Journal of Immunological Methods xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Immunological Methods

journal homepage: www.elsevier.com/locate/jim

Review

Measurement and interpretation of *Salmonella typhi* Vi IgG antibodies for the assessment of adaptive immunity

Antony R. Parker[a,*], Caroline Bradley[a], Stephen Harding[a], Silvia Sánchez-Ramón[b], Stephen Jolles[c], Sorena Kiani-Alikhan[d]

[a] The Binding Site Group Limited, Birmingham, UK
[b] Department of Clinical Immunology Hospital Universitario Clínico San Carlos, Madrid, Spain
[c] Immunodeficiency Centre for Wales, University Hospital of Wales, Cardiff, UK
[d] Department of Immunology, Barts and The London National Health Service Trust, London, UK

ARTICLE INFO

Keywords:
Vaccine response
Humoral immunodeficiency
Immunoglobulin replacement
Vi polysaccharide antigen
Typhim Vi
Pneumococcal polysaccharide antigens
Pneumovax

ABSTRACT

Response to polysaccharide vaccination can be an invaluable tool for assessing functionality of the adaptive immune system. Measurement of antibodies raised in response to Pneumovax®23 is the current gold standard test, but there are significant challenges and constraints in both the measurement and interpretation of the response. An alternative polysaccharide vaccine approach (*Salmonella typhi* Vi capsule (ViCPS)) has been suggested. In the present article, we review current evidence for the measurement of ViCPS antibodies in the diagnosis of primary and secondary antibody deficiencies. In particular, we review emerging data suggesting their interpretation in combination with the response to Pneumovax®23 and comment upon the utility of these vaccines to assess humoral immune responses while receiving immunoglobulin replacement therapy (IGRT).

1. Introduction

Primary immunodeficiencies (PIDs) are a group of over 300 diseases caused by inherited or genetic defects in one or more components of the immune system (Picard et al., 2015). Timely and appropriate diagnosis of PID is imperative to optimise patient treatment, reduce the risk of infections, comorbidities and avoid permanent tissue or organ damage (Chapel et al., 2014; Sanges et al., 2017; Yazdani et al., 2017). Moreover, patient healthcare costs have been demonstrated to be substantially reduced after a diagnosis of PID (Modell et al., 2011). Secondary immunodeficiencies (SID) originate from external underlying factors that are not primary in origin but compromise the function of the immune system. Causes that may suppress the immune system include haematological malignancies, immunosuppressive drugs for example B cell ablation therapies like rituximab and pathogens such as the human immunodeficiency virus (HIV; reviewed in Dhalla and Misbah (2015))(Sánchez–Ramón et al., 2016).

Impairment of specific antibody responses is characteristic of a number of humoral immunodeficiencies, rendering individuals susceptible to recurrent and severe infections with encapsulated bacteria as well as rare opportunistic pathogens (McCusker and Warrington, 2011; de Vries, 2012; Sanges et al., 2017). The measurement of responses to T-cell dependent and T-cell independent antigens is essential for evaluation of the adaptive immune system (de Vries, 2008) and is recommended in peer-reviewed guidelines to aid in the clinical recognition and diagnosis of antibody deficiencies (de Vries, 2012; Orange et al., 2012; Bonilla et al., 2015). There are several primary antibody disorders in which assessment particularly rests on the determination of vaccine responses: transient hypogammaglobulinaemia of infancy (THI), IgG subclass 1, 2 and 3 deficiency, IgA deficiency (IgAD) and specific polysaccharide antibody deficiency (SPAD). The growing category of undefined hypogammaglobulinaemia also requires careful assessment of vaccine responses. Likewise, utilising the antibody response to specific antigens has also been recommended in the diagnostic assessment and subsequent monitoring of IGRT in immunodeficient patients (Jolles et al., 2017).

The clinical measurement of T-cell independent immunity can be achieved by measuring the antibody response to several polysaccharide antigens such as isohaemagglutinins, meningococcal and pneumococcal polysaccharide vaccines (Menactra® and Pneumovax®23, respectively), as well as alternative vaccines such as *Salmonella typhi* Vi polysaccharide (Typhim Vi®). At present, the gold standard for assessment of T-cell independent responses is to determine the IgG response to Pneumovax®23, which contains extracts of 23 pneumococcal capsular serotypes. Pneumovax®23 provides protection against 80–90% of pneumococcal serotypes that cause invasive pneumococcal disease and

* Corresponding author.
E-mail address: antony.parker@bindingsite.co.uk (A.R. Parker).

https://doi.org/10.1016/j.jim.2018.05.013
Received 21 November 2017; Received in revised form 26 April 2018; Accepted 21 May 2018

Table 1
Challenges in the interpretation of response to Pneumovax®23 and comparison with the use of ViCPS.

Challenges in the interpretation of response to Pneumovax®23	Solutions provided by measurement of response to ViCPS vaccines
Lack of consensus analytical approach to measure response to Pneumovax®23 makes inter-laboratory comparisons difficult	ELISA based technology is consistently used to measure response to ViCPS
Analytical discrepancies are evident between techniques used to determine antibody concentrations to individual serotypes and when compared to the overall antibody response to all Pneumovax®23 containing serotypes (Janssen et al., 2014; Reynolds et al., 2015; Lopez et al., 2016; Dziadzio et al., 2017)	Consistency has been demonstrated between laboratory designed tests (LDT) and commercially available ELISAs (Bausch-Jurken et al., 2017)
Development of normal reference ranges for a healthy population has proven difficult in the background of prevalent pneumococcal disease (Hare et al., 2009; Orange et al., 2012; Bonilla et al., 2015)	Published normal reference ranges are available. Cut-offs to identify responders and non-responders have been identified (Ferry et al., 2004; Sánchez–Ramón et al., 2016; Bausch-Jurken et al., 2017; Kumarage et al., 2017).
High baseline pneumococcal antibody concentrations are prevalent and affects interpretation of response to Pneumovax®23 (Hare et al., 2009)	Low baseline concentrations of Typhi Vi IgG antibodies has been demonstrated in areas where disease prevalence is low and where it is endemic (Ferry et al., 2004; Sánchez–Ramón et al., 2016; Kumarage et al., 2017)
Use of pneumococcal conjugate vaccines in immunisation and re-immunisation schedules have made the interpretation of antibody response to Pneumovax23® potentially challenging: misleadingly elevated responses to serotypes contained in conjugated pneumococcal vaccines are evident in individuals who have previously received the conjugated vaccine, masking a true polysaccharide response (Janssen et al., 2014; Schaballie et al., 2016)	Limited availability of conjugated vaccines against typhoid fever makes interpretation of antibody response to ViCPS less complicated (Szu, 2013; MacLennan et al., 2014; Mitra et al., 2016; Jin et al., 2017)
	Conjugated vaccines are only licensed in India and China and their use will be more restricted than conjugated pneumococcal vaccines, especially in countries without endemic typhoid fever (Szu, 2013; MacLennan et al., 2014; Mitra et al., 2016; Jin et al., 2017).
Lack of consensus on interpretation of response to Pneumovax®23	Cross reactivity lower as Typhim Vi does not possess multiple serotypes Interpretation not complicated by antibodies to multiple serotypes
Future availability of conjugated vaccines with increasing serotype coverage will render interpretation and use even more challenging	Conjugated vaccines are only licensed in certain countries and its use will be more restricted than conjugated pneumococcal vaccines (Szu, 2013; MacLennan et al., 2014; Mitra et al., 2016; Jin et al., 2017).
High concentrations of pneumococcal IgG are present in antibody replacement products	Typhi Vi IgG concentrations are low in antibody replacement products (Bausch-Jurken et al., 2017)

is recommended in all adults 65 years of age and older, as well as in individuals at-risk of infection who are > 2 years of age (Centers for Disease Control and Prevention, 2010; Daniels et al., 2016; Public Health England, 2017).

There have been a number of reports highlighting the utility of the antibody response to Pneumovax®23 in assessment of immune system functionality, however, despite being the most commonly used test and employed in many laboratories (Edgar et al., 2018), both measurement and interpretation remains challenging. Furthermore, widespread vaccination of children using conjugated pneumococcal vaccines, such as Prevenar 13™, adds to the complexity of result interpretation (summarised in Table 1). These factors have spurred the search for alternative polysaccharide antigens to assess T-cell independent humoral responses and consequently measurement of the antibodies raised in response to Typhim Vi® has gathered momentum in recent years. The focus of this review is to discuss the evidence in support of ViCPS antibody assessment as an additional tool to identify individuals with poor T-cell independent adaptive immunity.

2. Vi capsular polysaccharide (ViCPS) vaccines

ViCPS is a linear homopolymer of poly-alpha(1 → 4)GalNAc*p* whose immunogenicity, in the organism *Salmonella typhi*, may depend on post translation modifications (Szu et al., 1991). Purified Vi antigen is a potent immunogen (Ahmadi et al., 2013) and hence a prime target for vaccine development against typhoid fever. Two main types of typhoid vaccines are currently available; ViCPS vaccines and a live-attenuated oral vaccine that contains the *Salmonella typhi* strain (Ty21a). Additionally, there is a limited availability of Vi-polysaccharide-protein conjugate (Vi-conjugate) vaccines, which are currently licensed for use in China and India only (Schadich et al., 2016) (Table 2).

ViCPS vaccines are licensed for use in adults and children over 2 years old and are used in areas where typhoid fever is endemic, as well as for travellers to those areas (Table 2, (Schadich et al., 2016)). ViCPS vaccines have been shown to be effective in preventing *Salmonella typhi* Vi infection (Acharya et al., 1987; Klugman et al., 1987; Dizer et al., 2002), a recent Japanese study reported seroconversion 28 days post-vaccination occurring in > 90% of individuals (Miyazu et al., 2015). Vaccination with ViCPS vaccines induces a predominantly IgG2 antibody response (Jin et al., 2017) but does not induce long term immunological memory as it provokes a T-cell independent response (Keitel et al., 1994). It is therefore recommended that at risk individuals receive revaccination every two years (Froeschle and Decker, 2010).

