REVIEW

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

Protein carriers of conjugate vaccines

Characteristics, development, and clinical trials

Michael E Pichichero

Rochester General Hospital Research Institute; Rochester, NY USA

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

*Correspondence to: Michael E Pichichero;
Email: Michael.Pichichero@rochestergeneral.org
Submitted: 02/04/2013; Revised: 07/23/2013; Accepted: 08/11/2013
http://dx.doi.org/10.4161/hv.26109

Table 1. Early human studies of PRP conjugate vaccine

Reference	Authors	Year Published	Vaccine	Population	Country
A. Protein carrier CRM					
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.

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

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.

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]

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].

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.

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).

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

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.

Acknowledgment

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

References

1. Weller PF, Smith AL, Smith DH, Anderson P. Role of immunity in the clearance of bacteremia due to Haemophilus influenzae. J Infect Dis 1978; 138:427-36; PMID:309494; http://dx.doi.org/10.1093/infdis/138.4.427
2. Kelly DF, Moxon ER, Pollard AJ. Haemophilus influenzae type b conjugate vaccines. Immunology 2004; 113:163-74; PMID:15379976; http://dx.doi.org/10.1111/j.1365-2567.2004.01971.x
3. Lesinski GB, Westerink MA. Novel vaccine strategies to T-independent antigens. J Microbiol Methods 2001; 47:135-49; PMID:11576678; http://dx.doi.org/10.1016/S0167-7012(01)00290-1
4. Landsteiner K. The specificity of serologic reactions. Cambridge, Mass: Harvard University Press 2013.
5. Avery OT, Goebel WF. CHEMO-IMMUNOLOGICAL STUDIES ON CONJUGATED CARBOHYDRATE-PROTEINS : II. IMMUNOLOGICAL SPECIFICITY OF SYNTHETIC SUGAR-PROTEIN ANTIGENS. J Exp Med 1929; 50:533-50; PMID:19869645; http://dx.doi.org/10.1084/jem.50.4.533
6. Schneerson R, Barrera O, Sutton A, Robbins JB. Preparation, characterization, and immunogenicity of Haemophilus influenzae type b polysaccharide-protein conjugates. J Exp Med 1980; 152:361-76; PMID:6967514; http://dx.doi.org/10.1084/jem.152.2.361
7. Zahradnik JM, Gordon L. Augmented antibody (Ab) responses in infants administered a new *Haemophilus influenzae* type b capsular polysaccharide (PRP) diphtheria toxoid conjugate vaccine (PRP-D). Pediatr Res 1984; 18:289A; http://dx.doi.org/10.1203/00006450-198404001-01178
8. Anderson PW, Pichichero ME, Insel RA, Betts R, Eby R, Smith DH. Vaccines consisting of periodate-cleaved oligosaccharides from the capsule of Haemophilus influenzae type b coupled to a protein carrier: structural and temporal requirements for priming in the human infant. J Immunol 1986; 137:1181-6; PMID:3016088
9. Marburg S, Jorn D, Tolman RL. Bimolecular Chemistry of Macromolecules: Synthesis of Bacterial Polysaccharide Conjugates with *Neisseria meningitidis* Membrane Protein. J Am Chem Soc 1986; 108:5282-7; http://dx.doi.org/10.1021/ja00277a037
10. Giannini G, Rappuoli R, Ratti G. The amino-acid sequence of two non-toxic mutants of diphtheria toxin: CRM45 and CRM197. Nucleic Acids Res 1984; 12:4063-9; PMID:6427753; http://dx.doi.org/10.1093/nar/12.10.4063
