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Review

Carrier priming or suppression: Understanding carrier priming enhancement of anti-polysaccharide antibody response to conjugate vaccines

Karl Pobre[a,1], Mohamed Tashani[a,b,*,1], Iman Ridda[a,b], Harunor Rashid[a], Melanie Wong[c], Robert Booy[a,d]

[a] National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The Children's Hospital at Westmead, New South Wales, Australia
[b] Sydney Medical School, The University of Sydney, New South Wales, Australia
[c] Department of Immunology, Children's Hospital at Westmead, Westmead, New South Wales, Australia
[d] Sydney Emerging Infections and Biosecurity Institute, University of Sydney, Australia

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ABSTRACT

Introduction: With the availability of newer conjugate vaccines, immunization schedules have become increasingly complex due to the potential for unpredictable immunologic interference such as 'carrier priming' and 'carrier induced epitopic suppression'. Carrier priming refers to an augmented antibody response to a carbohydrate portion of a glycoconjugate vaccine in an individual previously primed with the carrier protein. This review aims to provide a critical evaluation of the available data on carrier priming (and suppression) and conceptualize ways by which this phenomenon can be utilized to strengthen vaccination schedules.
Methods: We conducted this literature review by searching well-known databases to date to identify relevant studies, then extracted and synthesized the data on carrier priming of widely used conjugate polysaccharide vaccines, such as, pneumococcal conjugate vaccine (PCV), meningococcal conjugate vaccine (MenCV) and *Haemophilus influenzae* type b conjugate vaccines (HibV).
Results: We found evidence of carrier priming with some conjugate vaccines, particularly HibV and PCV, in both animal and human models but controversy surrounds MenCV. This has implications for the immunogenicity of conjugate polysaccharide vaccines following the administration of tetanus-toxoid or diphtheria-toxoid containing vaccine (such as DTP).
Conclusion: Available evidence supports a promising role for carrier priming in terms of maximizing the immunogenicity of conjugate vaccines and enhancing immunization schedule by making it more efficient and cost effective.

1. Introduction

Conjugate vaccines are one of the greatest triumphs in modern medicine. Since their introduction into routine vaccination schedules they have had a tremendous impact in reducing the burden of childhood disease and mortality from the polysaccharide encapsulated bacteria; *Haemophilus influenzae* type b (Hib), *Neisseria meningitidis* serogroup C and *Streptococcus pneumoniae* [1–3]. In children under the age of two years, capsular polysaccharide (CPS) antigens are believed to elicit a T-independent immune response, characterized by lack of memory and poor immunogenicity [4]. Efforts to overcome the poor immunogenicity of CPS have led to the development of conjugate vaccines. Studies have shown that by conjugating CPS to proteins, both T and B cell arms of the immune system are activated such that a vigorous antibody response and immunological memory is achieved [5,6].

A paper by Avci et al. [7] in *Nature Medicine* has shed light on the molecular mechanisms of conjugate vaccines. The model proposes a role of the carrier peptide, where it acts to anchor the polysaccharide to the B cell Major Histocompatibility Complex II

* Corresponding author at: National Centre for Immunisation Research and Surveillance of Infectious Diseases (NCIRS), The Children's Hospital at Westmead, Cnr Hawkesbury Road and Hainsworth Street, Locked Bag 4001,Westmead, NSW 2145, Australia. Tel.: +61 43 575 2969; fax: +61 298451418.
E-mail addresses: Mohamed.tashani@health.nsw.gov.au, toshani2003@gmail.com (M. Tashani).
[1] These authors have made equal contributions.

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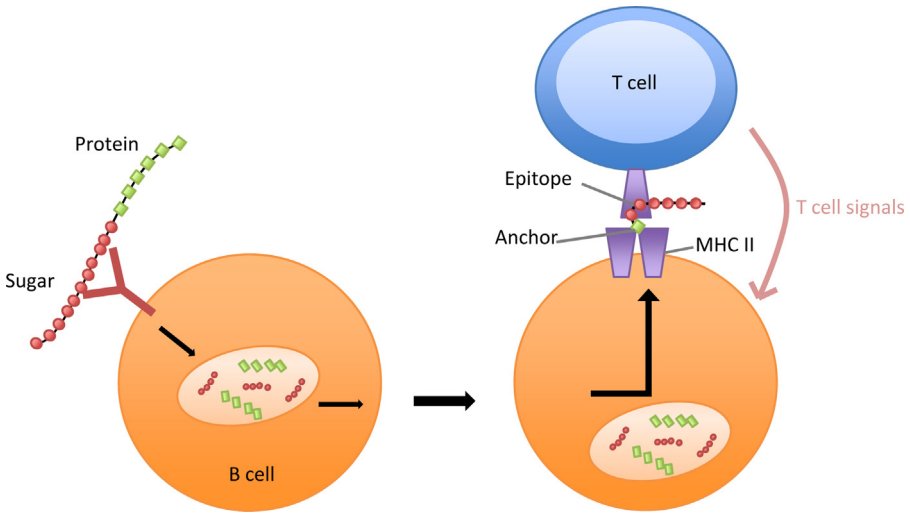

Fig. 1. Proposed molecular mechanisms for conjugate vaccines. A novel mechanism proposes that peptide from carrier acts to anchor the sugar epitope to the MHC and allows presentation of the sugar epitope to polysaccharide specific T cell. Necessary signals are then produced for B cell activation, maturation and production of specific antibodies against the polysaccharide moiety of the target bacteria [7].

