Human Vaccines & Immunotherapeutics 9:12, 2505–2523; December 2013; © 2013 Landes Bioscience

Protein carriers of conjugate vaccines

Characteristics, development, and clinical trials

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Keywords: carrier proteins, conjugate vaccines, CRM197, diphtheria toxoid, *Haemophilus influenzae* protein D, meningococcal outer membrane protein complex, *Streptococcus pneumoniae*, tetanus toxoid

Abbreviations: CIES, carrier induced epitope suppression; CRM, cross reacting material of diphtheria toxin with amino acid 197 substitution (CRM_{197}); D, diphtheria toxoid; *Hib*, *Haemophilus influenzae* type b; HiD, Haemophilus influenzae protein D; LPS, lipopolysaccharide; MCV, meningococcal conjugate vaccine, containing 4 polysaccharides A, C, W, and Y (MCV4); *N. mening*, *Neisseria meningitidis*; OMPC, meningococcal outer membrane protein complex; PCV, pneumococcal conjugate vaccine, containing 7 serotypes (PCV7) or 13 serotypes (PCV13); PRP, polyribosyl ribitol phosphate; *Spn*, *Streptococcus pneumoniae*; T, tetanus toxoid

The immunogenicity of polysaccharides as human vaccines was enhanced by coupling to protein carriers. Conjugation transformed the T cell-independent polysaccharide vaccines of the past to T cell-dependent antigenic vaccines that were much more immunogenic and launched a renaissance in vaccinology. This review discusses the conjugate vaccines for prevention of infections caused by *Hemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. Specifically, the characteristics of the proteins used in the construction of the vaccines including CRM, tetanus toxoid, diphtheria toxoid, *Neisseria meningitidis* outer membrane complex, and Hemophilus influenzae protein D are discussed. The studies that established differences among and key features of conjugate vaccines including immunologic memory induction, reduction of nasopharyngeal colonization and herd immunity, and antibody avidity and avidity maturation are presented. Studies of dose, schedule, response to boosters, of single protein carriers with single and multiple polysaccharides, of multiple protein carriers with multiple polysaccharides and conjugate vaccines administered concurrently with other vaccines are discussed along with undesirable consequences of conjugate vaccines. The clear benefits of conjugate vaccines in improving the protective responses of the immature immune systems of young infants and the senescent immune systems of the elderly have been made clear and opened the way to development of additional vaccines using this technology for future vaccine products.

Introduction

Hemophilus influenzae type b (*Hib*), *Streptococcus pneumoniae* (*Spn*), and *Neisseria meningitidis* (*N mening*) have polysaccharide capsules that facilitate their survival in the blood during disease pathogenesis by conferring resistance to complement-mediated killing and phagocytosis.[1] First-generation vaccines against *Hib*, *Spn* and *N mening* were based on polysaccharides used as antigens.[2,3] Unfortunately, these polysaccharide vaccines were not immunogenic in young children and failed to produce immunologic memory.[2]

Work described in the 1920s and '30s conducted by Landsteiner, Avery, and Goebel showed that the immunogenicity of polysaccharides could be enhanced by coupling to a protein.[4,5] In 1980 the research group of John Robbins and Rachel Schneerson at the US. Food and Drug Administration Center of Biologics Evaluation and Research described conjugates of *Hib* polysaccharides to diphtheria and tetanus toxoid proteins that enhanced the antibody response in animal models.[6] This technology was adopted by Connaught and Merieux eventually to make vaccines "PRP-D" and "PRP-T"[7]. Porter Anderson and David Smith described a *Hib* oligosaccharide-protein conjugate, and in 1983 this was reported to elicit memory-type antibody responses in a human infant.[8] The Anderson/Smith prototype later became the Lederle-Praxis "PRP-CRM" vaccine. Merck devised a "bi-molecular" conjugation of PRP to an outer membrane protein complex of *N. mening*[9] thereby making the vaccine "PRP-OMPC." Cumulatively, this work introduced a new generation of conjugate vaccines, creating a renaissance in vaccinology. Conjugation transformed the T-cell independent polysaccharide vaccines of the past to T cell-dependent vaccines that were much more immunogenic in children.[2] These vaccines were shown to have the ability to produce antibodies with high avidity, establish immunologic memory, and create a herd immunity effect. Additionally, they improved the protective responses of the immature immune system of young infants and the senescent immune system of the elderly. In 1996 Robbins, Schneerson, Anderson, and Smith received the prestigious Albert Lasker Award for their leadership in developing *Hib* conjugate vaccines.

The search strategy for this review on conjugate vaccines was as follows: Medline search terms were: experimental vaccines, conjugate (1979 citations), and *Hib* (742 citations) and both terms

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Submitted: 02/04/2013; Revised: 07/23/2013; Accepted: 08/11/2013
http://dx.doi.org/10.4161/hv.26109

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Table 1. Early human studies of PRP conjugate vaccine

A. Protein carrier CRM					
Reference	**Authors**	**Year Published**	**Vaccine**	**Population**	**Country**
14	Anderson, Pichichero, Insel	1985	PRP-CRM	Toddlers and Adults	USA
15	Anderson, Pichichero, Insel et al.	1985	PRP-CRM	Toddlers	USA
16	Anderson, Pichichero, Insel	1985	PRP-CRM	Infants	USA
18	Anderson, Pichichero, Stein et al.	1989	PRP-CRM	Adults and Infants	USA
19	Anderson, Porcelli, Pichichero	1992	PRP-CRM	Infants	USA
B. Protein carrier T					
Reference	**Authors**	**Year Published**	**Vaccine**	**Population**	**Country**
20	Schneerson, Robbins, Parke et al.	1986	PRP-T	Adults	USA
21	Claesson, Schneerson, Trollfors et al.	1990	PRP-T	Infants	Sweden
22	Claesson, Schneerson, Lagergard et al.	1991	PRP-T	Infants	Sweden
C. Protein carrier OMPC					
Reference	**Authors**	**Year Published**	**Vaccine**	**Population**	**Country**
23	Einhorn, Weinberg, Anderson et al.	1986	PRP-OMPC	Infants and Toddlers	USA
24	Weinberg, Einhorn, Lenoir et al.	1987	PRP-OMPC	Infants and Toddlers	USA
25	Lenoir, Granoff PD, Granoff DM	1987	PRP-OMPC	Infants	USA
D. Protein carrier D					
Reference	**Authors**	**Year Published**	**Vaccine**	**Population**	**Country**
26	Lepow, Samuelson, Gordon	1984	PRP-D	Adults	USA
27	Granoff, Boies, Munson	1984	PRP-D	Adults	USA
28	Lepow, Samuelson, Gordon	1985	PRP-D	Infants	USA
29	Berkowitz, Ward, Meier et al.	1987	PRP-D	Infants	USA