11. Comvax® [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine]. Merck & Co, Inc 2001.
12. Menactra Meningococcal. (Groups A, C, Y and W-135) Polysaccharide Diptheria Toxoid Conjugate Vaccine. Sanofi Pasteur 2008.
13. Ruan MR, Akkoyunlu M, Grubb A, Forsgren A. Protein D of Haemophilus influenzae. A novel bacterial surface protein with affinity for human IgD. J Immunol 1990; 145:3379-84; PMID:2230124
14. Anderson P, Pichichero ME, Insel RA. Immunogens consisting of oligosaccharides from the capsule of Haemophilus influenzae type b coupled to diphtheria toxoid or the toxin protein CRM197. J Clin Invest 1985; 76:52-9; PMID:3874882; http://dx.doi.org/10.1172/JCI111976
15. Anderson P, Pichichero M, Insel R, Farsad P, Santosham M. Capsular antigens noncovalently or covalently associated with protein as vaccines to Haemophilus influenzae type b: comparison in two-year-old children. J Infect Dis 1985; 152:634-6; PMID:3875668; http://dx.doi.org/10.1093/infdis/152.3.634
16. Anderson P, Pichichero ME, Insel RA. Immunization of 2-month-old infants with protein-coupled oligosaccharides derived from the capsule of Haemophilus influenzae type b. J Pediatr 1985; 107:346-51; PMID:3875705; http://dx.doi.org/10.1016/S0022-3476(85)80504-7
17. Anderson PW, Pichichero ME, Insel RA, Betts R, Eby R, Smith DH. Vaccines consisting of periodate-cleaved oligosaccharides from the capsule of Haemophilus influenzae type b coupled to a protein carrier: structural and temporal requirements for priming in the human infant. J Immunol 1986; 137:1181-6; PMID:3016088
18. Anderson PW, Pichichero ME, Stein EC, Porcelli S, Betts RF, Connuck DM, Korones D, Insel RA, Zahradnik JM, Eby R. Effect of oligosaccharide chain length, exposed terminal group, and hapten loading on the antibody response of human adults and infants to vaccines consisting of Haemophilus influenzae type b capsular antigen unterminally coupled to the diphtheria protein CRM197. J Immunol 1989; 142:2464-8; PMID:2784464
19. Anderson P, Porcelli S, Pichichero ME. Effect of phosphate ester residues on the immunogenicity of CRM197-coupled Haemophilus influenzae type b capsular saccharides in 2-month-old infants. J Infect Dis 1992; 165(Suppl 1):S160-1; PMID:1588154; http://dx.doi.org/10.1093/infdis/165-Supplement_1-S160
20. Schneerson R, Robbins JB, Parke JC Jr., Bell C, Schlesselman JJ, Sutton A, Wang Z, Schiffman G, Karpas A, Shiloach J. Quantitative and qualitative analyses of serum antibodies elicited in adults by Haemophilus influenzae type b and pneumococcus type 6A capsular polysaccharide-tetanus toxoid conjugates. Infect Immun 1986; 52:519-28; PMID:3516876
21. Claesson BA, Schneerson R, Trollfors B, Lagergård T, Taranger J, Robbins JB. Duration of serum antibodies elicited by Haemophilus influenzae type b capsular polysaccharide alone or conjugated to tetanus toxoid in 18- to 23-month-old children. J Pediatr 1990; 116:929-31; PMID:2348298; http://dx.doi.org/10.1016/S0022-3476(05)80655-9
22. Claesson BA, Schneerson R, Lagergård T, Trollfors B, Taranger J, Johansson J, Bryla D, Robbins JB. Persistence of serum antibodies elicited by Haemophilus influenzae type b-tetanus toxoid conjugate vaccine in infants vaccinated at 3, 5 and 12 months of age. Pediatr Infect Dis J 1991; 10:560-4; PMID:1891286; http://dx.doi.org/10.1097/00006454-199108000-00002
