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Review

Polysaccharide conjugate vaccine protein carriers as a "neglected valency" – Potential and limitations

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ABSTRACT

The development of vaccines against polysaccharide-encapsulated pathogens (e.g. *Haemophilus influenzae* type b, pneumococci, meningococci) is challenging because polysaccharides do not elicit a strong and long-lasting immune response (i.e. T-cell independent). This can be overcome by conjugating the polysaccharide to a protein carrier (e.g. tetanus toxoid, cross-reacting material 197 [CRM]), which vastly improves the immune response and induces memory to the polysaccharide (T-cell dependent). Although it is well documented that protein carriers additionally induce an immune response against themselves, this potential "additional valency" has so far not been recognized. The only exception is for the protein D carrier (derived from non-typeable *Haemophilus influenzae* [NTHi]) used in a pneumococcal conjugate vaccine, which may have a beneficial impact on NTHi acute otitis media. In this review, we describe the immunogenicity of various protein carriers and discuss their potential dual function: as providers of T-cell helper epitopes and as protective antigens. If this "additional valency" could be proven to be protective, it may be possible to consider its potential effect on the number of required immunizations. We also describe the potential for positive or negative interference between conjugate vaccines using the same protein carriers, the resulting desire for novel carriers, and information on potential new carriers. The range of conjugate vaccines is ever expanding, with different carriers and methods of conjugation. We propose that new conjugate vaccine trials should assess immunogenicity to both the polysaccharide and carrier. Ultimately, this so-far "neglected valency" could be an exploitable characteristic of polysaccharide conjugate vaccines.

Contents

Abbreviations: AOM, acute otitis media; CI, confidence interval; CRM, cross-reacting material 197; DT, diphtheria toxoid; DTaP, diphtheria, tetanus, acellular pertussis; DTwP, diphtheria, tetanus, whole-cell pertussis; dPly, detoxified pneumolysin; EPA, exotoxin A of *Pseudomonas aeruginosa*; GBS, group B *Streptococcus*; GMC, geometric mean concentration; Hib, *Haemophilus influenzae* type b; IgA, immunoglobulin A; IgG, immunoglobulin G; IPV, inactivated poliovirus; ITT, intent-to-treat; MenA, meningococcal capsular group A; MenACWY, meningococcal capsular groups A, C, W, Y; MenB, meningococcal capsular group B; MenC, meningococcal capsular group C; MenCY, meningococcal capsular groups C, Y; MenY, meningococcal capsular group Y; NTHi, non-typeable *Haemophilus influenzae*; OMPC, outer membrane protein complex; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, non-typeable *Haemophilus influenzae* protein D conjugate vaccine; PhtD, pneumococcal histidine triad D; PP, per protocol; PPV23, 23-valent pneumococcal polysaccharide vaccine; PspA, pneumococcal surface protein A; RCT, randomized controlled trial; Td, tetanus-diphtheria; Tdap, tetanus-diphtheria-acellular pertussis; TT, tetanus toxoid.

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1. Introduction

The development of vaccines against polysaccharide-encapsulated pathogens is challenging due to an insufficient immune response to the polysaccharides, particularly in young children [1,2]. Polysaccharide vaccines only elicit a B-cell response, so although antibodies are produced, there is no long-term memory (Fig. 1A). Repeated doses do not seem to be beneficial, and may result in lower antibody concentrations than those after primary immunization [3], so-called "hypo-responsiveness".

The lack of a T-cell response with polysaccharide vaccines has been overcome by conjugation to protein carriers [4]. This invokes a T-cell response, resulting in antibodies and immune memory (non-highlighted portion of Fig. 1B). While the mechanisms for this are not fully understood [5–7], polysaccharide conjugate vaccines have several advantages over plain polysaccharide vaccines [2]: induction of higher antibody concentrations, for a longer time; high immunogenicity in young children; and repeated doses boost the immune response without causing hypo-responsiveness.

The carrier protein also induces an immune response to itself (highlighted portion of Fig. 1B). Conjugate vaccines may, therefore, induce immunity against the pathogen from which the carrier protein is derived – a potential "additional valency". This phenomenon has largely been overlooked. Hence, the aims of this review are to provide information on current and novel protein carriers and discuss the potential implications of this "neglected valency".

In this review, an underscore between polysaccharide antigen and carrier protein identifies a conjugate (e.g. *Haemophilus influenzae* type b conjugated to tetanus toxoid = Hib_TT), while a hyphen indicates a combination of antigens (e.g. diphtheria, tetanus, acellular pertussis, inactivated poliovirus, Hib = DTaP-IPV-Hib).

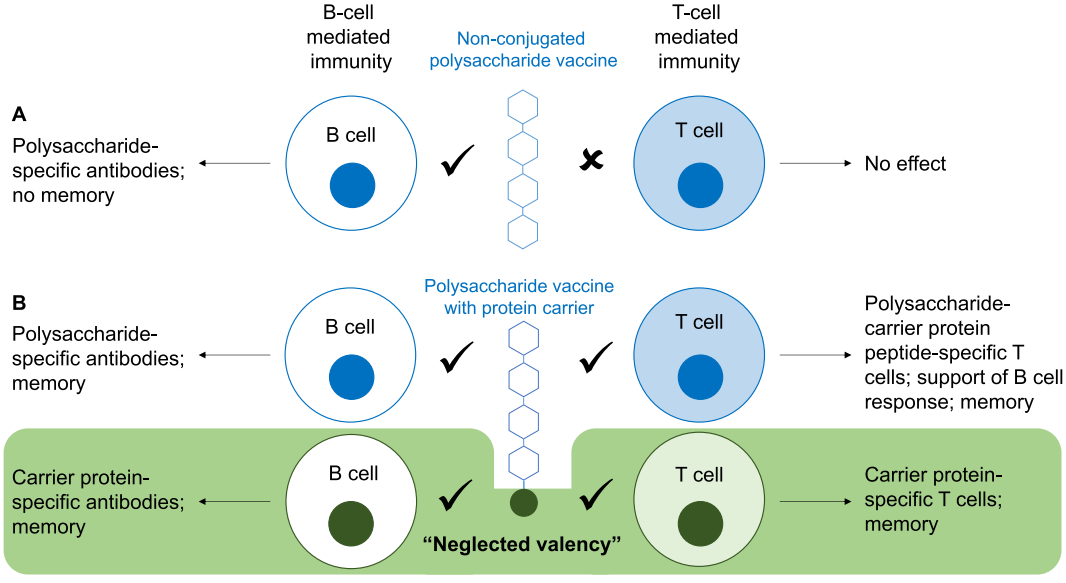

Fig. 1. (A) Non-conjugated polysaccharide vaccines induce only B-cell immunity, but no immune memory. (B) Polysaccharide conjugated to a protein carrier induce both B- and T-cell immunity to the polysaccharide, and immune memory. Polysaccharide conjugated to a protein carrier also induce both B-cell immune response and T-helper cell response to the protein carrier, resulting in antibodies to the protein carrier and immune memory (the "neglected valency" effect – highlighted portion).

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