2.1. B cells analysis and Typhi Vi IgG production

The antibody response to ViCPS vaccination generates antigen-specific plasmablasts (Kantele et al., 1986; Kantele, 1990; Kantele and Makela, 1991; Sundstrom et al., 2008; Lundgren et al., 2009; Pakkanen et al., 2010) which aids distribution and localisation of the humoral response to effector sites using tissue specific homing receptors (Kantele et al., 2013). Post Typhim Vi® vaccination, the homing profile of ViCPS induced plasmablasts consisted of the following homing receptors: 84% peripheral lymph node, L-selectin, 56% intestinal, $\alpha_4\beta_7$-integrin, and 4% cutaneous, cutaneous lymphocyte antigen (CLA). Ty21a plasmablasts had a different homing profile. Capsular polysaccharides are regarded as T cell independent Type II antigens and in mice the antibody response to the Vi antigen is governed by B1b cells (Marshall et al., 2012). In humans, the ViCPS antibody response involves splenic marginal zone B cells (Guinamard et al., 2000; Martin et al., 2001; Martin and Kearney, 2002; Weill et al., 2009) and a B1b analogue has been proposed in human common variable immunodeficiency (CVID) patients (Rakhmanov et al., 2009; Griffin et al., 2011). Two recent studies have investigated the presence of B cell populations in response to Typhim Vi® vaccination; Bausch-Jurken et al. report IgG responders to Typhim Vi® vaccination have a higher percentage of both B cells and switched memory B cells (Bausch-Jurken et al., 2017) and Evans et al. report the total number of B cells, but not percentage of B cells, to be higher in IgG responders than non-responders (Evans et al., 2018).

Table 2
Commercially available vaccines licensed for use against *Salmonella typhi*.

Vaccine type	Vaccine name	Developer	Licensed for use	Reference
Live attenuated	Ty21a (Vivotif®)	Crucell	Adults and Children > 5 years	(Ivanoff et al., 1994; Pakkanen et al., 2015)
Vi Polysaccharide (ViCPS)	Typhim Vi™	Sanofi Pasteur	Adults and Children ≥2 years	(Acharya et al., 1987; Klugman et al., 1996; MacLennan et al., 2014; World Health Organization, 2014; Schadich et al., 2016)
	Typherix™	GSK		
	Typbar®	Bharat Biotech		
	Typho-Vi®	Biomed		
	Vax-tyVi®	Finlay Institute		
	Zerityph inj®	Boryung		
	Typhevac inj®	Shanghai Institute of Biological Products		
Vi-TT conjugate	Peda-Typh™	Biomed	Licensed in India	(MacLennan et al., 2014) (Chinnasami et al., 2015) (Mitra et al., 2016)
	Typbar-TCV®	Bharat Biotech	Licensed in India	(MacLennan et al., 2014) (Jin et al., 2017)
Vi-rEPA conjugate	Vi-rEPA®	Lanzhou Institute (China)	Licensed in China	(Szu, 2013; MacLennan et al., 2014)

The assessment of the IgG response to ViCPS is recommended (Bonilla, 2018) but T cell independent type II antigens, such as ViCPS, produce a predominately IgM antibody response. The measurement of IgM response to polysaccharide vaccines has been suggested as additional tools to assess humoral immunity. Poor IgM responses to pneumococcal antigens in patients with antibody deficiencies has been associated with increased risk of infections and co-morbidities, and may have a particular utility in patients receiving IgG replacement therapy (Cavaliere et al., 2012; Schutz et al., 2012; Echeverria de Carlos et al., 2017). It can be envisaged that the IgM antibody response to polysaccharide ViCPS vaccinations may also have utility in assessing humoral immunity, but to date there are no publications exploring this avenue.

2.2. Baseline concentrations of Typhi Vi IgG antibodies

Independent studies have reported low baseline concentrations of Typhi Vi IgG antibodies in children and adult blood donors (median children 1.4 AU/mL, median adults 5.3 AU/mL, assay measuring range of 0–95 AU/mL and median adult 8.6 U/mL, assay measuring range 7.4–600 U/mL) (Ferry et al., 2004; Sánchez–Ramón et al., 2016). The percentage of individuals with baseline concentrations below assay measuring ranges has been reported to be 40–71% (Fig. 1) (Parker et al., 2014; Kumarage et al., 2017; Evans et al., 2018)) and age specific adult baseline concentrations suggest peaks in concentration between 32–41 years and 72–81 years (Parker et al., 2014). Median baseline Typhi Vi IgG concentrations are generally higher in adults compared to children (Kim et al., 1995; Ferry et al., 2004; Parker and Harding, 2016; Kumarage et al., 2017) and the range of concentrations wider (7.4–300 U/mL *vs.* 7.4–39 U/mL assay measuring range 7.4–600 U/mL) (Kumarage et al., 2017), however, confirmation of this trend in larger cohorts is required (Fig. 1). Global baseline Typhi Vi IgG concentrations will likely remain relatively low since administration of the conjugate vaccine will only be directed towards countries with endemic typhoid fever and individuals travelling to them.

Some healthy individuals have been reported to have high pre-vaccination concentrations, significantly above the baseline concentrations ranges determined. Ferry et al. report 2/23 (Ferry et al., 2004), Kumarage et al. report 2/24 (Kumarage et al., 2017) and Evans et al. report 4/215 (Evans et al., 2018) healthy individuals with significantly higher baseline Typhi Vi concentrations, which may be indicative of prior pathogen contact, previous vaccination or cross reactivity with similar polysaccharide structures (Ferry et al., 2004).

Baseline concentrations have been suggested to be higher in areas of endemic Typhoid fever (19% to 58% levels, > 1 μg/mL) in the absence of vaccination (Klugman et al., 1996; Keddy et al., 1999; Panchanathan et al., 2001; Staats et al., 2010). A direct comparison between the baseline concentrations from an area with endemic typhoid fever to an area without the fever, using the same commercial assay, provides some support for this (median 8.6 (range 7.4–31.8) *vs* 10 (range 7.4–232)) (Sánchez–Ramón et al., 2016; Kumarage et al., 2017). As with antibody responses to other vaccinations, high base-line concentrations of Typhi Vi IgG antibodies could affect the magnitude of response achieved (Evans et al., 2018), however Kumarage et al. demonstrated that even in an area endemic of typhoid fever > 95% of a control group had a concentration below 100 U/mL suggesting that pre-vaccination concentrations may not be a limiting factor in the interpretation of response to Typhi Vi vaccination.

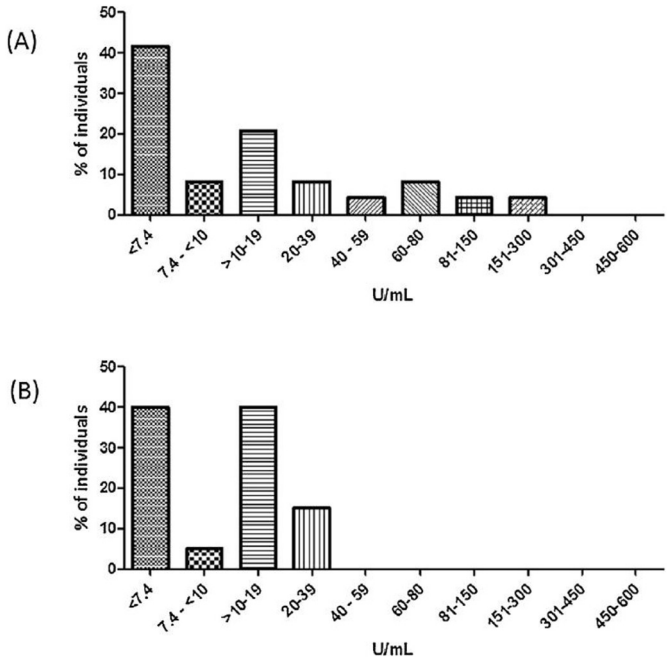


Fig. 1. Baseline concentrations of Typhi Vi IgG are low in both healthy children and adults.
Baseline Typhi Vi IgG concentrations in children and adult control groups. The Typhi Vi pre-vaccination concentrations were determined in the two control groups and separated into concentration ranges. The % individuals in the different concentration ranges were calculated. (A) Adult control group (n = 24) and (B) Children control group (n = 20).
Measuring range of the assay is 7.4–600 U/mL.
Reprinted with permission (Kumarage et al., 2017).

2.3. Response to ViCPS vaccines in a control population

Several studies have identified fold increase cut-offs in order to define an adequate response to ViCPS in healthy control populations. Using a one-sided 95% prediction interval, Schaballie and colleagues demonstrated a 2-fold increase and 11.2 U/mL post-vaccination

Table 3
Summary of post-vaccination ViCPS antibody concentrations and fold increases in healthy controls and primary antibody deficiency patients.