23. Einhorn MS, Weinberg GA, Anderson EL, Granoff PD, Granoff DM. Immunogenicity in infants of Haemophilus influenzae type B polysaccharide in a conjugate vaccine with Neisseria meningitidis outer-membrane protein. Lancet 1986; 2:299-302; PMID:2874327; http://dx.doi.org/10.1016/S0140-6736(86)90001-2
24. Weinberg GA, Einhorn MS, Lenoir AA, Granoff PD, Granoff DM. Immunologic priming to capsular polysaccharide in infants immunized with Haemophilus influenzae type b polysaccharide-Neisseria meningitidis outer membrane protein conjugate vaccine. J Pediatr 1987; 111:22-7; PMID:3110388; http://dx.doi.org/10.1016/S0022-3476(87)80336-0
25. Lenoir AA, Granoff PD, Granoff DM. Immunogenicity of Haemophilus influenzae type b polysaccharide-Neisseria meningitidis outer membrane protein conjugate vaccine in 2- to 6-month-old infants. Pediatrics 1987; 80:283-7; PMID:3112729
26. Lepow ML, Samuelson JS, Gordon LK. Safety and immunogenicity of Haemophilus influenzae type B polysaccharide-diphtheria toxoid conjugate vaccine in adults. J Infect Dis 1984; 150:402-6; PMID:6332863; http://dx.doi.org/10.1093/infdis/150.3.402
27. Granoff DM, Boies EG, Munson RS Jr. Immunogenicity of Haemophilus influenzae type b polysaccharide--diphtheria toxoid conjugate vaccine in adults. J Pediatr 1984; 105:22-7; PMID:6610736; http://dx.doi.org/10.1016/S0022-3476(84)80350-9
28. Lepow ML, Samuelson JS, Gordon LK. Safety and immunogenicity of Haemophilus influenzae type b-polysaccharide diphtheria toxoid conjugate vaccine in infants 9 to 15 months of age. J Pediatr 1985; 106:185-9; PMID:3871477; http://dx.doi.org/10.1016/S0022-3476(85)80284-5
29. Berkowitz CD, Ward JI, Meier K, Hendley JO, Brunell PA, Barkin RA, Zahradnik JM, Samuelson J, Gordon L. Safety and immunogenicity of Haemophilus influenzae type b polysaccharide and polysaccharide diphtheria toxoid conjugate vaccines in children 15 to 24 months of age. J Pediatr 1987; 110:509-14; PMID:3550021; http://dx.doi.org/10.1016/S0022-3476(87)80540-1
30. Eskola J, Peltola H, Takala AK, Käyhty H, Hakulinen M, Karanko V, Kela E, Rekola P, Rönnberg PR, Samuelson JS, et al. Efficacy of Haemophilus influenzae type b polysaccharide-diphtheria toxoid conjugate vaccine in infancy. N Engl J Med 1987; 317:717-22; PMID:3306379; http://dx.doi.org/10.1056/NEJM198709173171201
31. Eskola J, Käyhty H, Takala AK, Peltola H, Rönnberg PR, Kela E, Pekkanen E, McVerry PH, Mäkelä PH. A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive Haemophilus influenzae type b disease. N Engl J Med 1990; 323:1381-7; PMID:2233904; http://dx.doi.org/10.1056/NEJM199011153232004
32. Santosham M, Wolff M, Reid R, Hohenboken M, Bateman M, Goepp J, Cortese M, Sack D, Hill J, Newcomer W, et al. The efficacy in Navajo infants of a conjugate vaccine consisting of Haemophilus influenzae type b polysaccharide and Neisseria meningitidis outer-membrane protein complex. N Engl J Med 1991; 324:1767-72; PMID:1903846; http://dx.doi.org/10.1056/NEJM199106203242503
33. Booy R, Moxon ER, MacFarlane JA, Mayon-White RT, Slack MP. Efficacy of Haemophilus influenzae type B conjugate vaccine in Oxford region. Lancet 1992; 340:847; PMID:1357260; http://dx.doi.org/10.1016/0140-6736(92)92719-V