(179 citations); or for *Spn* and both terms (282 citations); or for *N. mening* and both terms (188 citations). The Cochrane Central Register of Controlled Trials was also searched, identifying 164 citations for *Hib* conjugates, 82 citations for *Spn* conjugates and 49 citations for *N. mening* conjugates; many were duplicative to the Medline Search. Review of the abstracts of the 944 citations identified many review papers on guidelines for use of conjugate vaccines, and on success of conjugate vaccines when introduced in multiple countries. These papers were not further examined and from the >600 remaining, I prepared this review to provide an overview of conjugate vaccines from the perspective of the carrier protein emphasizing foundational trials, characteristics, and clinical studies.

Characteristics of Carrier Proteins

To date, 5 carrier proteins have been used in licensed conjugate vaccines: a genetically modified cross-reacting material (CRM) of diphtheria toxin, tetanus toxoid (T), meningococcal outer membrane protein complex (OMPC), diphtheria toxoid (D), and *H. influenzae* protein D (HiD). Clinical trials have demonstrated the efficacy of these conjugate vaccines in preventing infectious diseases and altering the sp.read of *Hib*, *Spn,* and *N. mening*. All 5 carrier proteins have been effective in increasing vaccine immunogenicity but differ in the quantity and avidity of antibody they elicit, ability to carry multiple polysaccharides in the same product and to be given concurrently with other vaccines.

CRM_{197} is a nontoxic variant of diphtheria toxin isolated from *Corynebacterium diphtheriae* C7 (β197) cultures. CRM_{197} differs from wild-type diphtheria toxin, in that a point mutation at amino acid position 52 substitutes glycine with glutamic acid, which eliminates enzymatic activity and toxicity.[10] CRM_{197} is indistinguishable antigenically from diphtheria toxin but has advantages as a conjugate protein: it is nontoxic, and has more lysyl side-chains available for conjugation. Another form of CRM being used as a conjugate is purified native diphtheria toxin that is subsequently detoxified with formaldehyde. This product is called diphtheria toxoid (D) and should not be confused with CRM_{197}. T is prepared by formaldehyde detoxification of tetanus toxin produced by *Clostridium tetani* cultures. OMPC is produced from *N mening* serogroup B outer membrane protein complex.[11] D is prepared by formaldehyde detoxification of diphtheria toxin produced by *C. diphtheriae* cultures.[12] HiD is an *H. influenzae* surface protein[13] originally isolated from *H. influenzae* by solubilization with sonication and sarcosyl-extraction by a single SDS-PAGE step but now included in a current vaccine after preparation as a recombinant protein.

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Table 2. Major efficacy trials of PRP-D, PRP-CRM, PRP-OMPC and PRP-T

Reference	Authors	Year Published	Vaccine	Population	Country
30	Eskola, Peltola, Takala et al.	1987	PRP-D	Infants	Finland
31	Eskola, Kayhty, Takala et al.	1990	PRP-D	Infants, Children	Finland
32	Santosham, Wolff, Reid et al.	1991	PRP-OMPC	Infants	USA
33	Booy, Moxon, MacFarlane et al.	1992	PRP-T	Infants	UK
47	Decker, Edwards, Bradley et al.	1992	PRP-CRM_{197}	Infants	USA
35	Peltola, Eskola, Kayhty et al.	1994	PRP-D CRM_{197}	Infants	Finland
34	Mulholland, Hilton, Adegbola et al.	1997	PRP-T	Infants	The Gambia

Early Pivotal Trials with *Hib* Conjugate Vaccines

CRM_{197}

Table 1A[14-19]details several studies in humans by the Anderson/Smith group evaluating CRM as a potential protein carrier for *Hib* capsular polysaccharide (polyribosyl ribitol phosphate PRP). The studies showed that pure PRP, nonconjugated CRM_{197}, or simple mixtures of CRM_{197} and PRP oligosaccharides were poorly immunogenic but PRP-CRM_{197} elicited increasingly stronger anti-PRP responses and after boosters anti-PRP antibody levels reached >1000 times pre-vaccination levels.

T

Table 1B[20-22]describes several studies by the Robbins/Schneerson group and others in the evaluation of PRP-T vaccine. They showed that PRP-T induced protective serum anti-PRP antibody with bactericidal activity; that PRP antibody responses increased with simultaneous injection of T and PRP-T; and that children developed antibody levels 1000 times higher after PRP-T vaccine than unconjugated PRP.

OMPC

Table 1C[23-25] details several studies involving PRP-OMPC vaccine led by Dan Granoff. This research established a unique feature of this *Hib* conjugate vaccine—after the first dose of vaccine relatively high anti-PRP antibody are elicited (unlike PRP-CRM, PRP-T and PRP-D conjugates) and higher yet after a second dose but no further boosting with a third dose.

D

Table 1D[26-29] describes early studies of PRP-D conjugate vaccine led by Marti Lepow, Joel Ward and Lance Gordon.