		Healthy controls			Antibody deficiency	
Reference	Units	Post vaccination concentration (95% CI)	Fold increase in concentration (95% CI)	% obtaining ≥4fold increase /seroconversion rate	Post vaccination concentration (95% CI)	Fold increase in concentration (95% CI)
Children						
(Kim et al., 1995)	GMT	69.4	29††	98.4		
(Lim et al., 2007)	GMT	142.6	24††	96.9		
(Miyazu et al., 2015)	GMT	2–11 years 501.7 (305.3–824.5) 12-17 years 320 (230.6–444.2)	2–11 years 135.6 (82.5–222.8) 12–17 years 31.4 (9.2–107.9)	2–11 years 100 12–17 years 85.7		
(Acharya et al., 1987)	μg/mL	1.89 (0.4–8.9)	8	76.9		
(Kumarage et al., 2017)†	U/mL	679 (60–3029)	59 (7–236)		219 (12–815)	18 (1–56)
Adults						
(Evans et al., 2018)	U/mL	107 (31–542)‡		100*	23 (10–372)‡	
(Sánchez–Ramón et al., 2016)†	U/mL	171 (32–600)‡	12.3 (3.4–76.9)‡		CVID 21 (7.4–277)‡ HYPOG 63.3 (7.4–600)‡	CVID 1.8 (1–37.4)‡ HYPOG 8.6 (1–81.1)‡
(Kumarage et al., 2017)†	U/mL	519 (80–2779)	32 (5–135)		11 (7.4–1746)	2 (1–56)
(Kim et al., 1995)	GMT	79.1	12††	88.2		
(Lim et al., 2007)	GMT	58.7	10††	89.0		
(Acharya et al., 1987)	μg/mL	15–44 years 3.7 (0.4–38.8) 45–55 years 4.4 (0.31–63.2)	15–44 years 10 45–55 years 8	15–44 years 79.1 45–55 years 62.5		
(Keitel et al., 1994)	μg/mL	3.2	16††	93		
(Klugman et al., 1987)	ELISA OD	0.2 (0.1–0.3)	4††			
(Bausch-Jurken et al., 2017)			6.0 (2.1–16.8)‡	100 **		1.0 (0.8–1.8)‡
(Moore et al., 2012)	ELISA U	7.2 (6.1–8.5)	13††	63		
(Miyazu et al., 2015)	GMT	148.6 (126.9–174.0)	22.6 (19.1–26.8)	92		
(Kroon et al., 1999) †††	AU/L	105.6	20	89	$CD4^+$ > 200×10^6/L 35.4 $CD4^+$ < 200×10^6/L 4.3	$CD4^+$ > 200×10^6/L 29 $CD4^+$ < 200×10^6/L 4.4
Adults/children combined						
(Schaballie et al., 2017)	U/mL	71.5	15			

HYPOG: Hypogammaglobulinaemia.
CI: Confidence Interval.
* % ≥3 fold increase.
** % ≥2 fold increase.
‡ Median concentration and range.
† Post vaccination concentrations have been obtained from the same commercial assay for comparison.
†† Fold increase results determined using vaccination data taken 1 months post and pre vaccination.
††† Study compared response in two cohorts; those with < 200×10^6/L $CD4^+$ cells and those with > 200×10^6/L $CD4^+$ cells.

concentration to define an adequate response to Typhim Vi® (Schaballie et al., 2017). Bausch-Jurken and colleagues used receiver operator characteristic (ROC) analysis to establish that a 1.95 fold-increase in ViCPS antibodies resulted in an area under the curve of 1.00 ($p < 0.0001$) and thus proposed that a 2-fold increase cut-off accurately discriminated between the control population and cohort of patients with known immunodeficiencies (Bausch-Jurken et al., 2017). Several studies have defined > 3-fold increases in antibody concentration post-vaccination as a normal response based on antibody concentration increases in > 94%, > 95% and 100% of control groups (Ferry et al., 2004; Sánchez–Ramón et al., 2016; Kumarage et al., 2017; Evans et al., 2018). Sanchez-Ramon and colleagues also used ROC analysis to demonstrate a 10 fold increase in antibody production to be 90.9% sensitive and 62.5% specific in the differentiation between healthy controls and patients with CVID (Sánchez–Ramón et al., 2016).

Many studies have demonstrated highly immunogenic IgG responses to ViCPS vaccines in healthy control populations (Table 3). A large clinical trial evaluating the immunogenicity of ViCPS vaccines in Nepal, an area of endemic typhoid fever, reported 76.9%, 79.1% and 62.5% of individuals (aged 5-14 yrs., 15-44 yrs. and 45–55 years old, respectively) achieved seroconversion, compared with a 95.5% seroconversion rate in French and US individuals (Acharya et al., 1987). More recently, two independent studies evaluated the response to ViCPS vaccines using the same commercial assay (The Binding Site, UK), allowing direct comparison between areas where the occurrence of typhoid fever is low with an area where it is endemic. A higher post vaccination concentration was reported where typhoid fever is endemic (median 519 U/mL [95% CI 80–2779] (Kumarage et al., 2017) *vs.* median 171 U/mL [range 32–600](Sánchez–Ramón et al., 2016)), which may be consequential to slightly higher baseline concentrations in areas where individuals may have prior exposure to the pathogen and thus forms part of a secondary response.

In a study to determine predictors of response to ViCPS vaccines, multivariate analysis revealed pre-vaccination concentration of ViCPS antibodies to be a significant predictor of antibody response (Moore et al., 2012). Klugman et al. (1987) also demonstrated a greater

increase in *Salmonella typhi* Vi antibody titres one month post vaccination in cohorts with lower pre-vaccination concentrations; a cohort with pre-vaccination ELISA readings of < 0.1 OD elicited a 4.11 fold increase, *versus* a 1.74 fold increase in those with a pre-vaccination ELISA reading of > 0.1 OD (Klugman et al., 1987). Despite these reports, in the context of a low prevalence of typhoid fever in developed countries and the absence of routine use of conjugated vaccines, the impact of pre-vaccination concentrations is unlikely to have as much impact on the interpretation of response (Table 3).

Evaluation of immunotolerance to ViCPS vaccines is essential to ensure interpretation of response is not hampered by pre-exposure to ViCPS polysaccharide vaccines. Similar levels of antibody concentrations against ViCPS antigens have been shown to be elicited after primary and booster vaccinations (Keitel et al., 1994). In a study comparing response to ViCPS vaccines in cohorts who had received multiple vaccinations *vs.* a cohort who had not previously been vaccinated against typhoid fever, there was no evidence of immunotolerance (Roggelin et al., 2015). However, in a subsequent study a proportion of the population of the study failed to produce plasmablasts specific to ViCPS after a booster vaccination (Pakkanen et al., 2017) indicating this is an area requiring further investigation.

The comparison between children and adult responses in a healthy population has been demonstrated by Kumarage and colleagues; a greater response was elicited in the paediatric group compared with the adult group but it did not reach statistical significance (post vaccination: median concentration (95% CI) (U/mL) children: 679 (60–3029) *versus* adults: 519 (80–2779); median fold increase (95% CI, U/mL) children: 59 (7–236) *versus* adults: 32 (5–135) (Kumarage et al., 2017). Additionally, Kim and colleagues also report a higher seroconversion rate in children compared with adults, 98.4% *versus* 88.2% one month post vaccination (Kim et al., 1995). Data from paediatric populations is of particular interest given the wide spread use of pneumococcal conjugate vaccines (PCV) in childhood vaccination schedules.

Given that infants are unable to mount polysaccharide-specific responses before the age of 2 years, SPAD can only be assessed after this time point (Durandy et al., 2013). A diagnosis of a memory phenotype of SPAD has been described, which is an adequate initial response to a polysaccharide antigen that is not maintained at 6 months post vaccination (Orange et al., 2012). It is therefore essential that vaccines used in the diagnosis of antibody deficiencies are able to induce responses in healthy individuals that are relatively stable for at least a year post vaccination. Studies have assessed the longevity of response to ViCPS vaccines confirming a stable response at 12 months post-vaccination and beyond (Table 4).

3. Utility of ViCPS vaccines as diagnostic tools for antibody deficiency

3.1. Primary immunodeficiency

Response to ViCPS vaccines has been recommended for the assessment of humoral immunity in individuals undergoing evaluation for antibody deficiencies (Anonyms, 1999; Ferry et al., 2004; Orange et al., 2012; De Silva et al., 2013) and could be of particular use in patients who have been vaccinated with a conjugated pneumococcal vaccine. Several studies have demonstrated the utility of measuring response to ViCPS vaccines as an indicator of humoral immunity in patients with primary antibody deficiencies, in differentiating responses in patients with hypogammaglobulinaemia (HYPOG) and CVID from healthy controls as well as stratifying PID patients who are at increased risk of infection.

3.1.1. Response to ViCPS vaccines is restricted in patients with primary antibody deficiencies

The IgG response to ViCPS vaccine may be defective in patients with primary antibody deficiencies (Sánchez–Ramón et al., 2016; Bausch-Jurken et al., 2017; Kumarage et al., 2017; Evans et al., 2018). Using a laboratory developed test (LDT) ELISA, antibody response to Typhim Vi® vaccination was determined in healthy controls, patients diagnosed with primary antibody deficiencies and patients with possible humoral immune deficiency (Bausch-Jurken et al., 2017). All patients diagnosed with an antibody deficiency had an abnormal antibody response to Typhim Vi®, as did seven patients with possible immunodeficiency that were subsequently determined to have primary or secondary immunodeficiencies (Fig. 2). Kumarage and colleagues used a commercially available ELISA assay to measure the antibody response to the polysaccharide Typhi Vi vaccine, Typbar®, in patients referred for immunological evaluation in Sri Lanka, an area where typhoid fever is endemic. In both paediatric and adult patients with primary antibody deficiencies (CVID and HYPOG), antibody response to Typbar® vaccination was lower than in the age-matched controls with 89% of paediatric PID patients and 45% of adult PID patients obtaining a three-fold increase in concentration post vaccination compared with 94% of the control groups (median fold-increase [95% CI]: adult control group 32 (5–135) *versus* adult PID group 2 (1–56) and children control group 59 (7–236) *versus* children PID group 18 (1–56) (Kumarage et al., 2017)). Evans and colleagues determined response to Typhim Vi® in 20 newly diagnosed antibody deficient patients; 40% did not respond to Typhim Vi® (< 7.4 U/mL) and 30% achieved a > 3 fold increase (Evans et al., 2018). The median post-vaccination concentrations were statistically different between this cohort and healthy volunteers ($p = 0.02$).

3.1.2. Differentiation between healthy individuals and patients with HYPOG and CVID

Two studies describe that the antibody response to ViCPS vaccination may differentiate between some CVID patients and HYPOG patients. Sánchez–Ramón and colleagues reported a multi-centre evaluation of the use of Typhim Vi® in previously diagnosed PID patients (Sánchez–Ramón et al., 2016). A ten-fold increase in Typhim Vi® antibodies provided good discrimination between healthy individuals and some patients with HYPOG and CVID (Fig. 3A) (Sánchez–Ramón et al., 2016). Kumarage and colleagues also demonstrated that a three-fold increase in Typhi Vi IgG differentiated between some CVID and HYPOG patients and their corresponding controls groups (Kumarage et al.,

Table 4
Stability of ViCPS vaccine response up to 36 months post-vaccination in healthy populations. Individuals were vaccinated with a single dose of 25 μg/0.5 mL ViCPS.

