MILESTONE 12

The sweet success of conjugate vaccines

Credit: Photology1971 / Alamy Stock Photo

Polysaccharide-encapsulated bacteria (such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis*) can cause serious bacterial infections, including bacterial meningitis and pneumonia, and have been a deadly scourge on humans for centuries. Before the introduction of effective vaccines in the 1980s, *H. influenzae* type b (Hib) was the leading cause of invasive bacterial disease in young children worldwide, affecting approximately 1 in 200 children under the age of 5 years in the USA. Even with the availability of antibiotic treatment, Hib infection resulted in thousands of deaths annually, necessitating effective prevention methods.

In the late 1960s, two groups, one led by John Robbins and Rachel Schneerson and the other led by Porter Warren Anderson and David Hamilton Smith, began independent investigations into the biology of Hib and potential vaccine strategies, a line of research that would eventually jointly earn these four researchers the prestigious Albert Lasker Clinical Medical Research Award in 1996.

Both research groups undertook the unusual strategy of focusing on the polysaccharide (sugar) capsule covering the surface of Hib, a structure that provides protection against host immune responses and is a major virulence factor. Given that the development of antibodies to this capsule was known to be crucial for acquiring immunity to Hib, they postulated that this polysaccharide capsule, in particular its primary component polyribosyl ribitol phosphate (PRP), could be leveraged as a vaccine. Such an approach differed notably from other vaccine strategies at the time, which mostly focused on using whole bacteria.

Several pure polysaccharide PRP vaccines were developed that provided some protection in adults and were subsequently licensed in the USA in 1985. However, these pure polysaccharide vaccines were ineffective in children under the age of 18 months, the age group most at risk of disease, and failed to induce immunological memory at any age owing to the T cell-independent nature of the PRP antigen response.

To overcome this issue, and drawing inspiration from work by Avery and Goebel in the 1920s, both groups independently developed a method for improving the immunogenicity of PRP by conjugating it to a protein carrier with strong antigenic properties, leading to the first protein–polysaccharide conjugate vaccines. Notably, such vaccines could induce features of T cell-dependent humoral immunity, including a memory response to booster doses of the vaccine.

The first invented and approved conjugate vaccine, developed by the group of Robbins and Schneerson, consisted of PRP conjugated to diphtheria toxoid (known as PRP-D). This vaccine was highly efficacious in Finnish infants and received FDA approval in 1987. Unfortunately, the vaccine was ineffective in Alaska Native infants, a population at high risk of disease.

Since the development of PRP-D, other more effective PRP conjugate vaccines that use different protein carriers (meningococcal outer membrane protein (PRP-OMP), CRM_{197} (PRP-CRM) or tetanus toxoid (PRP-T)) have superseded PRP-D, leading to its withdrawal from the market in 2000. These PRP conjugate vaccines are now part of routine immunization schedules in many countries worldwide.

The introduction of PRP conjugate vaccines saw a rapid reduction in the number of cases of invasive Hib disease in multiple countries and in the past three decades has undoubtedly saved the lives of millions. The success of these vaccines inspired the development of other conjugate vaccines targeting various polysaccharide-encapsulated bacteria, including *S. pneumoniae* and *N. meningitidis*, and led to a renaissance in vaccine discovery that has rapidly changed the epidemiology of many childhood diseases and that continues to grow to this day.

Indeed, before the 2010s, *N. meningitidis* serogroup A accounted for the majority of cases of meningococcal disease in the meningitis belt of sub-Saharan Africa. The widespread introduction of a conjugate vaccine in the 2010s led to the virtual elimination of serogroup A in this high-risk region.

A more recent example is *Salmonella enterica*, a bacterium responsible for a serious and sometimes fatal complication known as typhoid fever. Two typhoid vaccines are currently available and recommended by the WHO: a live attenuated version of the bacterium (Ty21a) and a vaccine consisting of the purified capsular polysaccharide Vi (ViCPS). However, these vaccines are either unsuitable or are not immunogenic enough in young children, reminiscent of the experience with Hib in the 1970s.

A new typhoid conjugate vaccine, consisting of Vi conjugated to tetanus toxoid (Typbar TCV), has shown promising immunogenicity and safety results in clinical trials. This vaccine is currently licensed for private use in India and Nepal and received WHO prequalification in 2018. Multiple large studies of this vaccine in various Asian and African countries are currently ongoing. Only time will tell whether this vaccine mirrors the success of the first conjugate vaccines.

Jessica McHugh,
Nature Reviews Rheumatology

ORIGINAL ARTICLE Schneerson, R. et al. Preparation, characterization, and immunogenicity of *Haemophilus influenzae* type b polysaccharide-protein conjugates. *J. Exp. Med.* **152**, 361–376 (1980)
FURTHER READING Gobel, W. F. & Avery, O. T. Chemo-immunological studies on conjugated carbohydrate protein. I. The synthesis of *p*-aminophenol 3-glucoside, *p*-aminophenol 13-galactoside and their coupling with serum globulin. *J. Exp. Med.* **50**, 521–531 (1929) | Smith, D. H. et al. Responses of children immunized with the capsular polysaccharide of *Haemophilus influenzae*, type b. *Pediatrics* **52**, 637–644 (1973) | Parke, J. C. et al. Interim report of a controlled field trial of immunization with capsular polysaccharides of *Haemophilus influenzae* type b and group C *Neisseria meningitidis* in Mecklenburg county, North Carolina (March 1974–March 1976). *J. Infect. Dis.* **136**, S51–S56 (1977) | Anderson, P. Antibody responses to *Haemophilus influenzae* type b and diphtheria toxin induced by conjugates of oligosaccharides of the type b capsule with the nontoxic protein CRM197. *Infect. Immun.* **39**, 233–238 (1983) | Eskola, J. et al. Efficacy of *Haemophilus influenzae* type b polysaccharide-diphtheria toxoid conjugate vaccine in infancy. *N. Engl. J. Med.* **317**, 717–722 (1987) | Ward, J. et al. Limited efficacy of a *Haemophilus influenzae* type b conjugate vaccine in Alaska Native infants. The Alaska *H. influenzae* Vaccine Study Group. *N. Engl. J. Med.* **323**, 1393–1401 (1990) | Murphy, T. V. et al. Declining incidence of *Haemophilus influenzae* type b disease since introduction of vaccination. *JAMA* **269**, 246–248 (1993) | Lingani, C. et al. Meningococcal meningitis surveillance in the African meningitis belt, 2004–2013. *Clin. Infect. Dis.* **61**, S410–S415 (2015) | Miller, E. et al. Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. *Vaccine* **20**, S58–S67 (2002) | Mohan, V. K. et al. Safety and immunogenicity of a Vi polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. *Clin. Infect. Dis.* **61**, 393–402 (2015) | Jin, C. et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet* **390**, 2472–2480 (2017)