia (reviewed in [26]). In this study the PPV IgM and IgA responses, but not the PPV IgG responses were influenced by age. With increasing age the pre-vaccination concentration of PPV IgM antibodies decreased, and at post-vaccination time points (4–6 weeks, and 6 years) the concentrations of both PPV IgM and IgA decreased.

The pneumococcal responses for all four immunoglobulins did not correlate with their total respective immunoglobulins, whereas the concordance between PPV IgA and PPV IgG were significant. Using LLNR or median concentrations as a cut-off, PPV IgG did not always predict PPV IgM.

The intra-subject variation (CV_I) for PPV IgM, IgA, IgG and IgG2 was higher than the inter-subject variation (CV_G) leading to high indices of individuality (II). The high II was driven by the concentration variation that exists between pre, 4–6 weeks and 6 years post-vaccination.

A major topic of debate has been the expected rate of decrease of antibody concentrations post-vaccination. Definition of an expected rate would allow identification of those who fail to maintain production post-vaccination as an indicator of antibody deficiency. Moschese and colleagues identified the failure to maintain pneumococcal IgM, IgA and IgG concentrations post-vaccination in a child diagnosed with unclassified hypogammaglobulinemia [5]. We identified a significant number of individuals who retain a concentration of PPV IgA, IgG and IgG2 antibodies within the age-specific ranges developed at 4–6 weeks. A high percentage of individuals, however, had PPV IgM concentrations below the age-specific ranges developed at 4–6 weeks post-vaccination. The number of individuals with a PPV IgG concentration within the normal adult ranges and PPV IgM and/or IgA less than LLNR was 4% 4–6 weeks post-vaccination and increased to 67% 6 years post-vaccination.

Using the responses to PPV, antibody-deficient patients may be stratified according to their risk of infection. Hanitsh and colleagues reported that 13/28 hypogammaglobulinemia patients had pneumococcal responses for IgM, IgA and IgG below the lower limit of normal recorded in this study. Those with no detectable

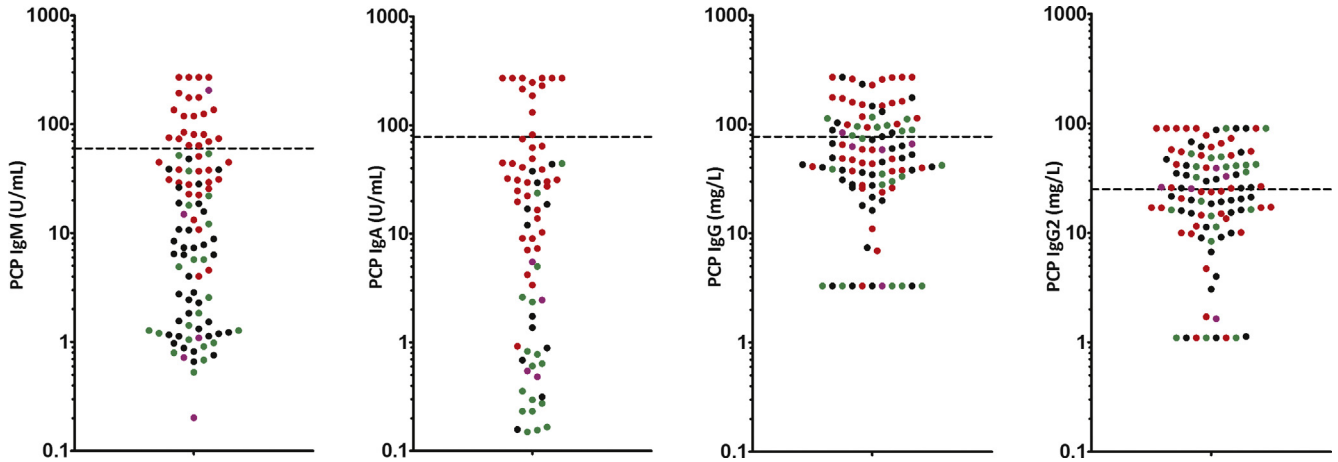

Fig. 3. Measurement of PPV IgM, IgA, IgG and IgG2 concentrations 4–6 weeks post-vaccination in PID patients. The concentrations are plotted for each of 102 PID patients. The dotted line in each graph is the LLNR for each specification. Black circles, CVID patients; green circles, CVID-GLILD patients; red circles, other PID and blue circles, XLA patients.

IgM or IgA responses had a higher percentage of pneumonia and sinusitis [18]. Cavaliere et al., identified four phenotypes with response to IgA and IgM in CVID patients receiving antibody replacement therapy. Using data derived from this study, a significant proportion of patients would have had IgM and IgA concentrations below the normal ranges, and correspondingly, a higher proportion with pneumonia and bronchiectasis [4].

In conclusion, we report the development of age-specific reference ranges for PPV IgM, IgA, IgG and IgG2 in a healthy adult population at pre, 4–6 weeks and 6 years post PPV-vaccination. These ranges are useful in defining what constitutes a normal response to PPV, with the intention of facilitating clinical classification of patients who may have a global humoral immunodeficiency, or impaired antigen-specific antibody responses. This study highlights the relevance of assessing more than IgG-specific antibody response to pneumococcal polysaccharide, and provides a practical framework for evaluating multiple immunoglobulin isotypes to better define the antibody response and deficiency to a specific vaccine.

Conflicts of interest

ARP and SH are employees of The Binding Site Group Limited who manufacture the PPV IgM, IgG, IgA and IgG2 ELISAs.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.01.035.

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