(MHC-II), allowing for the presentation of the carbohydrate moiety to the T cell. This suggests that that some T cell receptors (TCR) have the specificity to recognize the saccharide portion of the peptide–polysaccharide conjugate, which is presented to it by MHC-II. The recognition allows development of the saccharide-specific T cell memory, which is independent of the peptide portion of the conjugate carrier (Fig. 1).

Carrier priming refers to the improved antibody response to a carbohydrate portion of a glycoconjugate vaccine when an individual has been previously primed with the carrier protein as compared to those that have not. There are three commonly used carrier proteins in the conjugate vaccine industry: tetanus toxoid (TT), diphtheria toxoid (DT) and cross reacting material of diphtheria toxin with amino acid 197 substitution (CRM_{197}) [8]. Since the carrier protein is most likely to be TT or DT-like, carrier priming may occur upon prior exposure to a TT or DT-containing vaccine such as diphtheria, tetanus and pertussis vaccine (DTP). It is believed that priming with the carrier molecule enhances the response to conjugate vaccines by increasing the number of carrier-specific T lymphocytes, which can provide the necessary "help" for the expansion and differentiation of polysaccharide specific B-lymphocytes [9,10]. The increase in memory cells after priming means that the acquired secondary response is faster and greater [11]. In many settings, enhancement of the response is observed. However, suppression may occur, particularly when the conjugate contains a low ratio of hapten to carrier [12,13]. There are two problems associated with the use of carrier molecules. The first problem is related to the structure of the MHC molecule; only one peptide is allowed to bind in its heterodimeric groove which creates a competitive setting [14]. The second problem is epitope-specific suppression, which is an anti-carrier antibody induced by previous immunization with the carrier alone. Carrier induced epitopic suppression (CIES) is the interference with the antibody response to a hapten coupled to a carrier protein among recipients previously immunized with that specific carrier protein. The interference is thought to arise from competition between peptides or capsular polysaccharides bound to homologous carrier proteins for a limited number of carrier specific primed helper T cells. As a result, there will be an increase in the antibody response to the carrier and a decrease in the response to conjugated peptides or polysaccharides [15]. In this respect, an ideal carrier would be a molecule that is unable to induce a significant antibody response to itself.

This review summarizes the available data on carrier priming and epitopic suppression. The objectives of this paper are to (a) consolidate the data related to carrier priming enhancement in conjugated vaccines, (b) identify gaps in knowledge as well as contradictory findings of carrier suppression in this area research and (c) conceptualize ways by which this phenomenon can be utilized to strengthen vaccination schedules, particularly in resource-depleted sectors of the world.

2. Methods

A review of contemporary literature was conducted to identify relevant studies describing carrier priming leading to the enhanced immunogenicity of related conjugate vaccines in animal studies, human children and adults. Inclusion criteria for the inclusion of scientific literature were immunological studies on carrier priming in animal and human models, molecular studies investigating the mechanisms of conjugate vaccines and review articles on vaccine interactions. Searches were completed in Ovid MEDLINE from (1928 to September 2013), Pub Med (1928 to September 2013) and Embase (1928 to September 2013) The Cochrane Library databases – *Cochrane Database of Systematic Reviews*. Both database-specific controlled vocabulary and general free text terms were used to maximize retrieval. The primary controlled vocabulary terms used were carrier priming, conjugate vaccine, *H. influenza* type b, *N. meningitidis* serogroup C and *S. pneumoniae*. Hand searching of key article reference lists was also used to locate additional relevant articles. A copy of the search strategy used is available if required upon application to authors.

3. Results

3.1. Animal studies

Carrier priming has been shown to enhance the immunogenicity of conjugate vaccines in several trials in animals [16–22]. For example, mice with pre-existing carrier immunity to (TT) had an enhanced polysaccharide-specific antibody response when pneumococcal conjugate vaccine (PCV) and meningococcal conjugate vaccine (MenCV), utilizing TT carrier, were given (Table 1) [16]. A dose-dependent relationship of the priming agent to the antibodies produced against the polysaccharide molecule of the conjugate vaccine was also observed. The study showed that pre-immunization