		Reference	Pre-vaccination	Post-vaccination				
				1 month	3 months	6 months	12 months	36 months
Sero-conversion (90%CI)	Adult	(Kim et al., 1995)		88.2	96.2		75.3	56.5
		(Lim et al., 2007)		89.1 (83.3–94.7)				
	Children	(Kim et al., 1995)		98.4	100		98.2	52.6
		(Lim et al., 2007)		96.9 (93.4–100.4)				
Geometric mean Titer (GMT) ± SD	Adult	(Kim et al., 1995)	6.6	79.1	120.3		41.7	28.3
		(Lim et al., 2007)	5.7 ± 1.31	64.0 ± 2.81		105.0 ± 2.29	84.1 ± 2.12	
	Children	(Kim et al., 1995)	2.4	69.4	49.2		36.7	7.2
		(Lim et al., 2007)	6.0 ± 1.37	151.3 ± 2.28		110.0 ± 1.91	100.2 ± 1.67	

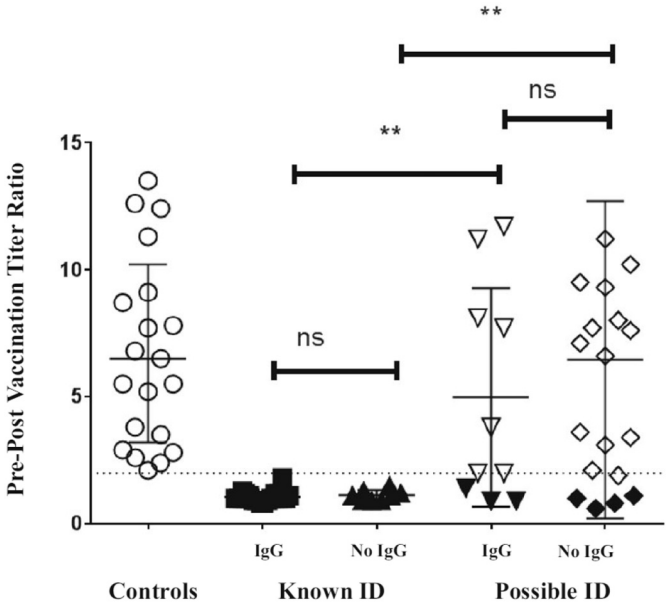


Fig. 2. Identification of 7 patients with defective response to Typhim Vi®.
Specific antibody response to Typhim Vi® in healthy controls and patients with known and possible immunodeficiencies (separated according to treatment with IgG therapy). All patients with known immunodeficiency had abnormal response to Typhim Vi®, as did 7/20 patients with possible immunodeficiency; all were subsequently determined to have primary or secondary immunodeficiencies.
The dotted line indicates the pre-post-vaccination titer ratio ≥ 2 (normal response), solid lines indicate median and IQR. Ig indicates immunoglobulin replacement therapy at the time of vaccination. Statistical significance indicated as follows: ns not significant, **p ≤ 0.01.
Reprinted with permission (Bausch-Jurken et al., 2017).

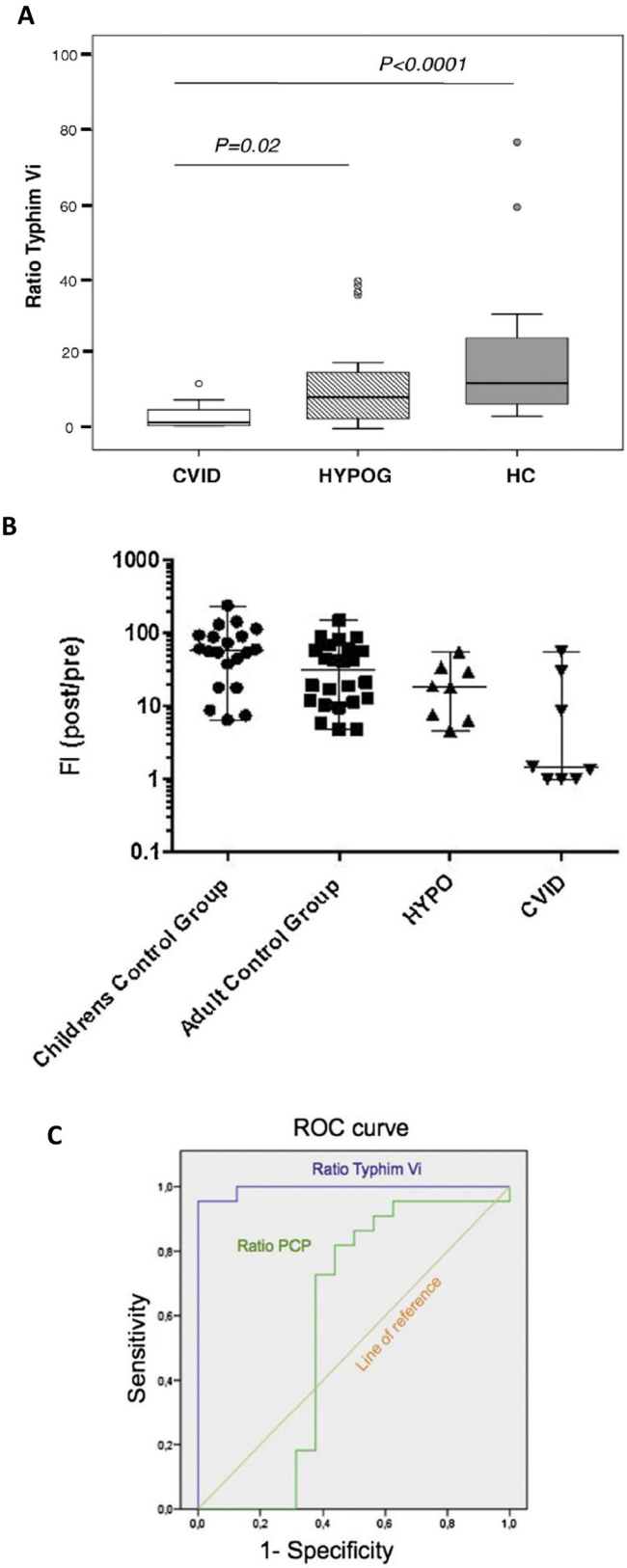
2017) (Fig. 3B). ROC curve analysis highlighted Typhim Vi® to be the more sensitive assay in distinguishing between CVID and healthy controls compared with Pneumovax®23 (AUC 0.893 *versus* 0.538) (Sánchez–Ramón et al., 2016) (Fig. 3C). The failure to respond to ViCPS vaccination has been used to aid diagnosis of antibody deficiencies, particularly CVID (De Silva et al., 2013; Bausch-Jurken et al., 2017).

3.1.3. Stratification of patients at risk of infection

Ferry and colleagues demonstrated an approximate 10-fold increase between mean pre- and post-vaccination concentrations in 23 healthy adults (geometric mean and 95% CI pre-vaccination 3.9 (2.4–6.5) and post-Typhim Vi® vaccination 39.2 (24.8–61.3) (Ferry et al., 2004). Sánchez–Ramón and colleagues proposed that differentiation of CVID patients using a 10-fold increase cut-off may identify a subset of CVID patients with a more proficient humoral immunological response and thus may possess lower risk of infection and possibly CVID associated disorders. Supporting this, although not statistically significant, they reported two patients with a diagnosis of CVID with increased responses > 10-fold in concentration who had a lower number of respiratory infections and none of the inflammatory conditions linked with a diagnosis of CVID (Sánchez–Ramón et al., 2016).

3.2. Utility of measuring IgG antibodies in response to both Pneumovax®23 and ViCPS vaccines

Individuals may respond very differently to similar types of antigen that vary in structure *e.g.* between different pneumococcal serotypes and between Pneumovax®23 and Typhim Vi®. Guidelines have suggested measuring the response to two protein vaccines for the assessment of antibody deficiency (Chapel and Cunningham-Rundles, 2009). Currently, data analysing the response to two polysaccharides,



Variable	Area	P	95% CI	
			Lower limit	Upper limit
Ratio Typhim Vi	0.994	<0.0001	0.979	1.009
Ratio PCP	0.577	0.425	0.357	0.797

(caption on next page)

Fig. 3. Differentiation of HYPOG and CVID patients using measurement of Typhim Vi® antibodies.
A) Reprinted with permission (Sánchez–Ramón et al., 2016).
Box plots showing that the Ratio Typhim Vi was significantly higher in healthy control-group (HC) compared to CVID-group ($p < 0.0001$), but not with respect to HYPOG-group ($p = 0.138$). Each box plot represents the median (thick band) and the 25th and 75th centiles. The error bars represent the smallest and largest values that are not outliers.
B) Reprinted with permission (Kumarage et al., 2017).
Responses to Typhi Vi vaccination in control groups, HYPOG and CVID patients. Typhi Vi responses were assessed in the children control group (n = 20), adult control group (n = 24), HYPOG (n = 8) and CVID (n = 8) groups. FI: fold increase.
C) Reprinted with permission (Sánchez–Ramón et al., 2016).
Receiver operating characteristic (ROC) curve analyses using Typhim Vi and PCP ratio as predictor of diagnosis of CVID. The curves show the trade-off between sensitivity and specificity. An increase in sensitivity will be accompanied by a decrease in specificity. The accuracy of the prediction increases as the curve approaches the left-hand and top portions of the ROC space. The area under the curve (AUC) is the percentage of randomly drawn pairs for which the prediction is true. As observed, the ratio Typhim Vi better defined CVID patients ($p < 0.0001$). PCP: pneumococcal capsular polysaccharides.

Pneumovax®23 and Typhim Vi®, are lacking.

