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Dr Lizelle Nagel, Dr Sylvia van den Berg

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# A NEW 23-SEROTYPE PNEUMOCOCCAL IgG IMMUNOASSAY TO SUPPORT DIAGNOSTIC VACCINATION

Diagnosing immunodeficiency early is essential to prevent infections, preserve organ function and optimise healthcare in patients with primary or secondary immunodeficiencies. Antigen-specific antibodies tested before and after vaccination are a useful tool to evaluate patients for antibody deficiency. Vaccine testing with Pneumovax 23 evaluates antigen-specific antibody production to the 23 vaccine serotypes of Streptococcus *pneumoniae,* and identifies patients who may benefit from prophylactic antibiotics and/or immunoglobulin replacement therapy.

## The role of the polysaccharide response

The polysaccharide response is triggered by direct interaction of bacterial cell membrane polysaccharides with B-cell receptors on B lymphocytes. The polysaccharide response is a critical defence mechanism against infections by encapsulated bacteria like S. *pneumoniae*, H. *influenzae* and M. *catarrhalis*. Community-acquired otosinopulmonary infections by encapsulated bacteria are common, especially in small children <5 years of age who normally have an immature polysaccharide response and high rates of nasopharyngeal colonisation. These infections are invasive and life-threatening in patients with immunodeficiency. Frequent infections also greatly impair quality of life and may result in end-organ damage such as hearing loss or bronchiectasis.

## When to consider testing the polysaccharide response

A diagnostic vaccination to test the polysaccharide response should be considered in patients with:

- Severe, persistent, unusual or recurrent (SPUR) infections
- Frequent otosinopulmonary infections by encapsulated bacteria
- A history of invasive pneumococcal disease
- If there are risk factors for secondary immunodeficiency, for example, frequent corticosteroid use, cancer therapy, immunosuppressive therapy, protein-losing conditions, chronic kidney or liver disease, haematological disorders, post-splenectomy, etc.

## Testing the polysaccharide response: 13 or 23 serotypes?

Vaccination with pneumococcal polysaccharide vaccine induces production of serotype-specific IgG antibodies, which peak after about 4-6 weeks and wane within 2-5 years in the absence of exposure. The polyvalent vaccine Pneumovax 23 contains 23 clinically relevant serotypes, 13 of which are shared with the conjugate vaccine Prevenar 13, and 11 of which are targeted only by Pneumovax 23.

Uptake of pneumococcal conjugate vaccines in vaccination programmes makes accurate interpretation of the polysaccharide response more challenging. Conjugate vaccination with Prevenar 13 induces potent T cell-dependent immunity with long-lasting memory to the 13 shared serotypes. Patients who received Prevenar 13, therefore, show both a T cell-dependent memory response and a T cell-independent polysaccharide response when vaccinated with Pneumovax 23. This may cause normal post-vaccination results in patients who respond normally to protein and conjugate vaccines, but have an impaired polysaccharide response. This problem can be overcome by measuring the 11 “pure” polysaccharide

serotypes targeted by Pneumovax 23 (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F). Including these serotypes improves the reliability and diagnostic accuracy of the assay.

Ampath's new pneumococcal IgG assay measures polysaccharide responses to 23 disease-causing serotypes which include the 11 pure polysaccharide serotypes targeted by only Pneumovax 23. Poor or absent polysaccharide responses are seen in many primary and secondary immunodeficiencies. These patients may have normal or decreased total serum IgG levels. Common primary immunodeficiencies that are diagnosed through vaccine testing include common variable immunodeficiency (CVID) and specific antibody deficiency (SAD).

### Interpreting the results of pre- and post-vaccination testing

The normal polysaccharide response is poorly memory-forming and short-lived. It is therefore very common for healthy subjects with normal polysaccharide responsiveness to have low baseline levels of serotype-specific antibodies at the time of the first test. This does not necessarily indicate an antibody deficiency, and a vaccine test should be performed if immunodeficiency is strongly suspected based on clinical grounds. Normal baseline values also don't exclude an abnormality of the polysaccharide response.

The correct approach to testing and interpretation requires a baseline pre-vaccination test, a peak test at 4-6 weeks post-vaccination, and a 6-month post-vaccination test to evaluate B cell memory formation. The correct timing of vaccination and sample collection is crucial. In a patient suspected of having an immunodeficiency, diagnostic vaccination is indicated even if baseline levels are normal.

### Adequate Response:

1. A post-vaccination level of ≥1.3 µg/ml plus a 2-fold increase should be observed in at least 70% of serotypes in patients older than 6 years. Levels ≥1.3 µg/ml should be maintained for at least 6 months.
2. In children aged 2-6 years, a post-vaccination level of ≥1.3 µg/ml plus a 2-fold increase should be observed in at least 50% of serotypes. Levels ≥1.3 µg/ml should be maintained for at least 6 months.

An inadequate response to vaccination suggests impairment of the polysaccharide response, and further investigation is recommended.

It is important to note that repeated doses of Pneumovax 23 within a short time frame (<5 years) may cause paradoxical inhibition of polysaccharide responsiveness that may confound the clinical interpretation. Pneumovax 23 vaccine should therefore be used judiciously, and only when immunodeficiency is strongly suspected.

### Clinical Integration and Next Steps

Testing of vaccine responses forms part of the basic immunological evaluation together with other tests such as serum immunoglobulins (IgG, IgA, IgM, IgE), lymphocyte subpopulations and memory B cells. Vaccine testing with protein vaccines such as tetanus and diphtheria toxoid evaluates T cell-dependent pathways of antibody production, while vaccine testing with Pneumovax 23 evaluates the pure polysaccharide response (T cell-independent).

Referral to a specialist experienced with the management of immunodeficient patients is recommended for further assessment of end-organ damage and preventative management. Patients with antibody deficiency may benefit from prophylactic antibiotics and/or immunoglobulin replacement therapy.

Genetic testing with a commercially available next-generation sequencing gene panel is also recommended to obtain a genetic diagnosis in patients with confirmed primary immunodeficiency. Many immunodeficient patients are children, and a known genetic diagnosis is particularly useful for family genetic counselling.

**Key Takeaways**

- Diagnostic vaccination and antigen-specific antibody measurement in clinical practice improve the identification of patients with primary or secondary immunodeficiency, and support the management of patients with frequent infections.
- Vaccine testing should be performed with both protein and polysaccharide vaccines.
- Protein and conjugate vaccines induce T cell-mediated immunity, while polysaccharide vaccine induces T cell-independent immunity (the polysaccharide response).
- Conjugate pneumococcal vaccination with Prevenar 13 confounds interpretation of the polysaccharide response because it induces T cell-dependent immunity to serotypes shared with Pneumovax 23. This may cause a false normal vaccine test in some patients.
- Measuring the pure polysaccharide serotypes present only in Pneumovax 23 identifies patients with primary polysaccharide non-responsiveness that respond normally to protein and conjugate vaccines.
- The inclusion of pure polysaccharide serotypes in the pneumococcal IgG assay enhances the assay's reliability and accuracy for impaired polysaccharide responsiveness.

For more information or assistance with specific patient cases, please contact the Immunology Department: 012 678 0613/4