Efficacy trials

The pivotal clinical efficacy studies in humans of PRP-CRM, PRP-T, PRP-OMPC, and PRP-D from 1987 to 1997 are shown in **Table 2**.[30-35]

Dose and schedule studies

Unlike antimicrobials and other pharmaceuticals where dose is typically dictated by side effects in dose escalation studies, with conjugate vaccines dose selection was driven by optimization of immunologic effect (antibody levels). Dose schedule studies generally showed that higher doses, more frequent doses and wider dose spacing was better (in terms of antibody quantity and avidity) than lower doses, less frequent doses and closer dosing intervals.[36-44] In 2012, Griffiths et al.[45] published a systematic review and meta-analysis of controlled clinical trends evaluating dose-sp.ecific efficacy of *Hib* conjugate vaccines. Eight studies were included and pooled vaccine efficacies against invasive *Hib* disease were 59%, 92%, and 93% after 1, 2, or 3 primary doses, respectively. Because of the influence of maternal antibody capturing vaccine antigen and thereby suppressing an active immune response and the immaturity of the immune system in infants, three primary doses in the first 6 mo of life are generally superior to two. Booster doses solidify the robustness of the immune response to conjugate vaccines, producing dramatic increases in antibody quantity, antibody with higher avidity (and functionality) and memory cells.

Four studies have directly compared PRP-CRM, PRP-T, PRP-OMPC and PRP-D.[46-49] An importance of differences among the vaccines was the failure of PRP-D to prevent *Hib* disease[50] and development of breakthrough infections when PRP-CRM was substituted for PRP-OMPC in Alaskan infants.[51]

Studies That Established Key Features of Conjugate Vaccines

Memory induction

The immunologic mechanisms to establish memory involves activation of T-helper cells leading to generation of both memory B cells and memory T cells.[52] Conjugate vaccines induce immunologic memory. Studies that evaluated memory booster responses following PRP conjugate vaccination are numerous.[17,24,53-58] Memory was proposed to be sufficient to protect against *Hib* disease after circulating antibody waned, precluding the need for boosters: this view was challenged.[59] Shortly thereafter an increase of *Hib* cases was reported in 2003 among children with waning anti-PRP antibody levels.[60] This was shown to be facilitated by a reduction in anti-PRP antibody among children receiving a *Hib* conjugate vaccine combined with a DTaP vaccine[61,62]. We showed that the kinetics of a memory response required 4–7 d for memory B cell re-activation until maturation to antibody-secreting plasma cells occurred.[63] Subsequently others have confirmed a 4–7 d window between memory B-cell exposure to antigen and consequent production of detectable antibody.[64,65] The antibody must be of high avidity to be bactericidal.[66] The key correlate of protection against infection caused by *Hib*, *Spn* and *N. mening* is the level of serum antibody.[67] Because the pace of pathogenesis for *Hib*, *Spn*, and *N. mening* infection is very rapid (1–2 d from nasopharyngeal (NP) colonization to invasion) it is necessary to maintain minimal circulating levels of anti-capsular polysaccharide antibody to

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Table 3. *N mening* conjugate C, A and A + C vaccine studies

Reference	Authors	Year Published	Vaccine	Population	Country	Study Design
149	Fairley, Begg, Borrow et al.	1996	Men A and C-CRM$_{197}$	Infants	UK	S and I
82	Leach, Twumasi, Kumah et al.	1997	Men A + C-CRM$_{197}$	Children	The Gambia	Immune Memory
83	MacDonald, Halperin, Law et al.	1998	Men C-CRM$_{197}$	Toddlers	Canada	Immune Memory
84	Richmond, Borrow, Miller et al.	1999	Men C-CRM$_{197}$	Infants	UK	S and I
85	MacLennan, Shackley, Heath et al.	2000	Men C-CRM	Infants	UK	S and I and Immune Memory
150	Campagne, Garba, Fabre et al.	2000	Men A + C-D	Infants	Niger	S and I
153	Zhang, Lakshman, Burkinshaw et al.	2001	Men A + C-CRM$_{197}$	Adolescents/ Adults	UK	Mucosal I
86	Richmond, Borrow, Goldblatt et al.	2001	Men C – T/CRM$_{197}$	Toddlers	UK	Immune Memory
87	MacLennen, Obaro, Deeks et al.	2001	Men A + C-CRM$_{197}$	Children	The Gambia	Immune Memory
151	Miller, Salisbury, Ramsay et al.	2001	Men C – T/CRM$_{197}$	Children/Adults	UK	Effectiveness
152	Ramsay, Andrews, Kaczmarski et al.	2001	Men C – T/CRM$_{197}$	Toddlers/ Adolescents	UK	Effectiveness
154	Rennels, Edwards, Keyserling et al.	2001	Men C-CRM$_{197}$	Infants	USA	S and I
88	Borrow, Goldblatt, Andrews et al.	2002	Men C-CRM$_{197}$	Children	UK	Immune Memory
89	McVernon, MacLennan, Buttery et al.	2002	Men C-CRM$_{197}$	Infants/Children	UK	S and I
155	Joseph, Ryall and Bybel et al.	2003	Men A + C-D	Children	UK	I + Immune Memory
135	De Wals, Deceuninck, Boulianne et al.	2004	Men C-CRM$_{197}$	Infants to Adults	Canada	Effectiveness
136	Trotter, Andrews, Kaczmrski et al.	2004	Men C – T/CRM$_{197}$	Infants to Adolescents	UK	Effectiveness
156	De Wals, Deceuninck, De Serres et al.	2005	Men C-CRM$_{197}$	Children/ Adolescents	Canada	Effectiveness
157	Gray, Trotter, Ramsay et al.	2006	Men C – T/CRM$_{197}$	Children/ Adolescents	UK	Effectiveness
158	de Greeff, de Melker, Spanjaard et al.	2006	Men C-T	Toddlers	Netherlands	Effectiveness
159	Snape, Kelly, Salt et al.	2006	Men C-CRM$_{197}$	Adolescents	UK	Immune Memory
160	Trotter, Chandra, Cano et al.	2007	Men C – T/CRM$_{197}$	Children/ Adolescents	Europe	Effectiveness
161	Kshirsagar, Mur, Thatte et al.	2007	Men A-T	Adults	India	S and I
162	Maiden, Ibarz-Pavon, Urwin et al.	2008	Men C – T/CRM$_{197}$	Adolescents	UK	Efficacy on NP carriage
163	Bettinger, Scheifele, Le Saux et al.	2009	Men C-CRM$_{197}$	Infants to Adults	Canada	Effectiveness
164	De Wals, Deceuninck, Lefebvre et al.	2011	Men C-CRM$_{197}$	Infants to Adults	Canada	Effectiveness

S, Safety; I, Immunogenicity; E, Efficacy.