Schaballie et al. identified 2/100 healthy individuals with abnormal response to Pneumovax®23 and Typhim Vi® vaccines. Upon subsequent investigation both had a history of repeated infections and the clinical characteristics of one patient were suggestive of SPAD diagnosis. A history indicative of immunodeficiency was not noted in any individual who had a poor response to just one vaccine (Schaballie et al., 2017) (Fig. 4).

In patients undergoing immunological evaluation, the responses to Typhim Vi® and Pneumovax®23 can divide the patients into 4 groups. Data from Sánchez-Ramón suggested that 13/45 (29%) HYPOG and CVID patients did not have a similar response to both Typhim Vi® and Pneumovax®23 (Fig. 5). Evans and colleagues demonstrated equivalent responses to Typhim Vi and Pneumovax in 8/9 antibody deficient patients (Evans et al., 2018). Further investigations will be of interest to determine if stratification of patients using both polysaccharide vaccines can identify patients at increased risk of infection. Moreover, Ochoa-Grullón and colleagues investigated the response to Typhim Vi® and Pneumovax®23 in 28 patients diagnosed with various haematological malignancies (Ochoa-Grullón et al., 2017). 11/28 (39%) of all patients did not have a similar response to both Typhim Vi® and Pneumovax®23 (Fig. 6). Given that there is a high incidence of infection among patients with haematological disorders and recipients of hematopoietic cell transplants (Blimark et al., 2015; Dhalla and Misbah, 2015) stratification using both polysaccharide vaccines may be of particular interest. Additional studies are needed to determine the utility of measuring response to Typhi Vi polysaccharide vaccines to aid identification of patients with increased risk of infection.

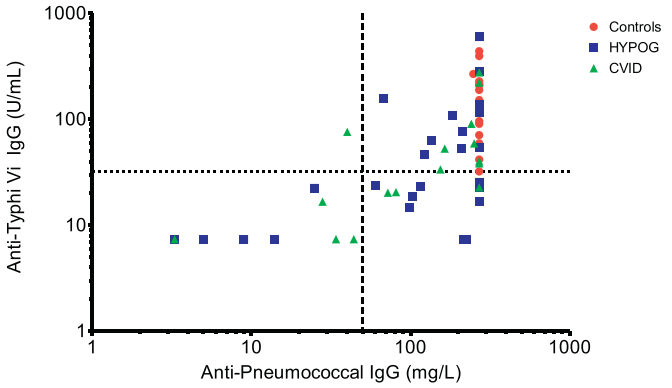


Fig. 5. Combined measurement of IgG antibodies to Typhim Vi® and Pneumovax®23 identifies 4 groups of patients with immunodeficiency.
Specific antibody responses post-vaccination with Pneumovax®23 and Typhi Vi® in healthy controls and patients diagnosed with PID. Dashed line (50 mg/L) represents lower end of normal response to Pneumovax®23 in health individuals (Chua et al., 2011); dotted line (32 U/mL) represents lowest response to Typhim Vi® in healthy individuals (Sánchez–Ramón et al., 2016).
Data from Sánchez–Ramón

3.3. Secondary immunodeficiency

B-cell lineage lymphoproliferative diseases such as chronic lymphocytic leukaemia and multiple myeloma (Dhalla and Misbah, 2015) as well as treatment related immunosuppression such as with rituximab or other biologicals can prevent antibody production resulting in severe or prolonged HYPOG (Sánchez–Ramón et al., 2016).

Kroon and colleagues demonstrated that the response to Typhim Vi® is compromised in individuals infected with the human immunodeficiency virus (HIV) (Kroon et al., 1999). Thirty HIV positive individuals were vaccinated with Typhim Vi® and divided into 2 groups; those with greater than or $< 200 \times 10^6$/L $CD4^+$ T lymphocytes. In the group with $> 200 \times 10^6$/L $CD4^+$ T lymphocytes, 86% of individuals achieved a ≥ 4 fold increase in concentration (mean fold increase 29) compared to 89% in the healthy control group (mean fold increase 20). The response was significantly lower in those HIV patients with $< 200 \times 10^6$/L $CD4^+$ T lymphocytes (25% achieving a ≥ 4 FI, mean 4.4).

Bausch-Jurken and colleagues reported the vaccination of 29 patients referred for immune system evaluation with the suspicion of PID

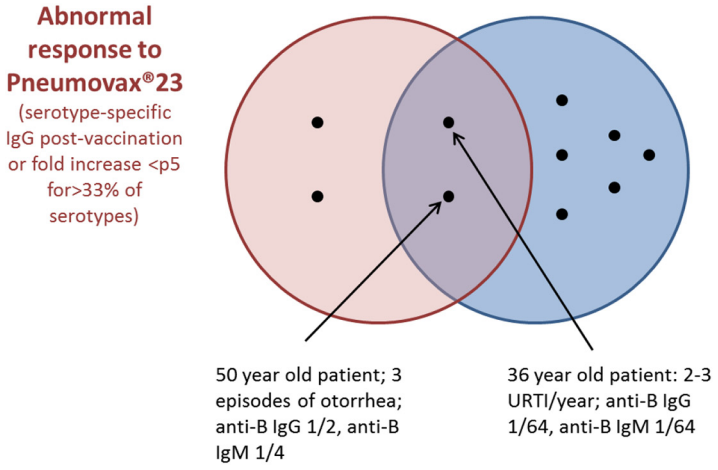


Fig. 4. Failure to produce IgG antibodies in response to Pneumovax®23 and/or Typhim Vi® in healthy volunteers.
Venn diagram showing subjects (black dots) with abnormal antibody response for each detection method, among 100 healthy subjects (fifth percentile cut-off values were used). Subjects with normal test results are not shown. Arrows indicate the clinical history of two subjects with abnormal results for both tests. URTI, upper respiratory tract infections.
Adapted from Schaballie et al. (2017).

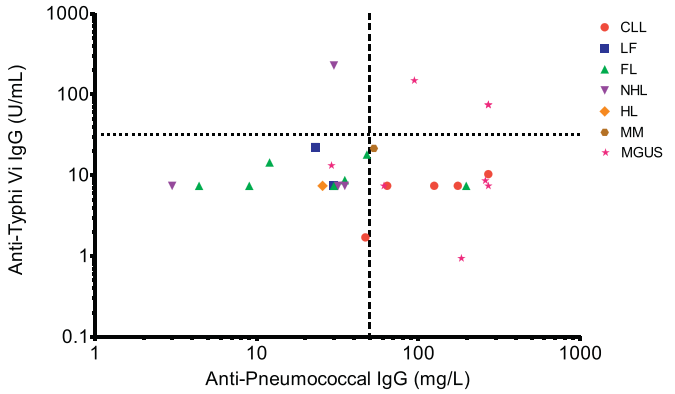


Fig. 6. Combined measurement of IgG antibodies to Typhim Vi® and Pneumovax®23 identifies 4 groups of patients with haematological malignancies.

Specific antibody responses post-vaccination with Pneumovax and Typhim Vi in patients diagnosed with haematological malignancy and recurrent infection. Dashed line (50 mg/L) represents lower end of normal response to Pneumovax in health individuals (Chua et al., 2011); dotted line (32 U/mL) represents lowest response to Typhim Vi in healthy individuals (Sánchez–Ramón et al., 2016). CLL: chronic lymphocytic leukaemia; LF: lymphoma; FL: follicular lymphoma; NHL: non-Hodgkin lymphoma; HL: Hodgkin lymphoma; MM: multiple myeloma; MGUS: monoclonal gammopathy of undetermined significance.

Data adapted from Ochoa-Grullón et al. (2017).

(based largely on a history of recurrent upper respiratory tract infections) (Bausch-Jurken et al., 2017). Two patients were diagnosed with secondary antibody deficiency: one with hemophagocytic lymphohistiocytosis secondary to Epstein-Barr virus infection who was treated with repeated doses of rituximab; and the other, HYPOG and T cell lymphopenia secondary to non-Hodgkin's lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Both exhibited a $<$ 2 fold increase in Typhim Vi® responses.

Furthermore, the response to Typhim Vi® was investigated in 28 patients diagnosed with various haematological malignancies (Ochoa-Grullón et al., 2017). Only 5/28 achieved a post vaccination concentration of Typhim Vi antibodies $>$ 32 U/mL and 5/28 achieved a more that 3 fold increase (Sánchez–Ramón et al., 2016). All patients with chronic lymphocytic leukaemia (n = 5) and follicular lymphoma (n = 7) were non-responders (Fig. 6).

4. Measurement of Typhim Vi® IgG antibodies as tool for monitoring patients with antibody deficiency

IGRT has been the mainstay for the management of primary and secondary immunodeficiencies, particularly in those with a more severe clinical phenotype (Orange et al., 2012; Jolles et al., 2017). Monitoring of patients' total IgG concentrations is performed on regular basis by measurement of the trough IgG levels and in particular situations, such as SPAD, assessment of specific antibody levels may also be undertaken.

It has been proposed that for patients who are receiving IGRT, a potential way to assess underlying endogenous vaccine responses is to use immunisations not included in the standard vaccination schedules, as baseline levels of these antibodies in immunoglobulin preparations and endogenous levels would be expected to be low (Sobh and Bonilla, 2016; Jolles et al., 2017). Although several studies have reported a lack of correlation between the measurement of total IgG and specific antibody production, others have reported an adequate correlation (Mikolajczyk et al., 2004; Chua et al., 2011; Adam and Church, 2015; Jolles et al., 2017; Lee et al., 2017; Simao-Gurge et al., 2017).

The baseline concentration of Typhim Vi® antibodies in patients receiving IGRT has been shown to be low (Bausch-Jurken et al., 2017; Evans et al., 2018) and undetectable in four commercial preparations of gammaglobulin (Gammagard®, Gamunex®–C, Subgam®, and Hizentra®) (Bausch-Jurken et al., 2017) and so detection of ViCPS antibody response in these patients is feasible.

