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REVIEW ARTICLE

Pneumococcal vaccine and opsonic pneumococcal antibody

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Abstract *Streptococcus pneumoniae* is a major human pathogen responsible for the majority of bacterial pneumonia cases as well as invasive pneumococcal diseases with high mortality and morbidity. Use of conjugate vaccines targeting the pneumococcal capsule has dramatically reduced the incidence of invasive diseases, and there are active efforts to further improve the conjugate vaccines. However, in children new pneumococcal vaccines can no longer be tested with placebo-based clinical trials because effective vaccines are currently available. Thus, vaccine studies must depend on surrogate markers of vaccine efficacy. Although traditional antibody levels (e.g., ELISA) are useful as a surrogate marker of protection, they have limitations, and a bioassay measuring the capacity of antibodies to opsonize pneumococci has been developed. This opsonophagocytosis assay (OPA) replicates the in vivo mechanism of antibody protection and should therefore better reflect protection by vaccine-induced antibodies. Technical improvements of OPA have made this bioassay rapid, multiplexed, and practical for analyzing small samples including those from children. Strong correlations between ELISA and OPA have been observed in many studies of young children. However, poor correlations have been found in some important clinical situations (such as determination of protection by cross-reactive antibodies) and populations (such as elderly adults and immunodeficient patients). In these settings, OPA has become a useful supplementary measure of pneumococcal vaccine immunogenicity. Current efforts to standardize OPA will further expand its uses.

Keywords Opsonophagocytic killing assay · Pneumococcal vaccine · Immunogenicity · *Streptococcus pneumoniae*

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Introduction

The worldwide disease burden from *Streptococcus pneumoniae* remains both significant and widespread. The clinical implications of infection span a wide spectrum from mild illnesses, such as otitis media and sinusitis, to various invasive pneumococcal diseases (IPDs). Although the incidence of IPDs has decreased in recent years with the introduction of protein-conjugated vaccines, child deaths caused by *S. pneumoniae* still range from 700,000 to 1 million every year worldwide [1] and account for about 11 % of all deaths in children aged 1–59 months [2]. In the United States, *S. pneumoniae* was responsible for 22,000 deaths, 4 million

disease episodes, and direct medical care costs of $3.5 billion in 2004 [3], a year when the conjugate vaccine had significantly reduced IPDs among children [4]. Most of the deaths and medical costs were found to be associated with adult patients, who accounted for only half the disease episodes.

A major reason for such a high disease burden is the polysaccharide (PS) pneumococcal capsule, which shields pneumococci from host phagocytes and dramatically increases its virulence [5]. However, antibodies to the capsule can neutralize the shielding effect by opsonizing pneumococci for ingestion and killing by phagocytes. Although *S. pneumoniae* can express more than 90 different capsule types [6, 7], certain capsule types are more often associated with IPDs than others [8]. Thus, antibodies against 10 or 20 different serotypes can provide protection against a great majority of IPDs [8].

Despite antibiotic usage, morbidity and mortality from IPD remain high, in part because antibiotic resistance has become common. Therefore, vaccination has emerged as a key strategy against pneumococcal infections. A polysaccharide vaccine containing capsular PS from 23 different serotypes (PPV23; Pneumovax®) has been available since 1983. PPV23 is immunogenic and is widely used among adults, although its efficacy against IPD and pneumococcal pneumonia is somewhat controversial. The primary limitation of PPV23 is its lack of immunogenicity in young children. Efforts to develop vaccines for young children led to development of a protein–PS conjugate vaccine that included PS from 7 serotypes (PCV7; Prevnar®), which was introduced in 2000 in the USA. Clinical use of this vaccine dramatically reduced the incidence of IPDs in children [4, 9]. Later, PCV10 (Synflorix®) and PCV13 (Prevnar-13®) were licensed for children in 2008 and 2010, respectively. PCV13 was licensed for adults in the USA in 2012.

In the wake of these successes, there is a significant effort to improve the currently available conjugate vaccines. For various practical reasons, evaluation of the new vaccines will require the use of surrogate markers of vaccine efficacy rather than efficacy trials measuring clinical endpoints. First, because the conjugate vaccines are clinically efficacious, it would be unethical to randomize patients at risk for pneumococcal disease to placebo. Second, the use of the conventional vaccine would drastically lower the incidence of pneumococcal infections in the control group. Thus, an efficacy study would require a very large sample size, which would be prohibitive in terms of costs and logistics.

Surrogate markers of pneumococcal vaccine efficacy

One widely used surrogate marker of protection is the anti-capsular PS antibody levels determined by enzyme-linked immunosorbent assay (ELISA). Because the ELISA requires no special equipment and is amenable to scaling up for high-throughput needs, it was widely used in developing conjugate vaccines. Based on efficacy data from the Northern California study, an antibody level of 0.2 mg/l was established as the threshold that loosely correlates with protection [10]. Later, immunogenicity data from Native American children and South African children were added to the Northern California data, and a meta-analysis was performed that resulted in a threshold value of 0.35 mg/l for children [11], which was later accepted by the World Health Organization (WHO). Additional studies suggested that the threshold may be closer to 0.2 mg/l when the ELISA developed by GlaxoSmithKline (GSK) is used [12]. It should be noted that the GSK ELISA is slightly different from the WHO ELISA [12].

ELISA has some important limitations, however. First, early generations of the assay were not specific [13]. The specificity was improved by preabsorbing immune serum with capsular PS from serotype 22F, which is not clinically relevant. The improved ELISA procedure was adopted by WHO: a detailed protocol is at http://www.vaccine.uab.edu. Second, most adults have antibody levels above 0.35 mg/l before vaccination, and these high background levels make interpretation of ELISA results difficult in this population. Third, ELISA typically measures only IgG, minimizing any contributions by other isotypes (such as IgM) to overall immunity. Recent evidence has shown that older adults have a lower capacity to opsonize pneumococci despite normal IgG levels because of lack of anti-pneumococcal IgM antibodies [14]; this may be a result of deficient IgM-producing memory B cells, which decline with aging. A Finnish study demonstrated that IgM antibodies contribute to the postvaccination opsonophagocytic activity in infants as well [15]. This phenomenon (i.e., a poor correlation between opsonic activity and IgG levels) has also been shown in patients who have undergone bone marrow transplants [16] and emergency splenectomies [17]. It is unclear if these populations produce subnormal levels of IgM antibodies or produce nonopsonic antibodies.

Another limitation of the ELISA is that it does not measure the functional capacity of antibodies but rather their capacity to bind to PSs immobilized on a plastic surface. For example, PCV7 includes 19F PS but not the structurally related 19A PS. Although PCV7 can be shown to elicit antibodies cross-reactive with 19A by WHO ELISA, the antibodies do not cross-opsonize 19A [18]. Epidemiology data have shown that PCV7 does not provide cross-protection against 19A, thus supporting the results of the opsonophagocytosis assay (OPA). Also, studies of vaccine failures indicated that OPA predicts vaccine failures better than ELISA [19].