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Table 4. Spn-CRM

Reference	Authors	Year Published	Vaccine	Population	Country	Trial Design
77	Anderson, Kennedy, Geldmacher et al.	1996	PCV7	Infants	USA	S and I
170	Ahman, Kayhty, Tamminen et al.	1996	PCV5	Infants	Finland	S and I
171	Daum, Hogerman, Rennels et al.	1997	PCV5	Infants	USA	S and I
172	Shinefield, Black, Ray et al.	1999	PCV7	Infants/Toddlers	USA	S and I
79	Ahman, Kayhty, Lehtonen et al.	1998	PCV4	Infants	Finland	S and I
80	Rennels, Edwards, Keyserling et al.	1998	PCV7	Infants	USA	S and I
173	Black, Shinefield, Fireman et al.	2000	PCV7	Infants/Toddlers	USA	S and I and E
174	Choo, Seymour, Morris et al.	2000	PCV7	Infants	UK	S and I
216	Eskola, Kilpi, Palmu et al.	2001	PCV7	Infants	Finland	S and I and E
175	Schmitt, Faber, Lorenz et al.	2003	PCV7	Infants	Germany	S and I
217	O'Brien, Moulton, Reid et al.	2003	PCV7	Infants	USA	S and E
176	Kayhty, Ahman, Eriksson et al.	2005	PCV7	Infants	Sweden	S and I
177	Bryant, Block, Baker et al.	2010	PCV13	Infants	USA	S and I
178	Kieninger, Kueper, Steul et al.	2010	PCV13	Infants	Germany	S and I
179	Esposito, Tansey, Thompson et al.	2010	PCV7 PCV13	Infants/Toddlers	Italy	S and I
180	Yeh, Gurtman, Hurley et al.	2010	PCV13	Infants/Toddlers	USA	S and I
181	Snape, Klinger, Daniels et al.	2010	PCV7 PCV13	Infants	UK	S and I
182	Vanderkooi, Scheifele, Girgenti et al.	2012	PCV13	Infants/Toddlers	Canada	S and I
183	Huang, Lin, Juergens et al.	2012	PCV7 PCV13	Infants/Toddlers	Taiwan	S and I
184	Amdekar, Lalwani, Baudekar et al.	2013	PCV13	Infants/Toddlers	India	S and I

S, Safety; I, Immunogenicity; E, Efficacy.

afford protection.[68] More recently the *Hib* breakthrough infection saga repeated itself in the UK following *N. mening* C-conjugate vaccinations.[69,70] Persistence of serum antibody levels following primary and booster vaccinations with conjugate vaccines will require ongoing monitoring.[71-76]

Spn-CRM, *Spn*-T, *Spn*-OMPC, *Spn-D*, and *Spn*-HiD have consistently been shown to establish immune memory and booster doses induce large increases in pneumococcal antibodies.[41,44,77-81] Several meningococcal C and A and C polysaccharide conjugate vaccines have been produced using CRM, T, and D as carriers and immune memory has been demonstrated.[82-91]The quadrivalent meningococcal polysaccharide -D conjugate vaccine (containing serotypes A, C, Y, and W-135; MCV-4/D) was recently shown to establish immunologic memory[92] by a demonstrated response to a reduced dose (1/10 recommended dose) of quadrivalent meningococcal polysaccharide vaccine (to stimulate a bacterial challenge) 1.5 to 5 y after subjects received MCV-4/D vaccine.[93]

Reduction of nasopharyngeal colonization and herd immunity

Conjugate vaccination induces herd immunity because vaccination reduces the NP carriage of *Hib*, *Spn,* and *N. mening*; thereby the spread of disease is controlled. I conducted early studies to explore the effect of polysaccharide and conjugate vaccines on induction of mucosal and systemic antibody.[94-97] Subsequent work confirmed the induction of both systemic antibody and IgA mucosal antibody following conjugate vaccination.[98-105] However, work with various carrier protein PRP-conjugates established that PRP-conjugate vaccines reduce colonization primarily if not exclusively by induction of high-tittered serum antibody that transudates into the NP (and oropharynx, OP) and eradicates the potential pathogen.[106-108] A post-primary series *Hib* serum antibody concentration of ≥5 μg/ml is considered to be a level that predicts herd immunity.[62,109,110] Vaccinating about 30% of children <2 y old decreases *Hib* invasive disease incidence by >50%; when about 50% are immunized the incidence decreases >70%.[111] Interestingly, less serum antibody concentrations are indicated for protection against invasive Hib disease: >0.15 μg/ml, correlate for short-term protection and >1.0 μg/ml, correlate for long-term protection.[112]

For *Spn* conjugates, NP carriage was also shown to be correlated with *Spn* specific anticapsular IgG concentrations after vaccination.[113,114] Dagan et al. described the impact of *Spn*-D conjugate vaccine on pneumococcal NP carriage. Three months after the first dose of vaccine and persisting for one year after the first dose, carriage was reduced.[113] In a subsequent study of infants who received *Spn*-T, *Spn*-D, or placebo the NP carriage rate of vaccine serotypes was 10% in the *Spn*-T group, 5% in the *Spn*-D group, and 27% in the placebo group.[115]

