ARTICLE IN PRESS

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

Measuring immune responses to pneumococcal vaccines

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ARTICLE INFO

Keywords:
Streptococcus pneumoniae
Pneumococcal
Vaccine
Immune response
Immune deficiency

ABSTRACT

Quantitative assays that measure immune response to pneumococcal vaccines are not only important for the evaluation of vaccine immunogenicity and efficacy, but are also utilized in the clinical diagnosis of immune deficiency syndromes. Analytical methods have progressed in order to meet changing demands in both of these areas, from early methods to ELISA, and most recently multiplex bead array assays and opsonophagocytosis assays (OPA). It is necessary to understand the evolution of such techniques and the criteria for their interpretation in order to better inform the application of currently available methods, and to guide future investigation into assay development.

1. Introduction

Streptococcus pneumoniae (the pneumococcus) is a gram positive bacterium that represents an important human pathogen. Pneumococcal infections can cause significant morbidity and mortality, particularly among young children, elderly adults, and individuals with immune deficiencies (World Health Organization, 2007; World Health Organization, 2012). Its virulence is primarily mediated by a polysaccharide capsule, which is the basis for classification of pneumococci into over 90 known serotypes and constitutes an antigenic target for pneumococcal vaccines (Geno et al., 2015).

The 23-valent pneumococcal polysaccharide vaccine (PPV23) contains capsular polysaccharide from 23 serotypes of *Streptococcus pneumoniae* and has been licensed for use in adults since 1983 (See Table 1) (Centers for Disease Control and Prevention, 1997). Pneumococcal conjugate vaccines (PCVs) consist of pneumococcal capsular polysaccharide conjugated to a protein carrier and result in a T-cell dependent immune response. PCVs, which have been in use since 2000, were initially developed and implemented for use in young children, since PPV23 is not immunogenic in this population (World Health Organization, 2007; World Health Organization, 2012). In recent years, there has been growing evidence to support use of PCV in adults as well, particularly among the elderly and those with immune compromising conditions. 2014 US Advisory Committee on Immunization Practices (ACIP) guidelines recommend the administration of PCV13 and PPV23 in series to adults ≥65 years of age (Table 1) (Tomczyk et al., 2014). Among European countries, guidelines concerning routine administration of pneumococcal vaccines vary widely, particularly for healthy older adults (Castiglia, 2014).

Assays that measure responses to pneumococcal vaccines are important in evaluation of vaccine efficacy as well as in the diagnosis of certain immune deficiency syndromes. Such assays can be broadly divided into two categories: Assays which measure the amount of pneumococcal antibody present in serum, or functional assays that measure serum antibodies' capacity to kill pneumococci. Initial development and licensure of pneumococcal vaccines were based on quantitative assessment of serologic response (i.e., increase in pneumococcal antibody levels) following vaccine administration, which was correlated with incidence of pneumococcal infections (Centers for Disease Control and Prevention, 1997; Jodar et al., 2003). Vaccine evaluation served as the impetus for development of standardized, reproducible assays to measure serologic response. Various pneumococcal assays that were designed to address this need are described below.

2. Methodologies

2.1. Radioimmunoassay/hemagglutination

Radioimmunoassay (RIA) and hemagglutination assays were several of the early methods developed to measure responses to pneumococcal vaccines. RIA utilized radiolabeled capsular polysaccharide antigens, with precipitation of antigen-antibody complexes via the Farr technique (Schiffman et al., 1980; Farr, 1958). Expense, as well as potential safety issues related to use of radiolabeled pneumococcal polysaccharide, and lack of isotype specificity represented important limitations of RIA. Furthermore, pneumococcal antibody response as measured by RIA did

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https://doi.org/10.1016/j.jim.2018.08.002
Received 27 November 2017; Received in revised form 25 July 2018; Accepted 3 August 2018
0022-1759/ © 2018 Published by Elsevier B.V.

Please cite this article as: LaFon, D.C., Journal of Immunological Methods (2018), https://doi.org/10.1016/j.jim.2018.08.002

Table 1
Pneumococcal vaccines, with summaries of current ACIP recommendations for use.

Vaccine	Year licensed	Serotypes included	Indications
PPV23 (Pneumovax 23, Merck)	1983	1, 2, 3, 4, 5, 6B, 7F, 8, 9 V, 9 N, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	• Adults ≥65 years old (in series with PCV13) • Adults ages 19–64 with certain chronic medical conditions* • Children at increased risk for pneumococcal disease (following administration of PCV13)
PCV7 (Prevnar, Pfizer)	2000	4, 6B, 9 V, 14, 18C, 19F, 23F	N/A+
PCV10 (Synflorix, GlaxoSmithKline)	2008	PCV7 serotypes + 1, 5, 7F	N/A+
PCV13 (Prevnar 13, Pfizer)	2009	PCV10 serotypes + 3, 6A, 19A	• Infants • Adults ≥65 years old (in series with PPV23) • Adults ages 19–64 with immunocompromising conditions# (in series with PPV23)

* Chronic medical conditions include chronic heart/lung/liver disease, diabetes mellitus, alcoholism, cigarette smoking.
\+ While used in other countries, PCV10 was not implemented in US immunization guidelines and PCV7 was directly replaced by PCV13.
\# As well as adults with asplenia, CSF leaks, cochlear implants.

not correlate with the frequency or severity of infections in a study of diagnostic vaccination in evaluating immune deficiency syndromes (Webster et al., 1984).

