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Pneumococcal glycoconjugate vaccines produce antibody responses that strongly correlate with function

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The recent Review article by Astronomo and Burton (Carbohydrate vaccines: developing sweet solutions to sticky situations. *Nature Rev. Drug Discov.* **9**, 308–324 (2010))[1] highlighted advances in the use of glycoconjugate vaccines for protection against infection with encapsulated bacteria such as *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenzae* type b. The 23-valent pneumococcal polysaccharide vaccine (Pneumovax (PPS); Merck) has been used for many years in adults or children <2 years of age[2]. However, this vaccine is considered to be poorly immunogenic in young children and the introduction of the seven-valent pneumococcal conjugate vaccine (Prevnar (PCV7); Wyeth/Pfizer) has had a profound impact on vaccine-type invasive pneumococcal disease in children <2 years of age, with vaccine efficacy estimated to be between 77% and 97.4% based on the pivotal trials conducted in populations from the Northern California Kaiser Permanente, Navajo and White Mountain Apache, South African, and Gambian regions[3]. The success of these vaccines is attributed to the conjugation of protein carriers (for example, CRM197 and tetanus toxoid) to pneumococcal polysaccharides, which significantly enhances vaccine immunogenicity in this age group[4].

In their article, Astronomo and Burton suggest that for the evaluation of new carbohydrate-based vaccines, functional end points may be more useful than enzyme-linked immunosorbent assay (ELISA) titres. Studies with pneumococcal conjugate vaccines have generally supported this conclusion. There have been several instances in which clinical outcomes with pneumococcal vaccines have correlated with opsonophagocytic activity (OPA) — which is presumably the protective mechanism of anticapsule antibodies — but not with ELISA titres. For instance, pneumococcal polysaccharide immunization is not as protective in elderly adults compared with young adults despite similar serotype-specific immunoglobulin G (IgG) titres measured by ELISA. Yet, when OPA responses were studied in these subjects, young adults showed better functional responses than elderly adults[5]. Similarly, poor cross-protection against serotype 19A by PCV7 was not predicted by ELISA IgG titres but was predicted by OPA outcomes[6–8].

Nevertheless, pneumococcal vaccine studies have also revealed many instances in which ELISA titres were highly correlated with OPA results and were useful in predicting clinical outcomes following vaccination. Studies suggest that ELISA or OPA measures of PCV7 vaccine responses in young children are largely comparable. These studies have led to the conclusion that a serotype-specific IgG concentration of 0.35 μg per ml provides a useful threshold for measuring the efficacy of PCV7 in infancy using a WHO (World Health Organization)-defined ELISA[9]. In a randomized controlled pneumococcal vaccine trial in Fiji, we have recently found a strong correlation between ELISA IgG and OPA titres for PCV7 serotypes, particularly following booster immunization with pneumococcal polysaccharides, with correlation coefficients increasing above that observed following primary PCV7 series[10-15] (FIG. 1). These data suggest that ELISA IgG titres can be regarded as a suitable correlate of vaccine-induced immune protection in young children.

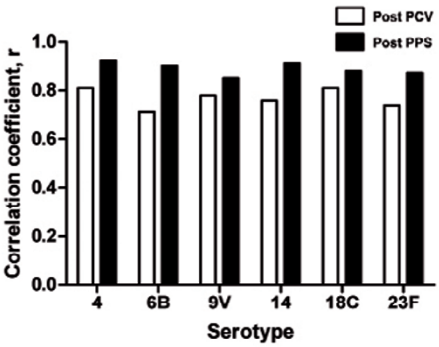

Figure 1 | **Correlation between IgG and OPA measurement for infants (*n* = 241) in the Fiji Pneumococcal Project (FiPP): a randomized controlled trial of pneumococcal vaccine immunogenicity.** A high degree of correlation was found for opsonophagocytic activity and enzyme-linked immunosorbent assay immunoglobulin G following a primary seven-valent pneumococcal conjugate vaccine series and a pneumococcal polysaccharide vaccine booster at 12 months of age[10–15].

Owing to a long history of development and standardization, the WHO-defined ELISA is currently widely accepted for the evaluation of pneumococcal vaccine immunogenicity. By contrast, OPA for the functional evaluation of pneumococcal antibodies remains less standardized than the ELISA, although significant efforts towards validation of OPA are ongoing. The ELISA is a robust immunoassay that can be readily replicated in many different laboratories. Furthermore, novel approaches using multiplex technology offer considerably improved efficiency for the ELISA approach. Thus, although we support the use of functional assays for the evaluation of vaccine immunogenicity in clinical studies, we believe that the standard ELISA is and will continue to be important in evaluating vaccine immunogenicity in many situations.

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Competing interests statement
The authors declare no competing financial interests.