Studies with *Spn*-CRM vaccine containing 7 serotypes, (PCV7) have consistently demonstrated a reduction of NP carriage by *Spn* serotypes contained in the PCV7 vaccine.[113,116-132]

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Table 5. PCV7 effectiveness

Reference	Authors	Year Published	Study	Vaccine	Population	Population
185	Black, Shinefield, Hansen et al.	2001	a	PCV7	Infants/Toddlers	USA
186	Black, Shinefield, Ling et al.	2002	Ph IV[b]	PCV7	Infants/Toddlers	USA
187	Whitney, Farley, Hadler et al.	2003	c	PCV7	Infants/Toddlers and Adults	USA
188	Black, Shinefield, Baxter et al.	2004	c	PCV7	Infants/Toddlers	USA
189	Whitney, Pilishvili, Farley et al.	2006	d	PCV7	Infants/Toddlers	USA
190	Sharma, Baughman, Holst et al.	2013	e	PCV7	Infants/Toddlers	USA

[a]Expanded postlicensure study of >200 000 children; [b]Postlicensure effectiveness in reducing risk of pneumonia; [c]Surveillance pre and post PCV7 licensure; [d]Postlicensure effectiveness against vaccine serotypes and catch-up vaccination schedules; [e]Carriage and IPD pre and post PCV7 licensure.

A quantitative model developed to estimate the herd effects of PCV7[133] showed that vaccination of young children with PCV7 significantly decreased the incidence of invasive pneumococcal disease due to vaccine serotypes not only in vaccinated children but also in older children and adults. Vaccination with *Spn*-CRM containing 13 serotypes (PCV13) reduces NP carriage of strains expressing the capsular types corresponding to the vaccine ingredients.[134]

Meningococcal C vaccination in the United Kingdom and Canada reduces NP colonization and also has been shown to produce a herd immunity effect.[135-138]

Spn-HiD vaccine reduces pneumococcal carriage.[139] However, the *Spn*-HiD vaccine does not appear to reduce NP colonization by *H. influenza*[140] and so it will not likely produce a herd immunity effect for prevention of *H. influenza* infections.

Antibody avidity and avidity maturation

Serum antibody binds to antigen with differing avidity that defines the overall interaction between antigen and antibody. Higher avidity antibodies are preferred because they offer better protection against disease. In 1992, Schlesinger and Granoff reported that anti-PRP antibody avidity correlated with functionality in sera from infants vaccinated with PRP-OMPC, PRP-CRM, or PRP-T.[141] They compared antibody avidity among PRP-OMPC, PRP-T and PRP-CRM conjugate vaccines and found that all 3 vaccines elicited high avidity antibody and PRP-OMPC vaccine elicited the highest.[141] In contrast, Lucas and Granoff analyzed pooled sera from vaccinated infants and reported that PRP-CRM had 3 times the avidity, significantly greater bactericidal activity, and increased protection against *Hib* bacteremia in infant rats when compared with PRP-OMPC vaccine.[142] Later studies showed that a process known as avidity maturation occurs with PRP conjugate vaccines between primary doses and in the time frame between the primary series and a booster dose several months later. A similar study was done testing immune sera from children vaccinated with MenACWY-D where there was a correlate of higher avidity antibodies eliciting higher protection in an infant rat model.[143] Avidity maturation refers to the immunologic process whereby B cells that produce the highest affinity antibody preferentially out-compete B- cells that produce lower affinity antibody for a sp.ecific antigen.[144] Although vaccine efficacy is dependent on antibody functionality which includes concentration, isotype, avidity and form of antigen presentation, the protective efficacy with the PRP-OMP vaccine was 95% in a placebo-controlled study conducted with high-risk children in US suggesting no impact of reduced avidity maturation on efficacy.[145]

Usinger et al.[146]analyzed sera from healthy adults and demonstrated high avidity antibodies were produced against *Spn*-CRM, and that higher-avidity antibodies were more effective in mediating protective functions.[147] When *Spn*-CRM, *Spn*-D, *Spn*-T, or *Spn*-OMPC conjugate vaccines were given to infants with subsequent boosting with homologous conjugate or polysaccharide vaccine avidity maturation occurred from 7 to 14 mo and after boosting with conjugate, but not with polysaccharide vaccine.[147] Higher avidity anti-*Spn* antibody was elicited by *Spn*-OMPC. As with PRP conjugates, *Spn* conjugates antibody avidity did not correlate with antibody concentration nor did it correlate with functional OPA killing.[148] Currently there are no data published on antibody avidity following HiD conjugate vaccination.

Safety, immunogenicity, and efficacy

N. mening conjugate vaccines involving conjugation of the polysaccharide to CRM, D or T have been shown to be safe, immunogenic, efficacious and effective. (**Table 3**).[82-89,135,136,149-164]

Studies of Single Protein Carriers with Multiple Polysaccharides

CRM

Foundational studies for development of *Spn* conjugates were published in the mid-1990s.[165-168] Subsequently, clinical studies assessed the safety and immunogenicity of combining these multiple polysaccharides with a single protein carrier in a single vaccine in healthy children (**Table 4**).[77,79,80,169-184]

In effectiveness studies, vaccination with PCV7 was credited with reducing invasive pneumococcal disease by up to 91% and AOM by 20% based on both direct protection of immunized infants and herd protection (**Table 5**).[185-190]

A meningococcal vaccine with 4 serotypes (A, C, Y, and W135) conjugated to CRM_{197} has been found to be safe and immunogenic (**Table 6A**).[191-199]

D

A quadrivalent *N. mening* D vaccine given to infants in a 3 dose schedule at 2, 4, 6 mo or as one dose to toddlers, children and adolescents as one dose has been shown to be safe, immunogenic and efficacious. (**Table 6B**)[40,92,143,200–205].