Hemagglutination involved mixing human red blood cells coated with pneumococcal polysaccharide with a serum sample, and documenting the highest serum dilution that still produced agglutination (Ammann and Pelger, 1972). This technique measured both IgM and IgG antibodies and was difficult to standardize (Schiffman et al., 1980), and therefore was not widely adopted.

2.2. ELISA

Largely based on the aforementioned limitations, RIA and hemagglutination were rapidly supplanted by enzyme-linked immunosorbent assay (ELISA) (Balmer et al., 2007a). ELISA for detection of pneumococcal IgG antibodies was developed and refined during the 1980s and 1990s, and was eventually standardized (Wernette et al., 2003), remaining the gold standard to the present day. As compared to RIA, ELISA was less expensive, logistically simpler, required smaller quantities of serum, and did not require use of radiolabeled materials.

Capsule-specific antibodies against pneumococcal polysaccharide are the primary mediators of opsonization and killing of pneumococci. However, antibodies against pneumococcal cell wall polysaccharide (C-PS) as well as other antibodies that do not opsonize (i.e., protect/function) in the immune response can also be found in serum (Wernette et al., 2003). First-generation ELISA to detect pneumococcal antibodies tended to overestimate antibody levels due to the presence of these non-protective antibodies (Wernette et al., 2003). Second-generation ELISA removed some of these non-functioning antibodies using preabsorption of test sera with pneumococcal cell wall polysaccharide, however was still not specific. Third-generation ELISA improved specificity via preabsorption with both C-PS and 22F polysaccharide to remove non-functioning antibodies, and was ultimately adopted as the WHO ELISA (Fig. 1) (Wernette et al., 2003).

WHO ELISA utilizes microwells coated with serotype-specific pneumococcal polysaccharide, to which serum antibodies bind. Anti-human IgG antibodies recognize bound serum antibody, and subsequently react with chromogenic substrate (Fig. 1). Optical density is then converted to antibody concentration (World Health Organization Pneumococcal Serology Reference Laboratories, n.d). WHO ELISA was initially standardized against reference serum 89SF, and was later validated using reference serum 007sp which is utilized today (Goldblatt et al., 2011a). Pneumococcal reference serum 007sp has been assigned reference values for 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C, 19A, 19F, and 23F) through an international collaboration (Goldblatt et al., 2011a). Reference values for additional serotypes were assigned outside of the international collaboration responsible for these 13 original serotypes (Goldblatt et al., 2015). WHO recommendations also suggested criteria for evaluating a new quantitative method for pneumococcal antibody testing, establishing that IgG concentrations for at least 75% of serum samples should fall within 40% error of standardized mean values via ELISA (Plikaytis et al., 2000).

2.3. Multiplex bead array methods

Since ELISA requires performance of a separate assay for each serotype tested, inclusion of additional serotypes in pneumococcal conjugate vaccines resulted in increased cost and decreased throughput (Pickering et al., 2002). In contrast, multiplex bead array assays allow for measurement of antibodies against multiple serotypes within a single serum sample. In addition to reducing costs and increasing throughput, they utilize smaller sample volumes and offer increased dynamic range (i.e., require fewer dilutions to obtain result) as compared to ELISA (Pickering et al., 2002; Lal et al., 2005). These assays, which use color coded beads, are commonly referred to as Luminex assays after the developer of the bead assay method. Luminex assays were first developed by commercial laboratories, national public health agencies, and pharmaceutical corporations beginning in the early 2000s (Pickering et al., 2002; Lal et al., 2005; Biagini et al., 2003). While assay developers evaluated their methods based on WHO ELISA performance criteria, laboratories that currently perform these assays may utilize their own proprietary techniques as well as different reference sera (personal communication, September 2017).

Generally, the bead array method uses sets of color coded microspheres, each of which is coated with pneumococcal polysaccharide of a given serotype (Pickering et al., 2002; Lal et al., 2005; Biagini et al., 2003). A set of microspheres is mixed with serum, then exposed to anti-human IgG antibody conjugated to a fluorescent marker, usually phycoerythrin. Mean fluorescence intensity is measured and converted to antibody concentration in μg/mL (Pickering et al., 2002; Lal et al., 2005; Biagini et al., 2003). Serum is preabsorbed with C-PS and/or 22F polysaccharide in concordance with prior methods for ELISA (Pickering et al., 2002; Biagini et al., 2003).

Multiplex bead array assays performed by individual labs have been demonstrated to produce different results from those performed by other labs as well as from WHO ELISA. Validation studies for various multiplex assays demonstrate variability in specificity and correlation with ELISA based on serotype (Pickering et al., 2002; Borgers et al., 2010). A 2010 study evaluated inter-assay variability between three multiplex assays that were available at that time, and their correlation with ELISA. The study analyzed the same 11 or 12 sera using the xMAP Pneumo 13 Luminex assay and two other in-house multiplex bead array assays utilized by the US Centers for Disease Control and Prevention and UK Health Protection Agency, respectively. Overall, the multiplex assays yielded higher antibody concentrations as compared to ELISA. Multiplex assays demonstrated greater inter-assay variability for certain serotypes as well as for certain sera across all three assays. Overall, none of the assays were able to satisfy the WHO stipulations for

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