Furthermore, Bausch-Jurken and colleagues reported the assessment of the response to Typhim Vi® in 10 individuals with unknown PID receiving IGRT. 7/10 had a $\geq$ 2 fold-increase response and 3/10 a $<$ 2 fold-increase (Fig. 2). *Re*-evaluation of these patients concluded that the 7 responders were immunologically normal and IGRT was discontinued (Bausch-Jurken et al., 2017). The suspected antibody deficiencies in these individuals were due to untreated atopic disease (*e.g.*, allergic rhinitis, asthma). The 3/10 non-responders remained on IGRT and were diagnosed with SPAD. The response to Typhim Vi® was used as a key tool to aid the decision to cease treatment.

5. Conclusions

The response to ViCPS vaccines is of particular interest in the assessment and risk stratification of patients with suspected primary and secondary immunodeficiency. Although measurement of antibodies raised against Pneumovax®23 is the current gold standard test to assess adaptive immunity to unconjugated T-cell independent polysaccharide antigens, additional options, such as response to ViCPS vaccines, are urgently needed to allow assessment where the utility of Pneumovax®23 may be limited.

The use of ViCPS vaccine response in assessment of adaptive immunity has advantages (summarised in Table 1). The use of conjugate vaccines is limited (Breukels et al., 1999; Janssen et al., 2014; Schaballie et al., 2016) and generally baseline antibody concentrations of Typhi Vi IgG are low, minimising memory B cell reactivation. Furthermore, antibody concentrations have been reported in healthy control populations enabling assessment of response to ViCPS antibodies to be relatively simple.

Current data suggests that combined measurement of antibodies to Pneumovax®23 and Typhim Vi® may provide a wider window for exploration of the immune system (Sánchez–Ramón et al., 2016; Ochoa-Grullón et al., 2017; Schaballie et al., 2017). This will be particularly important for the growing group of patients with undefined hypogammaglobulinaemia who present with a broad range of disease severity. The four groups for classifying non-responsiveness to polysaccharide antigens are currently based solely on the response to Pneumovax®23 (Orange et al., 2012). An additional marker may provide further patient stratification and standardisation of definitions as well as aid in treatment decisions (Perez et al., 2017).

The utility of ViCPS has mainly been focused on diagnosis (Sánchez–Ramón et al., 2016; Bausch-Jurken et al., 2017; Kumarage et al., 2017) but it may also be informative in individuals receiving IGRT (Bausch-Jurken et al., 2017).

In conclusion, the measurement of IgG antibodies raised in response to typhoid polysaccharide vaccines has utility for the investigation of adaptive immunity. This is likely to be an important addition to the diagnostic toolkit for immunologists, used alongside Pneumovax®23, in this complex and challenging area of immunological assessment.

References

Acharya, I.L., Lowe, C.U., Thapa, R., Gurubacharya, V.L., Shrestha, M.B., Cadoz, M., Schulz, D., Armand, J., Bryla, D.A., Trollfors, B., 1987. Prevention of typhoid fever in Nepal with the vi capsular polysaccharide of Salmonella typhi. A preliminary report. N. Engl. J. Med. 317, 1101–1104.

Adam, E., Church, J.A., 2015. Antibody levels to Bordetella pertussis and Neisseria meningitidis in immunodeficient patients receiving immunoglobulin replacement therapy. J. Clin. Immunol. 35, 213–217.

Ahmadi, H., Tabaraie, B., Maleknia, S., Shapouri, R., Nejati, M., Pour Mirza, G.F., Hedayati, M., Sadati, M., Zahednia, S., Sharifat, S.A., 2013. Immunological evaluation of Vi capsular polysaccharide of Salmonella enterica subsp. Typhi vaccine by serum bactericidal assay. J. Med. Microbiol. 62, 283–286.

Anonyms, 1999. Primary immunodeficiency diseases. Report of an IUIS scientific committee. International Union of Immunological Societies. Clin. Exp. Immunol. 118, 1–28.

Bausch-Jurken, M.T., Verbsky, J.W., Gonzaga, K.A., Elms, N.P., Hintermeyer, M.K., Gauld, S.B., Routes, J.M., 2017. The use of Salmonella Typhim vaccine to diagnose antibody deficiency. J. Clin. Immunol. 37, 427–433.

Blimark, C., Holmberg, E., Mellqvist, U.H., Landgren, O., Bjorkholm, M., Hultcrantz, M., Kjellander, C., Turesson, I., Kristinsson, S.Y., 2015. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica 100, 107–113.

Bonilla, F.A., 2018. Update: Vaccines in primary immunodeficiency. J. Allergy Clin. Immunol. 141, 474–481.

Bonilla, F.A., Khan, D.A., Ballas, Z.K., Chinen, J., Frank, M.M., Hsu, J.T., Keller, M., Kobrynski, L.J., Komarow, H.D., Mazer, B., Nelson Jr., R.P., Orange, J.S., Routes, J.M., Shearer, W.T., Sorensen, R.U., Verbsky, J.W., Bernstein, D.I., Blessing-Moore, J., Lang, D., Nicklas, R.A., Oppenheimer, J., Portnoy, J.M., Randolph, C.R., Schuller, D., Spector, S.L., Tilles, S., Wallace, D., Bonilla, F.A., Khan, D.A., Bernstein, D.I., Blessing-Moore, J., Khan, D., Lang, D., Nicklas, R.A., Oppenheimer, J., Portnoy, J.M., Randolph, C.R., Schuller, D., Spector, S.L., Tilles, S., Wallace, D., Bonilla, F.A., Ballas, Z.K., Chinen, J., Frank, M.M., Hsu, J.T., Keller, M., Kobrynski, L.J., Komarow, H.D., Mazer, B., Nelson Jr., R.P., Orange, J.S., Routes, J.M., Shearer, W.T., Sorensen, R.U., Verbsky, J.W., 2015. Practice parameter for the diagnosis and management of primary immunodeficiency. J. Allergy Clin. Immunol. 136, 1186–1205.

Breukels, M.A., Rijkers, G.T., Voorhorst-Ogink, M.M., Zegers, B.J., Sanders, L.A., 1999. Pneumococcal conjugate vaccine primes for polysaccharide-inducible IgG2 antibody response in children with recurrent otitis media acuta. J. Infect. Dis. 179, 1152–1156.

Cavaliere, F.M., Milito, C., Martini, H., Schlesier, M., Drager, R., Schutz, K., Brunetti, G., Pesce, A.M., Thon, V., Warnatz, K., Quinti, I., 2012. Quantification of IgM and IgA anti-pneumococcal capsular polysaccharides by a new ELISA assay: a valuable diagnostic and prognostic tool for common variable immunodeficiency. J. Clin. Immunol. 33, 838–846.

Centers for Disease Control and Prevention, A.C.i.I.P, 2010. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). MMWR Morb. Mortal. Wkly Rep. 59, 1102–1106.

Chapel, H., Cunningham-Rundles, C., 2009. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Br. J. Haematol. 145, 709–727.

Chapel, H., Prevot, J., Gaspar, H.B., Espanol, T., Bonilla, F.A., Solis, L., Drabwell, J., Editorial Board for Working Party on Principles of Care at, I (Eds.), 2014. Primary immune deficiencies - principles of care. Front. Immunol. 5, 1–12.

Chinnasami, B., Sadasivam, K., Vivekanandhan, A., Arunachalam, P., Pasupathy, S., 2015. A study on longevity of immune response after vaccination with Salmonella Typhi Vi conjugate vaccine (Pedatyph) in children. J. Clin. Diagn. Res. 9, SC01–SC03.

Chua, I., Lagos, M., Charalambous, B.M., Workman, S., Chee, R., Grimbacher, B., 2011. Pathogen-specific IgG antibody levels in immunodeficient patients receiving immunoglobulin replacement do not provide additional benefit to therapeutic management over total serum IgG. J. Allergy Clin. Immunol. 127, 1410–1411.

Daniels, C.C., Rogers, P.D., Shelton, C.M., 2016. A review of pneumococcal vaccine: current polysaccharide vaccine recommendations and future protein antigens. J. Pediatr. Pharmacol. Ther. 21, 27–e35.

De Silva, N.R., Gunawardena, S., Rathnayake, D., Wickramasingha, G.D., 2013. Spectrum of primary immunodeficiency disorders in Sri Lanka. Allergy, Asthma Clin. Immunol. 9, 50.

Dhalla, F., Misbah, S.A., 2015. Secondary antibody deficiencies. Curr. Opin. Allergy Clin. Immunol. 15, 505–513.

Dizer, U., Gorenek, L., Guner, O., Pehlivan, T., Ozguven, V., Pahsa, A., 2002. Assessment of the antibody response in 110 healthy individuals who have been subject to Vi capsular polysaccharide vaccine. Vaccine 20, 3052–3054.

Durandy, A., Kracker, S., Fischer, A., 2013. Primary antibody deficiencies. Nat. Rev. Immunol. 13, 519–533.

Dziadzio, M., Morales, G., Harvey, D., Smith, R., Lukawska, J., Tahami, F., Ceron-Gutierrez, L., Doffinger, R., Seneviratne, S., Chee, R., Baxendale, H., 2017. Comparison of 23- valent pneumococcal IgG ELISA with multiplex 13- valent serotype-specific antibody assay as Diagnositc tools in subjects with suspected antibody deficiency. J. Mol. Immunol. 2, 108.

Echeverria de Carlos, A., Gomez de la Torre, R., Garcia Carus, E., Caminal Montero, L., Bernardino Diaz Lopez, J., Suarez Casado, H., Molinos Matin, L., Tricas Aizpun, L., Harding, S., Parker, A.R., 2017. Concentrations of pneumococcal IgA and IgM are compromised in some individuals with antibody deficiencies. J. Immunoass. Immunochem. 38, 505–513.

Edgar, J.D.M., Richter, A.G., Huissoon, A.P., Kumararatne, D.S., Baxendale, H.E., Bethune, C.A., Garcez, T., Misbah, S.A., Sorensen, R.U., United Kingdom Primary Immunodeficiency Network Immunoglobulin Decision to Treat Study, G, 2018. Prescribing immunoglobulin replacement therapy for patients with non-classical and secondary antibody deficiency: an analysis of the practice of clinical immunologists in the UK and Republic of Ireland. J. Clin. Immunol. 38, 204–213.