34. Mulholland K, Hilton S, Adegbola R, Usen S, Oparaugo A, Omosigho C, Weber M, Palmer A, Schneider G, Jobe K, et al. Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants. Lancet 1997; 349:1191-7; PMID:9130939; http://dx.doi.org/10.1016/S0140-6736(96)09267-7
35. Peltola H, Eskola J, Käyhty H, Takala AK, Mäkelä PH. Clinical comparison of the Haemophilus influenzae type B polysaccharide-diphtheria toxoid and the oligosaccharide-CRM197 protein vaccines in infancy. Arch Pediatr Adolesc Med 1994; 148:620-5; PMID:8193690; http://dx.doi.org/10.1001/archpedi.1994.02170060074015
36. Huebner RE, Nicol M, Mothupi R, Käyhty H, Mbelle N, Khomo E, Klugman KP. Dose response of CRM197 and tetanus toxoid-conjugated Haemophilus influenzae type b vaccines. Vaccine 2004; 23:802-6; PMID:15542205; http://dx.doi.org/10.1016/j.vaccine.2004.06.052
37. Tamm E, Veronese A, Contorni M, Meriste S, Nacci P, Viviani S. Double-blind study comparing the immunogenicity of a licensed DTwPHib-CRM197 conjugate vaccine (Quattvaxem) with three investigational, liquid formulations using lower doses of Hib-CRM197 conjugate. Vaccine 2005; 23:1715-9; PMID:15705477; http://dx.doi.org/10.1016/j.vaccine.2004.09.028
38. Anderson EL, Frey S, Geldmacher K, Radley D, Lee A, Donnelly J, Mendelman PM, Dargan JM, Kaplan KM. Safety, tolerability and immunogenicity of low dose Haemophilus influenzae type b conjugated to the outer membrane protein complex of Neisseria meningitidis group B. Pediatr Infect Dis J 2002; 21:350-2; PMID:12075771; http://dx.doi.org/10.1097/00006454-200204000-00019
39. Kurikka S, Käyhty H, Saarinen L, Rönnberg P, Eskola J, Mäkelä PH. Comparison of five different vaccination schedules with Haemophilus influenzae type b-tetanus toxoid conjugate vaccine. J Pediatr 1996; 128:524-30; PMID:8618187; http://dx.doi.org/10.1016/S0022-3476(96)70364-5
40. Rennels M, King J Jr., Ryall R, Manoff S, Papa T, Weddle A, Froeschle J. Dose escalation, safety and immunogenicity study of a tetravalent meninogococcal polysaccharide diphtheria conjugate vaccine in toddlers. Pediatr Infect Dis J 2002; 21:978-9; PMID:12400528; http://dx.doi.org/10.1097/00006454-200210000-00019
41. Silfverdal SA, Hogh B, Bergsaker MR, Skerlikova H, Lommel P, Borys D, Schuerman L. Immunogenicity of a 2-dose priming and booster vaccination with the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine. Pediatr Infect Dis J 2009; 28:e276-82; PMID:20118683; http://dx.doi.org/10.1097/INF.0b013e3181b48ca3
42. McVernon J, Nolan T, Richmond P, Reynolds G, Nissen M, Lambert SB, Marshall H, Papa T, Rehm C. A randomized trial to assess safety and immunogenicity of alternative formulations of a quadrivalent meningococcal (A, C, Y, and W-135) tetanus protein conjugate vaccine in toddlers. Pediatr Infect Dis J 2012; 31:e15-23; PMID:22094636; http://dx.doi.org/10.1097/INF.0b013e31823e1e34
43. Daum RS, Siber GR, Ballanco GA, Sood SK. Serum anticapsular antibody response in the first week after immunization of adults and infants with the Haemophilus influenzae type b-Neisseria meningitidis outer membrane protein complex conjugate vaccine. J Infect Dis 1991; 164:1154-9; PMID:1955715; http://dx.doi.org/10.1093/infdis/164.6.1154
44. Goldblatt D, Southern J, Ashton L, Richmond P, Burbidge P, Tasevska J, Crowley-Luke A, Andrews N, Morris R, Borrow R, et al. Immunogenicity and boosting after a reduced number of doses of a pneumococcal conjugate vaccine in infants and toddlers. Pediatr Infect Dis J 2006; 25:312-9; PMID:16567982; http://dx.doi.org/10.1097/01.inf.0000207483.60267.e7