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Table 6. *N. mening*

A. *N. mening* – CRM_{197}						
Reference	**Authors**	**Year Published**	**Study**	**Vaccine**	**Population**	**Country**
191	Snape, Perrett, Ford et al.	2008	Ph II	4-Valent	Infants	UK and Canada
192	Jackson, Baxter, Reisinger et al.	2009	Ph III	4-Valent	Adolescents	USA
193	Perrett, Snape, Ford et al.	2009	Ph II	4-Valent	Infants	UK and Canada
194	Jackson, Jacobson, Reisinger et al.	2009	Ph II	4-Valent	Adolescents	USA
195	Halperin, Diaz-Mitoma, Dull et al.	2010	Ph II	4-Valent	Infants/Toddlers	Canada
196	Black, Klein, Shah et al.	2010	Ph II	4-Valent	Toddlers/ Children	USA
197	Arguedas, Soley, Loaiza et al.	2010	Ph III	4-Valent	Adolescents	Republic of Costa Rica
198	Gasparini, Conversano, Bona et al.	2010	Ph III	4-Valent	Adolescents to Young Adults	Italy
199	Klein, Reisinger, Johnston	2012	Ph III	4-Valent	Infants	USA
B. *N. mening* - D						
Reference	**Authors**	**Year Published**	**Vaccine**	**Study**	**Population**	**Country**
40	Rennels, King, Ryall et al.	2002	4-Valent	Ph I	Toddlers	USA
205	Campbell, Edelman, King et al.	2002	4-Valent	Ph 1/2	Adults	USA
200	Rennels, King, Ryall et al.	2004	4-Valent	Ph I	Infants	USA
143	Granoff and Harris	2004	4-Valent	a	Children	USA
201	Granoff, Morgan and Welsch	2005	4-Valent	a	Children	USA
202	Pichichero, Casey, Blatter et al.	2005	4-Valent	ND*	Children	USA
92	Keyserling, Papa, Koranyi et al.	2005	4-Valent	ND	Adolescents	USA
203	MacNeil, Cohn, Zell et al.	2011	4-Valent	b	Adolescents	USA
204	Pina, Bassily, Machmer et al.	2012	4-Valent	Ph III	Infants/Toddlers	USA
C. *N. mening* – T						
Reference	**Authors**	**Year Published**	**Study**	**Vaccine**	**Population**	**Country**
206	Knuf, Kieninger-Baum, Habermehl et al.	2010	PhII	4-Valent	Children	Germany, Austria
207	Ostergaard, Lebacq, Poolman et al.	2009	PhII	4-Valent	Adolescents and Young Adults	Belgium, Denmark
208	Vesikari, Forsten, Boutriau et al.	2012	PhII	4-Valent	Children	Finland
209	Vesikari, Karvonen, Bianco et al.	2011	PhIII	4-Valent	Toddlers	Finland
211	Baxter, Baine, Ensor et al.	2011	PhII	4-Valent	Adolescents and Young Adults	USA
210	Memish, Dbaibo, Montellano, et al.	2011	PhIII	4-Valent	Children	Philippines, India, Lebanon, Saudi Arabia
42	McVernon, Nolan, Richmond et al.	2012	ND*	4-Valent	Toddlers	Australia
212	Bermal, Huang, Dubey et al.	2011	PhIII	4-Valent	Adolescents	Philippines, India, Taiwan
213	Dbaibo, Macalalad, Reyes et al.	2012	PhIII	4-Valent	Adults	Lebanon, Philippines

[a]Serum antibody immunogenicity study; [b]Postlicensure surveillance; *Study phase not discerned.

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Table 7.

A. *Hib-N. mening* CY-T						
Reference	Authors	Year Published	Study		Population	Country
214	Marshall, Marchant, Blatter et al.	2011	Ph II		Infants	USA
215	Nolan, Richmond, Marshall et al.	2011	Ph II		Infants	USA
B. Spn-OMPC						
Reference	**Authors**	**Year Published**	**Study**	**Vaccine**	**Population**	**Country**
169	Kayhty, Ahman, Ronnberg et al.	1995	ND*	4-Valent	Infants/Toddlers	Finland
114	Dagan, Melamed, Mualiem et al.	1996	ND	7-Valent	Toddlers	Israel
238	Miernyk, Parkinson, Rudolph et al.	2000	ND	7-Valent	Infants	USA
275	Blum, Dagan, Mendelman et al.	2000	ND	7-Valent	Toddlers	Israel
218	Kilpi, Ahman, Jokinen	2003	ND	7-Valent	Infants	Finland
276	Zangwill, Greenberg, Chiu et al.	2003	ND	7-Valent	Infants	USA
C. Spn-HiD						
Reference	**Authors**	**Year Published**	**Study**	**Vaccine**	**Population**	**Country**
219	Prymula, Peeters, Chrobok et al.	2006	ND*	11-Valent	Infants	Czech Republic, Slovak Republic
220	Prymula, Chlibek, Splino et al.	2008	ND	11-Valent	Infants	Czech Republic, Slovak Republic
221	Knuf, Szenborn, Moro et al.	2009	ND	10-Valent†	Infants	Finland, France, Poland, Germany Spain, Philippines

*ND, study phase not discerned; †8 of the 10 vaccine serotypes conjugated to HiD.

T

A quadrivalent (A, C, W135, Y) *N. mening* T conjugate vaccine has been found to be safe and immunogenic and noninferior to other licensed *N. mening* vaccines (**Table 6C**).[42,205-213] A bivalent *Hib*-T conjugate vaccine that included meningococcal serotypes C and Y[212,214,215] when tested in infants has been found to be safe and immunogenic (**Table 7A**) .

OMPC

Spn-OMPC vaccines were studied that contained 4 to 7 serotypes. The vaccine was immunogenic and primed for a booster response (**Table 7B**).[169,186,216-218] The efficacy of the 7 valent *Spn*-OMPC vaccine against AOM was assessed in infants at 2, 4, 6, and 12 mo of age. Overall vaccine efficacy was 56% (95% CI 44–66%) and serotype-sp.ecific efficacy ranged from 37% for 19F to 82% for 9V.[216] In 3 other efficacy studies of PCV-7-OMPC protection against invasive disease, AOM and pneumonia was shown[186,216-218].