Evans, C., Bateman, E., Steven, R., Ponsford, M., Cullinane, A., Shenton, C., Duthie, G., Conlon, C., Jolles, S., Huissoon, A.P., Longhurst, H.J., Rahman, T., Scott, C., Wallis, G., Harding, S., Parker, A.R., Ferry, B.L., 2018. Measurement of Typhim vi antibodies can be used to assess adaptive immunity in patients with immunodeficiency. Clin. Exp. Immunol (Epub ahead of print).

Ferry, B.L., Misbah, S.A., Stephens, P., Sherrell, Z., Lythgoe, H., Bateman, E., Banner, C., Jones, J., Groome, N., Chapel, H.M., 2004. Development of an anti-Salmonella typhi Vi ELISA: assessment of immunocompetence in healthy donors. Clin. Exp. Immunol. 136, 297–303.

Froeschle, J.E., Decker, M.D., 2010. Duration of Vi antibodies in participants vaccinated with Typhim Vi (Typhoid Vi polysaccharide vaccine) in an area not endemic for typhoid fever. Vaccine 28, 1451–1453.

Griffin, D.O., Holodick, N.E., Rothstein, T.L., 2011. Human B1 cells in umbilical cord and adult peripheral blood express the novel phenotype CD20+ CD27+ CD43+ CD70. J. Exp. Med. 208, 67–80.

Guinamard, R., Okigaki, M., Schlessinger, J., Ravetch, J.V., 2000. Absence of marginal zone B cells in Pyk-2-deficient mice defines their role in the humoral response. Nat. Immunol. 1, 31–36.

Hare, N.D., Smith, B.J., Ballas, Z.K., 2009. Antibody response to pneumococcal vaccination as a function of preimmunization titer. J. Allergy Clin. Immunol. 123, 195–200.

Ivanoff, B., Levine, M.M., Lambert, P.H., 1994. Vaccination against typhoid fever: present status. Bull. World Health Organ. 72, 957–971.

Janssen, W.J., Bloem, A.C., Vellekoop, P., Driessen, G.J., Boes, M., van Montfrans, J.M., 2014. Measurement of pneumococcal polysaccharide vaccine responses for immunodeficiency diagnostics: combined IgG responses compared to serotype specific IgG responses. J. Clin. Immunol. 34, 3–6.

Jin, C., Gibani, M.M., Moore, M., Juel, H.B., Jones, E., Meiring, J., Harris, V., Gardner, J., Nebykova, A., Kerridge, S.A., Hill, J., Thomaides-Brears, H., Blohmke, C.J., Yu, L.M., Angus, B., Pollard, A.J., 2017. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. Lancet 390 (10111), 2472–2480.

Jolles, S., Chapel, H., Litzman, J., 2017. When to initiate immunoglobulin replacement therapy (IGRT) in antibody deficiency: a practical approach. Clin. Exp. Immunol. 188, 333–341.

Kantele, A., 1990. Antibody-secreting cells in the evaluation of the immunogenicity of an oral vaccine. Vaccine 8, 321–326.

Kantele, A., Makela, P.H., 1991. Different profiles of the human immune response to primary and secondary immunization with an oral Salmonella typhi Ty21a vaccine. Vaccine 9, 423–427.

Kantele, A., Arvilommi, H., Jokinen, I., 1986. Specific immunoglobulin-secreting human blood cells after peroral vaccination against Salmonella typhi. J. Infect. Dis. 153, 1126–1131.

Kantele, A., Pakkanen, S.H., Karttunen, R., Kantele, J.M., 2013. Head-to-head comparison of humoral immune responses to vi capsular polysaccharide and Salmonella Typhi Ty21a typhoid vaccines–a randomized trial. PLoS One 8, e60583.

Keddy, K.H., Klugman, K.P., Hansford, C.F., Blondeau, C., Bouveret le Cam, N.N., 1999. Persistence of antibodies to the Salmonella typhi vi capsular polysaccharide vaccine in south African school children ten years after immunization. Vaccine 17, 110–113.

Keitel, W.A., Bond, N.L., Zahradnik, J.M., Cramton, T.A., Robbins, J.B., 1994. Clinical and serological responses following primary and booster immunization with Salmonella typhi Vi capsular polysaccharide vaccines. Vaccine 12, 195–199.

Kim, Y., Yoo, J., Hur, J., Kang, J.H., Shin, W., K., M., 1995. Immunogenicity of Vi Capsular polysaccharide vaccine evaluated for three years in Korea. J. Korean Med. Sci. 10, 314–317.

Klugman, K.P., Gilbertson, I.T., Koornhof, H.J., Robbins, J.B., Schneerson, R., Schulz, D., Cadoz, M., Armand, J., 1987. Protective activity of Vi capsular polysaccharide vaccine against typhoid fever. Lancet 2, 1165–1169.

Klugman, K.P., Koornhof, H.J., Robbins, J.B., Le Cam, N.N., 1996. Immunogenicity, efficacy and serological correlate of protection of Salmonella typhi Vi capsular polysaccharide vaccine three years after immunization. Vaccine 14, 435–438.

Kroon, F.P., van Dissel, J.T., Ravensbergen, E., Nibbering, P.H., van Furth, R., 1999. Impaired antibody response after immunization of HIV-infected individuals with the polysaccharide vaccine against Salmonella typhi (Typhim-Vi). Vaccine 17, 2941–2945.

Kumarage, J., Seneviratne, S.L., Senaratne, V., Fernando, A., Gunasekera, K., Gunasena, B., Gurugama, P., Peiris, S., Parker, A.R., Harding, S., de Silva, N.R., 2017. The response to Typhi Vi vaccination is compromised in individuals with primary immunodeficiency. Heliyon 3, e00333.

Lee, S., Kim, H.W., Kim, K.H., 2017. Functional antibodies to Haemophilus influenzae type B, Neisseria meningitidis, and Streptococcus pneumoniae contained in intravenous immunoglobulin products. Transfusion 57, 157–165.

Lim, S.M., Jung, H.S., Kim, M.J., Cheong, H.J., Park, S.C., Lee, K.C., Shin, Y.K., Tan, H.K., Kim, S.L., Sohn, J.W., 2007. Immunogenicity and safety of Vi capsular polysaccharide typhoid vaccine in healthy persons in Korea. J. Microbiol. Biotechnol. 17, 611–615.

Lopez, B., Bahuaud, M., Fieschi, C., Batteux, F., Dubucquoi, S., Launay, D., Labalette, M., Lefèvre, G., 2016. Value of overall pneumococcal polysaccharide reponse in the diagnosis of primary humoral immunodeficiencies. In: Presented at ESID, 6-0221a.

Lundgren, A., Kaim, J., Jertborn, M., 2009. Parallel analysis of mucosally derived B- and T-cell responses to an oral typhoid vaccine using simplified methods. Vaccine 27, 4529–4536.

MacLennan, C.A., Martin, L.B., Micoli, F., 2014. Vaccines against invasive Salmonella disease: current status and future directions. Hum. Vaccin Immunother. 10, 1478–1493.

Marshall, J.L., Flores-Langarica, A., Kingsley, R.A., Hitchcock, J.R., Ross, E.A., Lopez-Macias, C., Lakey, J., Martin, L.B., Toellner, K.M., MacLennan, C.A., MacLennan, I.C., Henderson, I.R., Dougan, G., Cunningham, A.F., 2012. The capsular polysaccharide Vi from Salmonella typhi is a B1b antigen. J. Immunol. 189, 5527–5532.

Martin, F., Kearney, J.F., 2002. Marginal-zone B cells. Nat. Rev. 2, 323–335.

Martin, F., Oliver, A.M., Kearney, J.F., 2001. Marginal zone and B1 B cells unite in the early response against T-independent blood-borne particulate antigens. Immunity 14, 617–629.

McCusker, C., Warrington, R., 2011. Primary immunodeficiency. Allergy, Asthma Clin. Immunol. 7 (Suppl. 1), S11.

Mikolajczyk, M.G., Concepcion, N.F., Wang, T., Frazier, D., Golding, B., Frasch, C.E., Scott, D.E., 2004. Characterization of antibodies to capsular polysaccharide antigens of Haemophilus influenzae type b and Streptococcus pneumoniae in human immune