45. Griffiths UK, Clark A, Gessner B, Miners A, Sanderson C, Sedyaningsih ER, Mulholland KE. Dose-specific efficacy of Haemophilus influenzae type b conjugate vaccines: a systematic review and meta-analysis of controlled clinical trials. Epidemiol Infect 2012; 140:1343-55; PMID:22583474; http://dx.doi.org/10.1017/S0950268812000957
46. Granoff DM, Anderson EL, Osterholm MT, Holmes SJ, McHugh JE, Belshe RB, Medley F, Murphy TV. Differences in the immunogenicity of three Haemophilus influenzae type b conjugate vaccines in infants. J Pediatr 1992; 121:187-94; PMID:1640282; http://dx.doi.org/10.1016/S0022-3476(05)81186-2
47. Decker MD, Edwards KM, Bradley R, Palmer P. Comparative trial in infants of four conjugate Haemophilus influenzae type b vaccines. J Pediatr 1992; 120:184-9; PMID:1735812; http://dx.doi.org/10.1016/S0022-3476(05)80424-X
48. Käyhty H, Eskola J, Peltola H, Rönnberg PR, Kela E, Karanko V, Saarinen L. Antibody responses to four Haemophilus influenzae type b conjugate vaccines. Am J Dis Child 1991; 145:223-7; PMID:1994693
49. Bulkow LR, Wainwright RB, Letson GW, Chang SJ, Ward JI. Comparative immunogenicity of four Haemophilus influenzae type b conjugate vaccines in Alaska Native infants. Pediatr Infect Dis J 1993; 12:484-92; PMID:8345981; http://dx.doi.org/10.1097/00006454-199306000-00006
50. Ward J, Brenneman G, Letson GW, Heyward WL. 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 1990; 323:1393-401; PMID:2233906; http://dx.doi.org/10.1056/NEJM199011153232006
51. Singleton R, Hammitt L, Hennessy T, Bulkow L, DeByle C, Parkinson A, Cottle TE, Peters H, Butler JC. The Alaska Haemophilus influenzae type b experience: lessons in controlling a vaccine-preventable disease. Pediatrics 2006; 118:e421-9; PMID:16882783; http://dx.doi.org/10.1542/peds.2006-0287
52. Gourley TS, Wherry EJ, Masopust D, Ahmed R. Generation and maintenance of immunological memory. Semin Immunol 2004; 16:323-33; PMID:15528077; http://dx.doi.org/10.1016/j.smim.2004.08.013
53. Granoff DM, Lucas AH. Laboratory correlates of protection against Haemophilus influenzae type b disease. Importance of assessment of antibody avidity and immunologic memory. Ann N Y Acad Sci 1995; 754:278-88; PMID:7625664; http://dx.doi.org/10.1111/j.1749-6632.1995.tb44461.x
54. Insel RA, Anderson PW. Oligosaccharide-protein conjugate vaccines induce and prime for oligoclonal IgG antibody responses to the Haemophilus influenzae b capsular polysaccharide in human infants. J Exp Med 1986; 163:262-9; PMID:3484778; http://dx.doi.org/10.1084/jem.163.2.262
55. Goldblatt D, Vaz AR, Miller E. Antibody avidity as a surrogate marker of successful priming by Haemophilus influenzae type b conjugate vaccines following infant immunization. J Infect Dis 1998; 177:1112-5; PMID:9534995; http://dx.doi.org/10.1086/517407
56. Goldblatt D, Richmond P, Millard E, Thornton C, Miller E. The induction of immunologic memory after vaccination with Haemophilus influenzae type b conjugate and acellular pertussis-containing diphtheria, tetanus, and pertussis vaccine combination. J Infect Dis 1999; 180:538-41; PMID:10395878; http://dx.doi.org/10.1086/314901