HiD

Two *Spn* conjugate vaccines containing 11 serotypes conjugated to HiD (11-valent) or 8 serotypes conjugated to HiD along with two other serotypes conjugated to T or D (10-valent, PHiD-CV) was used to vaccinate infants at 2, 4, and 6 mo (**Table 7C**).[219-221] There was a significant increase in the IgG concentrations to vaccine serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F after 3 doses of the 11-valent *Spn* -HiD. *Spn* PS vaccine induced a better booster response than *Spn* -HiD. The antibody concentrations after the first dose of *Spn* -HiD administered at 12–15 mo increased significantly but were lower than after the fourth dose at the same age. The PHiD-CV vaccine was also evaluated in children younger than 19 mo for effectiveness against invasive pneumococcal disease.[173,221,222] The clinical effectiveness of this Finnish Invasive Pneumococcal disease trial were 100% in the 3 + 1 group and 92% in the 2 + 1 group which is very similar to what was observed in the Northern California Kaiser Permanete trial assessing the PCV7 vaccine.[173,221]

Studies of Multiple Protein Carriers with Multiple Polysaccharides

In response to a recognized need to increase the serotype coverage of pneumococcal conjugate vaccines and a concern that a single carrier protein could lead to a decrease in carrier-sp.ecific T helper cell support, a vaccine composed of a mixture of T- and D-conjugated polysaccharides was developed. The vaccine contained 11 *Spn* serotypes with 4 polysaccharides conjugated to D and 7 polysaccharides conjugated to T. Various quantities of polysaccharides were added to the carriers to optimize the immune response. The mixed D and T carrier *Spn* conjugate vaccine proved immunogenic and safe (**Table 8**)[223-232] but when co-administered with a DTaP vaccine the immune response to the polysaccharides was significantly reduced. Results of this study were attributed to Carrier Induced Epitope Suppression (CIES, discussed below).

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Table 8. Spn mixed carriers

Reference	Authors	Year Published	Study	Vaccine	Population	Country
223	Wuorimaa, Dagan, Eskola et al.	2001	ND*	11-Valent	Toddlers	Finland, Israel
224	Wuorimaa, Dagan, Vakevainen et al.	2001	ND	11-Valent	Infants	Finland, Israel
225	Puumalainen, Zeta-Capeding, Kayhty et al.	2002	ND	11-Valent	Infants	Philippines
227	Puumalainen, Dagan, Wuorimaa et al.	2003	ND	11-Valent	Infants	Finland, Israel, Philippines
228	Puumalainen, Ekstrom, Zeta-Capeding et al.	2003	ND	11-Valent	Infants	Philippines
229	Dagan, Goldblatt, Maleckar et al.	2004	Ph II	11-Valent	Infants	Israel
230	Lucero, Puumalainen, Ugpo et al.	2004	ND	11-Valent	Infants	Philippines
231	Dagan, Kayhty, Wuorimaa et al.	2004	Ph II	11-Valent	Infants	Finland, Israel

*ND, study phase not discerned.

A study in the Czech Republic and Slovakia assessed an 11-valent *Spn*-HiD conjugate vaccine when coadminstered with a combined hexavalent DTPa-HBV-IPV/Hib-conjugate vaccine in preventing AOM and the impact of the immune response of the co-administered hexavalent vaccine-.[219] The overall incidence of AOM was 83 episodes per 1000 person-years of follow-up in the *Spn* conjugate vaccine group compared with 125 in the control group. An important finding of the study was that the HiD protein carrier appeared to reduce AOM caused by *H. influenzae* by 36%. NP carriage was assessed about 3 mo after the conjugate or control vaccine booster dose. Vaccine serotype *Spn* were isolated from the NP of 6% of the infants in the HiD conjugate group vs. 11% of controls, and *H. influenzae* was isolated in 10% of infants in the HiD conjugate group vs. 18% in the controls. Another important observation from this study was that the 11-valent Spn-HiD conjugate vaccine did not impair the immunogenicity of the co-administered hexavalent vaccine. A similar result of noninferiority was observed in a study with the PHiD-CV co-administered with commonly used pediatric vaccines.[221] A subsequent study by Vesikari et al.[233]compared the immunogenicity of PHiD-CV compared with PCV7. The primary objective was to demonstrate non-inferiority of the 10-valent HiD to the 7 shared serotypes in PCV7 (defined as % of subjects with antibody concentrations >0.2 micrograms/mL and >0.35 µg/mL, respectively). Non-inferiority was shown for 5 of 7 serotypes, but not for types 6B or 23F.

Safety and Immunogenicity

Immunocompromized hosts

Results of Safety and Immunogenicity studies of conjugate vaccines administered to Immunocompromized hosts are shown in **Table 9**.[226,234-245] In general, the use of these vaccines has provided protection against the targeted bacterial strains expressing corresponding serotypes.

Adults

Results of safety and immunogenicity studies of conjugate vaccines in adults are shown in **Table 10**.[205,246-252] Imunosenesence sometimes results in poor responses to polysaccharide vaccines. Repeated vaccination with polysaccharide vaccines may result in hypo-responsiveness due to a process known as terminal B-cell differentiation. Even if responses to polysaccharide and conjugate vaccines are similar, only conjugate vaccines provide immune memory, boostability and herd protection.

