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Laboratory diagnosis of specific antibody deficiency to pneumococcal capsular polysaccharide antigens by multiplexed bead assay

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Abstract We evaluated a multiplexed bead-based assay (xMAP® Pneumococcal Immunity assay from Luminex) for the simultaneous determination of antibodies against 14 capsular polysaccharides. Post-vaccination (Pneumovax®) antibody concentrations were measured in 35 healthy children, 40 healthy adults, 99 consecutive patients with increased susceptibility to respiratory infection, and 24 patients with a deficient anti-polysaccharide antibody response. The serotype-specific lower 5th percentile (cutoff) value for the post-immunization antibody concentration was determined in healthy individuals. Eleven of 99 patients (11%) failed to mount a response that was >5th percentile of controls for at least 6 of the 14 serotypes tested, whereas only 3 of 75 controls (4%) failed to do so. All patients with known anti-polysaccharide antibody deficiency failed to mount a response that was >5th percentile of controls for at least 6 of the 14 serotypes tested. The XMAP® pneumococcal immunity panel appears useful for identifying individuals with a low response to the unconjugated pneumococcal vaccine.
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Introduction

Streptococcus pneumoniae (pneumococcus) causes common benign infections of the upper respiratory tract. It also causes lobar pneumonia and, in rare cases, invasive disease, such as septicemia and meningitis. Risk groups for invasive pneumococcal disease include young children, the elderly,

Abbreviation: Caps-PS, capsular polysaccharides

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and patients with immune defects [1,2]. Invasive pneumococcal disease is the highest risk factor, as recurrence occurs in 2–4% of the cases [3].

The immune response to *S. pneumoniae* relies on both innate and adaptive components. Antibody-initiated complement-dependent opsonisation is an important immune mechanism protecting the host against pneumococcal infections [4,5]. The capsular polysaccharides (caps-PS) of *S. pneumoniae* are a major determinant of the virulence of *S. pneumoniae*. High levels of antibodies directed against caps-PS confer clinical protection against invasive infections [6] and caps-PS-based vaccines are efficacious in reducing *S. pneumoniae* infection in the elderly and children after the age of 2. Although the 23-valent Pneumovax®/Pneumo23® vaccine is immunogenic in adults and children, young children under 2 years of age have an impaired antibody response to the non-conjugate vaccine. Children with a persisting defect in the production of antibodies specific for pneumococcal capsular antigens after 2 years of age have "specific antibody deficiency with normal immunoglobulins" [7,8]. These patients suffer from recurrent pneumococcal infections, although their immunoglobulin and immunoglobulin subclass levels and responses to protein antigens are normal [9]. It is estimated that 5% to 10% of the patients with recurrent pneumococcal infections have a defective antibody response to pneumococcal polysaccharides [10].

A number of defects in the Toll like receptor and NF-κβ pathway associated with increased susceptibility to recurrent pneumococcal infection have been described. Mutations in genes encoding the interleukin-1 receptor-associated kinase 4 (IRAK-4), MyD-88, and nuclear factor kappa B essential modulator protein (NEMO) have been associated with recurrent invasive pneumococcal infections and with decreased antibody response to caps-PS [11–15].

The response to pneumococcal polysaccharides is important in the evaluation of patients with documented immune abnormalities and of patients with normal total immunoglobulins [16]. A deficient antibody response to caps-PS is determined by measuring the anti-caps-PS antibody concentrations after vaccination with the 23-valent unconjugated vaccine [10]. Classically, a deficient response to pneumococcal caps-PS is identified by determining antibodies to a panel of pneumococcal serotypes. A standardized enzyme linked immunosorbent procedure (ELISA) to measure anti-pneumococcal antibodies has been developed. This procedure includes absorption of patient serum samples with polysaccharide C and serotype 22F [17]. However, the number of serotypes tested and the criteria used to define a deficient response differ from institution to institution [18–29].

Recently, the xMAP® Pneumococcal Immunity assay became available on the Luminex® system. This assay allows the simultaneous determination of antibodies in serum to 14 different caps-PS serotypes: 1, 3, 4, 6B, 7F, 8, 9N, 9V, 12F, 14, 18C, 19A, 19F, 23F. Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F are included in the conjugated vaccine Prevnar as well as in the unconjugated vaccine Pneumovax®/Pneumo23®. Serotypes 1, 3, 7F, 8, 9N, 12F, and 19A are included in Pneumovax / Pneumo23 but not in Prevnar. The Luminex® xMAP® Pneumoccal Immunity assay adheres to the international recommendations regarding preabsorption with polysaccharide C and serotype 22F. The technology is based on the use of color-coded tiny polystyrene microspheres. Each color-coded set of microspheres is coated with a different polysaccharide, allowing the simultaneous capture and detection of different specific antibodies. Lasers excite the internal dyes that identify each microsphere particle. The amount of sample antibodies captured during the assay is assessed. This is the first commercially available assay for measurement of serotype-specific anti-polysaccharide antibodies. In the present paper, we evaluated the Luminex® xMAP® Pneumoccal Immunity panel for the quantification of anti-caps-PS antibodies and the evaluation of the response to pneumococcal polysaccharides.

Methods

Control and patient populations

We measured the anti-caps-PS antibody response in 35 healthy children aged between 3 and 15 years (mean 8 years) and 40 healthy students aged between 19 and 30 years (mean 21 years) (recruited between 2000 and 2005). This control population has been described previously [18].

We measured the anti-caps-PS antibody response in 99 consecutive patients aged between 3 and 80 years (mean age 11 years) who were referred to our institution because of recurrent infections of the upper and/or lower airways (between 2007 and 2008). Recurrent infections of the upper respiratory tract were defined as at least 5 episodes (in a 1-year period) of upper respiratory tract infections complicated by otitis media or chronic (longer than 3 weeks duration) draining ears. Recurrent infection of the lower respiratory tract was defined as at least 3 lower respiratory tract infections in a 1-year period with radiographic evidence of pneumonia in at least 2 of these periods.

A final group of patients consisted of 24 historically selected patients aged between 2 and 26 years (mean 9 years) who had previously been diagnosed with deficient anti-polysaccharide antibody response according to the criteria described by Jeurissen et al. [18]. This included 6 patients with well-defined immune deficits: 3 patients (age: 26, 26, and 13 years old) with a mutation in IRAK-4 and 3 patients (ages 5, 7, 7 years old) with a mutation in NEMO.

In all individuals, antibody response was measured 3 weeks after vaccination with Pneumovax/Pneumo23.

Determination of anti-Caps-PS antibodies

Measurement of serotype specific anti-caps-PS antibodies by ELISA

Anti-caps-PS antibodies to serotypes 3, 4, 9N, 18C and 19F were determined by ELISA according to WHO-guidelines as described by Jeurissen et al. [18].

Measurement of total anti-caps-PS antibodies by ELISA

Anti-caps-PS antibodies to the mix of the 23 serotypes contained in Pneumovax®/Pneumo23® were determined as described by Jeurissen et al. [18] for the determination of serotype-specific antibodies, except that the plates were

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