57. Zepp F, Schmitt HJ, Kaufhold A, Schuind A, Knuf M, Habermehl P, Meyer C, Bogaerts H, Slaoui M, Clemens R. Evidence for induction of polysaccharide specific B-cell-memory in the 1st year of life: plain Haemophilus influenzae type b-PRP (Hib) boosters children primed with a tetanus-conjugate Hib-DTPa-HBV combined vaccine. Eur J Pediatr 1997; 156:18-24; PMID:9007484; http://dx.doi.org/10.1007/s004310050544
58. Granoff DM, Holmes SJ, Osterholm MT, McHugh JE, Lucas AH, Anderson EL, Belshe RB, Jacobs JL, Medley F, Murphy TV. Induction of immunologic memory in infants primed with Haemophilus influenzae type b conjugate vaccines. J Infect Dis 1993; 168:663-71; PMID:8354908; http://dx.doi.org/10.1093/infdis/168.3.663
59. Anderson P, Ingram DL, Pichichero ME, Peter G. A high degree of natural immunologic priming to the capsular polysaccharide may not prevent Haemophilus influenzae type b meningitis. Pediatr Infect Dis J 2000; 19:589-91; PMID:10917213; http://dx.doi.org/10.1097/00006454-200007000-00001
60. Ramsay ME, McVernon J, Andrews NJ, Heath PT, Slack MP. Estimating Haemophilus influenzae type b vaccine effectiveness in England and Wales by use of the screening method. J Infect Dis 2003; 188:481-5; PMID:12898433; http://dx.doi.org/10.1086/376997
61. McVernon J, Andrews N, Slack MP, Ramsay ME. Risk of vaccine failure after Haemophilus influenzae type b (Hib) combination vaccines with acellular pertussis. Lancet 2003; 361:1521-3; PMID:12737866; http://dx.doi.org/10.1016/S0140-6736(03)13171-6
62. Heath PT, Booy R, Azzopardi HJ, Slack MP, Bowen-Morris J, Griffiths H, Ramsay ME, Deeks JJ, Moxon ER. Antibody concentration and clinical protection after Hib conjugate vaccination in the United Kingdom. JAMA 2000; 284:2334-40; PMID:11066183; http://dx.doi.org/10.1001/jama.284.18.2334
63. Pichichero ME, Passador S. Administration of combined diphtheria and tetanus toxoids and pertussis vaccine, hepatitis B vaccine, and Haemophilus influenzae type b (Hib) vaccine to infants and response to a booster dose of Hib conjugate vaccine. Clin Infect Dis 1997; 25:1378-84; PMID:9431382; http://dx.doi.org/10.1086/516154
64. Halperin BA, Morris A, Mackinnon-Cameron D, Mutch J, Langley JM, McNeil SA, Macdougall D, Halperin SA. Kinetics of the antibody response to tetanus-diphtheria-acellular pertussis vaccine in women of childbearing age and postpartum women. Clin Infect Dis 2011; 53:885-92; PMID:21946190; http://dx.doi.org/10.1093/cid/cir538
65. Wing JB, Smart L, Borrow R, Findlow J, Findlow H, Heath AW, Read RC. Kinetics of immune responses to nasal challenge with meningococcal polysaccharide one year after serogroup-C glycoconjugate vaccination. Clin Infect Dis 2011; 52:1317-23; PMID:21596673; http://dx.doi.org/10.1093/cid/cir198
66. Lee YC, Kelly DF, Yu LM, Slack MP, Booy R, Heath PT, Siegrist CA, Moxon RE, Pollard AJ. Haemophilus influenzae type b vaccine failure in children is associated with inadequate production of high-quality antibody. Clin Infect Dis 2008; 46:186-92; PMID:18171249; http://dx.doi.org/10.1086/524668
67. Plotkin SA. Vaccines: correlates of vaccine-induced immunity. Clin Infect Dis 2008; 47:401-9; PMID:18558875; http://dx.doi.org/10.1086/589862
68. Pichichero ME. Booster vaccinations: can immunologic memory outpace disease pathogenesis? Pediatrics 2009; 124:1633-41; PMID:19933727; http://dx.doi.org/10.1542/peds.2008-3645
69. Auckland C, Gray S, Borrow R, Andrews N, Goldblatt D, Ramsay M, Miller E. Clinical and immunologic risk factors for meningococcal C conjugate vaccine failure in the United Kingdom. J Infect Dis 2006; 194:1745-52; PMID:17109348; http://dx.doi.org/10.1086/509619