Undesirable consequences of introduction of conjugate vaccines

Interference of immunogenicity in combination vaccines has been identified as an undesirable consequence of conjugate vaccines. Two major mechanisms of immunologic interference have been described: (1) antigen competition and (2) CIES.[253-260] Antigen competition among combination components probably arises at the level of antigen processing or transport. CIES is a phenomena whereby the polysaccharide antigen epitopes (e.g., from *Hib*, *Spn* or *N mening*) presented on a protein carrier are inhibited by prior or concurrent immunization with the sp.ecific protein carrier in the conjugate. When PRP conjugate vaccines were combined with DTaP vaccines and given simultaneously with IPV, it was shown that PRP antibody responses were lower; antibody levels to tetanus toxin was also reduced.[261] With DTaP vaccines, significant and clinically concerning drops in immunogenicity of anti-PRP antibody was observed with most products, eventually leading to the withdrawal of one of the US licensed DTaP vaccines. Only one combination DTaP-PRP-T vaccine was been licensed in the US; the reduction in anti-PRP antibody levels was absent or not clinically relevant for that product. Outside of the US, reduction in antibody levels to PRP in combination DTaP-PRP-T vaccines have been noted.[262,263] In other countries where DTwP is administered with PRP-T, there are also trends of reduced antibody levels to PRP, tetanus toxin and pertussis agglutinins.[264,265] CIES has been observed as an issue in several conjugate combination vaccines including a MenC-T conjugate administered T[266]and a *Spn* -T/ *Spn* -D mixed conjugate vaccine when administered with DTaP.[229-231] The decision by GlaxoSmithKline to use D as main carrier for 8of the 10 *Spn* polysaccharide serotypes was driven in part to avoid carrier-mediated suppression and possible bystander interference with coadministered conjugate vaccines.[221] As new vaccines are added to routine vaccination schedules, there is increasing concern about potential interactions that may reduce the desired protective effects. Antigen competition and/or CIES may play a

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Table 9. Spn – conjugates in immunocompromised hosts

Reference	Authors	Year Published	Condition	Vaccine	Population	Country
234	Chan, Molrine, George et al.	1996	Hodgkin's	7-Valent	Adults	USA
236	King, Vink, Farley et al.	1997	HIV	5-Valent	Infants/Toddlers	USA
237	Sorensen, Leiva, Giangrosso et al.	1998	Respiratory Infection	7-Valent	Toddlers/Children	
226	Klugman, Madhi, Huebner et al.	2003	HIV	9-Valent	Infants	South Africa
242	Kumar, Rotstein, Miyata et al.	2003	Renal Transplant	7-Valent	Adults	Canada
243	Nachman, Kim, King et al.	2003	HIV	7-Valent	Infants	USA
244	Madhi, Klugman, Kuwanda et al.	2009	HIV	7-Valent	Children	South Africa
245	Cordonnier, Labopin, Chesnel et al.	2009	Stem Cell Transplant	7-Valent	Adults	Australia, Finland, Israel, France, Spain, Sweden, Germany, Netherlands, UK, Belgium Italy, Austria, Ireland

Table 10. Studies in adults

Reference	Authors	Year Published	Study	Vaccine	Population	Country
246	Anderson, Bowers, Mink et al.	1994	ND*	Men A + C-CRM	Adults	USA
205	Campbell, Edelman, King et al.	2002	Ph I/II	MCV-D	Adults	USA
247	Harris, Finn and Granoff	2003	a	Men A + C-D	Adults	UK
248	Musher, Rueda, Nahm et al.	2008	b	PCV7	Adults	USA
249	Reisinger, Baxter, Block et al.	2009	PhIII	Men-CRM	Adults	USA
250	Miernyk, Butler, Bulkow et al.	2009	PhI	PCV7	Adults	USA
251	Stamboulian, Lopardo, Lopez et al.	2010	PhIII	Men- CRM	Adults	Latin Am.
252	Lazuras, Clutterbuck, Yu et al.	2011	PhIV	PCV7	Adults	UK

*ND, study phase not discerned; [a]Serum antibody immunogenicity study; [b]Response to vaccination after recovery from pneumococcal pneumonia.

role in reducing vaccine efficacy; this role will need to be evaluated with each new product. The possibility of vaccine interference should be an important consideration when co-administering new conjugate vaccines.

One of the problems with the development of conjugate vaccines that do not elicit antibody to all capsular serotypes within the bacterial species is the possibility that immunization will lead to the emergence of strains expressing new polysaccharide serotypes. With the PRP conjugate vaccines, production of antibody against the single polysaccharide capsular antigen of *Hib* was all that was needed to essentially eradicate the pathogen. Other capsular types of *H. influenzae* are infrequently virulent and emergence of replacement strains has not occurred.[267] Capsular switching can occur with *N mening*.[268]

Total protection from pneumococcal disease would require conjugate vaccines from potentially all known *S. pneumoniae* serotypes. Currently, there are at least 94 serotypes although not all are known to cause disease.[269,270] This may not be feasible and has led to study of protein-based vaccines that include multiple components.[271] The widespread use of the PCV7 vaccine produced a change in *Spn* serotypes responsible for infection.[272,273] The proportion of PCV7 serotypes decreased and the proportion of non-PCV7 serotypes increased. Emergence of a *Spn* 19A that was resistant to all antibiotics approved to treat AOM was responsible for cases of AOM between 2003 and 2006 as a result of widespread PCV7 vaccination.[274]

Conclusions

The discovery that conjugating a saccharide to a carrier protein enhanced immunogenicity and converted a T-cell independent to T-cell dependent antigens was one of the most important contemporary achievements in vaccinology, heralding a new era in vaccine development. All 5 carrier proteins have been shown to enhance immunogenicity of polysaccharides when conjugation to a protein carrier is achieved by various chemical manipulations. Among the 5 proteins CRM197 and have shown the greatest versatility in the ability of scientists to create conjugates to multiple polysaccharides in the same product and to be given concurrently with other vaccines.

Conflicts of Interest

The author has received research grants from and served as an advisor at various times to GlaxoSmithKline, Novartis, Sanofi Pasteur, and Wyeth (now Pfizer); vaccine companies that produce conjugate vaccines.

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Acknowledgment

I thank Porter Anderson, PhD and John Robbins MD for review of earlier versions of this manuscript and suggested revisions.

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