globulin intravenous preparations. Clin. Diagn. Lab. Immunol. 11, 1158–1164.
Mitra, M., Shah, N., Ghosh, A., Chatterjee, S., Kaur, I., Bhattacharya, N., Basu, S., 2016. Efficacy and safety of vi-tetanus toxoid conjugated typhoid vaccine (PedaTyph) in Indian children: school based cluster randomized study. Hum. Vaccin Immunother. 12, 939–945.
Miyazu, M., Kikuchi, H., Hamada, A., Fukushima, S., Ouchi, K., Bosch Castells, V., Mihara, H., Bonnet, M.C., 2015. A Japanese study to assess immunogenicity and safety of a typhoid vi polysaccharide vaccine. Vaccine 33, 6697–6702.
Modell, V., Gee, B., Lewis, D.B., Orange, J.S., Roifman, C.M., Routes, J.M., Sorensen, R.U., Notarangelo, L.D., Modell, F., 2011. Global study of primary immunodeficiency diseases (PI)-diagnosis, treatment, and economic impact: an updated report from the Jeffrey Modell Foundation. Immunol. Res. 51, 61–70.
Moore, S.E., Richards, A.A., Goldblatt, D., Ashton, L., Szu, S.C., Prentice, A.M., 2012. Early-life and contemporaneous nutritional and environmental predictors of antibody response to vaccination in young Gambian adults. Vaccine 30, 4842–4848.
Ochoa-Grullón, J., Benavente, C., Martinez, R., Perez, C., Pena, A., Rodriguez de la Pena, A., Llano Hernandez, K., Rodriguez Frias, E., Guevara Hoyer, K., Orte Cano, C., Sanchez-Ramon, S., 2017. Typhim Vi Anti-Polysaccharide Antibody for Primary Response in Hematological Malignancy. (Presented at FOCiS).
Orange, J.S., Ballow, M., Stiehm, E.R., Ballas, Z.K., Chinen, J., De La Morena, M., Kumararatne, D., Harville, T.O., Hesterberg, P., Koleilat, M., McGhee, S., Perez, E.E., Raasch, J., Scherzer, R., Schroeder, H., Seroogy, C., Huissoon, A., Sorensen, R.U., Katial, R., 2012. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the basic and clinical immunology interest section of the American Academy of Allergy, Asthma & Immunology. J. Allergy Clin. Immunol. 130, S1–24.
Pakkanen, S.H., Kantele, J.M., Moldoveanu, Z., Hedges, S., Hakkinen, M., Mestecky, J., Kantele, A., 2010. Expression of homing receptors on IgA1 and IgA2 plasmablasts in blood reflects differential distribution of IgA1 and IgA2 in various body fluids. Clin. Vaccine Immunol. 17, 393–401.
Pakkanen, S.H., Kantele, J.M., Savolainen, L.E., Rombo, L., Kantele, A., 2015. Specific and cross-reactive immune response to oral Salmonella Typhi Ty21a and parenteral vi capsular polysaccharide typhoid vaccines administered concomitantly. Vaccine 33, 451–458.
Pakkanen, S.H., Kantele, J.M., Rombo, L., Kantele, A., 2017. Specific and cross-reactive plasmablast response in humans after primary and secondary immunization with vi capsular polysaccharide typhoid vaccine. Scand. J. Immunol. 86 (4), 207–215.
Panchanathan, V., Kumar, S., Yeap, W., Devi, S., Ismail, R., Sarijan, S., Sam, S.M., Jusoh, Z., Nordin, S., Leboulleux, D., Pang, T., 2001. Comparison of safety and immunogenicity of a vi polysaccharide typhoid vaccine with a whole-cell killed vaccine in Malaysian air force recruits. Bull. World Health Organ. 79, 811–817.
Parker, A., Harding, S., 2016. Comparison of Salmonella Typhi vi IgG concentrations in children and adults. In: Presented at ESID. 0059.
Parker, A., Hemmings, O., Allen, S., Harding, S., 2014. Concentration of IgG Antibodies Specific to Salmonella Typhi Vi in Adult Blood Donors. J Clin Immunol 34. In: ESID-0362.
Perez, E., Bonilla, F.A., Orange, J.S., Ballow, M., 2017. Specific antibody deficiency: controversies in diagnosis and management. Front. Immunol. 8, 586.
Picard, C., Al-Herz, W., Bousfiha, A., Casanova, J.L., Chatila, T., Conley, M.E., Cunningham-Rundles, C., Etzioni, A., Holland, S.M., Klein, C., Nonoyama, S., Ochs, H.D., Oksenhendler, E., Puck, J.M., Sullivan, K.E., Tang, M.L., Franco, J.L., Gaspar, H.B., 2015. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for primary immunodeficiency 2015. J. Clin. Immunol. 35, 696–726.
Public Health England, 2017. The Green Book: Immunisation against Infectious Disease.
Rakhmanov, M., Keller, B., Gutenberger, S., Foerster, C., Hoenig, M., Driessen, G., Van der Burg, M., Van Dongen, J.J., Wiech, E., Visentini, M., Quinti, I., Prasse, A., Voelxen, N., Salzer, U., Goldacker, S., Fisch, P., Eibel, H., Schwarz, K., Peter, H.H., Warnatz, K., 2009. Circulating CD21 low B cells in common variable immunodeficiency resemble tissue homing, innate-like B cells. Proc. Natl. Acad. Sci. U. S. A. 106, 13451–13456.
Reynolds, M.M., Murray, D.L., Willrich, M.A., Parker, A., DuChateau, B.K., Snyder, M.R., 2015. Total vs antigen specific pneumococcal antibody response: a comparison of two different assay types. Clin. Chem. 61, a241.
Roggelin, L., Vinnemeier, C.D., Fischer-Herr, J., Johnson-Weaver, B.T., Rolling, T., Burchard, G.D., Staats, H.F., Cramer, J.P., 2015. Serological response following re-vaccination with Salmonella typhi vi-capsular polysaccharide vaccines in healthy adult travellers. Vaccine 33 (33), 4141–4145.
Sánchez–Ramón, S., de Gracia, J., Garcia-Alonso, A., Rodriguez Molina, J.J., Melero, J., de Andres, A., Garcia Ruiz de Morales, J.M., Ferreira, A., Ocejo-Vinyals, J.G., Cid, J.J., Garcia Martinez, J.M., Lasheras, T., Vargas, M.L., Gil-Herrera, J., Garcia Rodriguez, M.C., Castaner, J.L., Gonzalez Granado, L.I., Allende, L.M., Soler-Palacin, P., Herraiz, L., Lopez Hoyos, M., Bellon, J.M., Silva, G., Gurbindo, D.M., Carbone, J., Rodriguez-Sainz, C., Matamoros, N., Parker, A.R., Fernandez-Cruz, E., group, E, 2016. Multicenter study for the evaluation of the antibody response against salmonella typhi Vi vaccination (EMPATHY) for the diagnosis of Anti-polysaccharide antibody production deficiency in patients with primary immunodeficiency. Clin. Immunol. 169, 80–84.
Sanges, S., Wallet, F., Blondiaux, N., Theis, D., Verin, I., Vachee, A., Dessein, R., Faure, K., Viget, N., Senneville, E., Leroy, O., Maury, F., Just, N., Poissy, J., Mathieu, D., Prevotat, A., Chenivesse, C., Scherpereel, A., Smith, G., Lopez, B., Rosain, J., Fremeaux-Bacchi, V., Hachulla, E., Hatron, P.Y., Bahuaud, M., Batteux, F., Launay, D., Labalette, M., Lefevre, G., 2017. Diagnosis of primary antibody and complement immunodeficiencies in young adults after a first invasive bacterial infection. Clin. Microbiol. Infect. 23 (8), 576.e1–576.e5.
Schaballie, H., Wuyts, G., Dillaerts, D., Frans, G., Moens, L., Proesmans, M., Vermeulen, F., De Boeck, K., Meyts, I., Bossuyt, X., 2016. Effect of previous vaccination with pneumococcal conjugate vaccine on pneumococcal polysaccharide vaccine antibody responses. Clin. Exp. Immunol. 185, 180–189.
Schaballie, H., Bosch, B., Schrijvers, R., Proesmans, M., De Boeck, K., Boon, M.N., Vermeulen, F., Lorent, N., Dillaerts, D., Frans, G., Moens, L., Derdelinckx, I., Peetermans, W., Kantso, B., Jorgensen, C.S., Emonds, M.P., Bossuyt, X., Meyts, I., 2017. Fifth percentile cutoff values for Antipneumococcal polysaccharide and anti-Salmonella typhi vi IgG describe a normal polysaccharide response. Front. Immunol. 8, 546.
Schadich, E., Dzubak, P., Hajduch, M., 2016. Role of Salmonella Typhi Vi antigen and secretory systems on immune response. Curr. Pharm. Desig. 22, 6251–6260.
Schutz, K., Hughes, R.G., Parker, A., Quinti, I., Thon, V., Cavaliere, M., Wurfel, M., Herzog, W., Gessner, J.E., Baumann, U., 2012. Kinetics of IgM and IgA antibody response to 23-valent pneumococcal polysaccharide vaccination in healthy subjects. J. Clin. Immunol. 33, 288–298.
Simao-Gurge, R.M., Costa-Carvalho, B.T., Nobre, F.A., Gonzalez, I.G., de Moraes-Pinto, M.I., 2017. Prospective evaluation of Streptococcus pneumoniae serum antibodies in patients with primary immunodeficiency on regular intravenous immunoglobulin treatment. Allergol Immunopathol (Madr) 45, 55–62.
Sobh, A., Bonilla, F.A., 2016. Vaccination in primary immunodeficiency disorders. J Allergy Clin Immunol Pract 4, 1066–1075.
Staats, H.F., Kirwan, S.M., Whisnant, C.C., Stephenson, J.L., Wagener, D.K., Majumder, P.P., 2010. Development of a bead immunoassay to measure vi polysaccharide-specific serum IgG after vaccination with the Salmonella enterica serovar Typhi vi polysaccharide. Clin. Vaccine Immunol. 17, 412–419.
Sundstrom, P., Lundin, S.B., Nilsson, L.A., Quiding-Jarbrink, M., 2008. Human IgA-secreting cells induced by intestinal, but not systemic, immunization respond to CCL25 (TECK) and CCL28 (MEC). Eur. J. Immunol. 38, 3327–3338.
Szu, S.C., 2013. Development of vi conjugate - a new generation of typhoid vaccine. Expert Rev. Vac. 12, 1273–1286.
Szu, S.C., Li, X., Stone, A.L., Robbins, J.B., 1991. Relation between structure and immunologic properties of the vi capsular polysaccharide. Infect. Immun. 59, 4555–4561.
de Vries, E., 2008. Using vaccines to diagnose antibody deficiencies. Vaccine 21–22.
de Vries, E., 2012. Patient-centred screening for primary immunodeficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update. Clin. Exp. Immunol. 167, 108–119.
Weill, J.C., Weller, S., Reynaud, C.A., 2009. Human marginal zone B cells. Annu. Rev. Immunol. 27, 267–285.
World Health Organization, 2014. Information Sheet: Observed Rate of Vaccine Reactions - Typhoid Vaccine. http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/ 1–4.
Yazdani, R., Abolhassani, H., Asgardoon, M., Shaghaghi, M., Modaresi, M., Azizi, G., Aghamohammadi, A., 2017. Infectious and non-infectious pulmonary complications in primary Immunodeficiencies. J Investig Allergol Clin Immunol 27 (4), 213–224.