70. Perrett KP, Winter AP, Kibwana E, Jin C, John TM, Yu LM, Borrow R, Curtis N, Pollard AJ. Antibody persistence after serogroup C meningococcal conjugate immunization of United Kingdom primary-school children in 1999-2000 and response to a booster: a phase 4 clinical trial. Clin Infect Dis 2010; 50:1601-10; PMID:20459323; http://dx.doi.org/10.1086/652765
71. Blanchard Rohner G, Snape MD, Kelly DF, John T, Morant A, Yu LM, Borkowski A, Ceddia F, Borrow R, Siegrist CA, et al. The magnitude of the antibody and memory B cell responses during priming with a protein-polysaccharide conjugate vaccine in human infants is associated with the persistence of antibody and the intensity of booster response. J Immunol 2008; 180:2165-73; PMID:18250423
72. Borrow R, Andrews N, Findlow H, Waight P, Southern J, Crowley-Luke A, Stapley L, England A, Findlow J, Miller E. Kinetics of antibody persistence following administration of a combination meningococcal serogroup C and haemophilus influenzae type b conjugate vaccine in healthy infants in the United Kingdom primed with a monovalent meningococcal serogroup C vaccine. Clin Vaccine Immunol 2010; 17:154-9; PMID:19906895; http://dx.doi.org/10.1128/CVI.00384-09
73. Gill CJ, Baxter R, Anemona A, Ciavarro G, Dull P. Persistence of immune responses after a single dose of Novartis meningococcal serogroup A, C, W-135 and Y CRM-197 conjugate vaccine (Menveo®) or Menactra® among healthy adolescents. Hum Vaccin 2010; 6:881-7; PMID:21339701; http://dx.doi.org/10.4161/hv.6.11.12849
74. de Whalley PC, Snape MD, Kelly DF, Banner C, Lewis S, Diggle L, John TM, Yu LM, Omar O, Borkowski A, et al. Persistence of serum bactericidal antibody one year after a booster dose of either a glycoconjugate or a plain polysaccharide vaccine against serogroup C Neisseria meningitidis given to adolescents previously immunized with a glycoconjugate vaccine. Pediatr Infect Dis J 2011; 30:e203-8; PMID:21673612; http://dx.doi.org/10.1097/INF.0b013e318224fb14
75. Tregnaghi M, Zambrano B, Santos-Lima E. Antibody persistence after a primary series of a new DTaP-IPV-Hep B-PRP-T combined vaccine or separate DTaP-IPV//PRP-T and hepatitis B vaccines at 2, 4, and 6 months of age and the effect of a subsequent DTaP-IPV//PRP-T booster vaccination at 18 months of age in healthy Argentinean infants. Pediatr Infect Dis J 2012; 31:e24-30; PMID:22157567; http://dx.doi.org/10.1097/INF.0b013e318242460a
76. Booy R, Richmond P, Nolan T, McVernon J, Marshall H, Nissen M, Reynolds G, Ziegler JB, Stoney T, Heron L, et al. Three-year antibody persistence and safety after a single dose of combined haemophilus influenzae type b (Hib)-Neisseria meningitidis serogroup C-tetanus toxoid conjugate vaccine in Hib-primed toddlers. Pediatr Infect Dis J 2013; 32:169-74; PMID:23080288; http://dx.doi.org/10.1097/INF.0b013e3182787bff
77. Anderson EL, Kennedy DJ, Geldmacher KM, Donnelly J, Mendelman PM. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. J Pediatr 1996; 128:649-53; PMID:8627437; http://dx.doi.org/10.1016/S0022-3476(96)80130-2
78. Dagan R, Melamed R, Zamir O, Leroy O. Safety and immunogenicity of tetravalent pneumococcal vaccines containing 6B, 14, 19F and 23F polysaccharides conjugated to either tetanus toxoid or diphtheria toxoid in young infants and their boosterability by native polysaccharide antigens. Pediatr Infect Dis J 1997; 16:1053-9; PMID:9384339; http://dx.doi.org/10.1097/00006454-199711000-00010
79. Ahman H, Käyhty H, Lehtonen H, Leroy O, Froeschle J, Eskola J. Streptococcus pneumoniae capsular polysaccharide-diphtheria toxoid conjugate vaccine is immunogenic in early infancy and able to induce immunologic memory. Pediatr Infect Dis J 1998; 17:211-6; PMID:9535248; http://dx.doi.org/10.1097/00006454-199803000-00008
80. Rennels MB, Edwards KM, Keyserling HL, Reisinger KS, Hogerman DA, Madore DV, Chang I, Paradiso PR, Malinoski FJ, Kimura A. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants. Pediatrics 1998; 101:604-11; PMID:9521941; http://dx.doi.org/10.1542/peds.101.4.604
81. Knuf M, Pankow-Culot H, Grunert D, Rapp M, Panzer F, Köllges R, Fanic A, Habib A, Borys D, Dieussaert I, et al. Induction of immunologic memory following primary vaccination with the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine in infants. Pediatr Infect Dis J 2012; 31:e31-6; PMID:21909049; http://dx.doi.org/10.1097/INF.0b013e3182323ac2
82. Leach A, Twumasi PA, Kumah S, Banya WS, Jaffar S, Forrest BD, Granoff DM, LiButti DE, Carlone GM, Pais LB, et al. Induction of immunologic memory in Gambian children by vaccination in infancy with a group A plus group C meningococcal polysaccharide-protein conjugate vaccine. J Infect Dis 1997; 175:200-4; PMID:8985221; http://dx.doi.org/10.1093/infdis/175.1.200
83. MacDonald NE, Halperin SA, Law BJ, Forrest B, Danzig LE, Granoff DM. Induction of immunologic memory by conjugated vs plain meningococcal C polysaccharide vaccine in toddlers: a randomized controlled trial. JAMA 1998; 280:1685-9; PMID:9832000; http://dx.doi.org/10.1001/jama.280.19.1685
84. Richmond P, Borrow R, Miller E, Clark S, Sadler F, Fox A, Begg N, Morris R, Cartwright K. Meningococcal serogroup C conjugate vaccine is immunogenic in infancy and primes for memory. J Infect Dis 1999; 179:1569-72; PMID:10228085; http://dx.doi.org/10.1086/314753
85. MacLennan JM, Shackley F, Heath PT, Deeks JJ, Flamank C, Herbert M, Griffiths H, Hatzmann E, Goilav C, Moxon ER. Safety, immunogenicity, and induction of immunologic memory by a serogroup C meningococcal conjugate vaccine in infants: A randomized controlled trial. JAMA 2000; 283:2795-801; PMID:10838647; http://dx.doi.org/10.1001/jama.283.21.2795
86. Richmond P, Borrow R, Goldblatt D, Findlow J, Martin S, Morris R, Cartwright K, Miller E. Ability of 3 different meningococcal C conjugate vaccines to induce immunologic memory after a single dose in UK toddlers. J Infect Dis 2001; 183:160-3; PMID:11078484; http://dx.doi.org/10.1086/317646
87. MacLennan J, Obaro S, Deeks J, Lake D, Elie C, Carlone G, Moxon ER, Greenwood B. Immunologic memory 5 years after meningococcal A/C conjugate vaccination in infancy. J Infect Dis 2001; 183:97-104; PMID:11087205; http://dx.doi.org/10.1086/317667
88. Borrow R, Goldblatt D, Andrews N, Southern J, Ashton L, Deane S, Morris R, Cartwright K, Miller E. Antibody persistence and immunological memory at age 4 years after meningococcal group C conjugate vaccination in children in the United kingdom. J Infect Dis 2002; 186:1353-7; PMID:12402208; http://dx.doi.org/10.1086/344324
89. McVernon J, Maclennan J, Buttery J, Oster P, Danzig L, Moxon ER. Safety and immunogenicity of meningococcus serogroup C conjugate vaccine administered as a primary or booster vaccination to healthy four-year-old children. Pediatr Infect Dis J 2002; 21:747-53; PMID:12192163; http://dx.doi.org/10.1097/00006454-200208000-00010
90. McVernon J, MacLennan J, Pollard AJ, Oster P, Wakefield MJ, Danzig L, Moxon ER. Immunologic memory with no detectable bactericidal antibody response to a first dose of meningococcal serogroup C conjugate vaccine at four years. Pediatr Infect Dis J 2003; 22:659-61; PMID:12886896; http://dx.doi.org/10.1097/01.inf.0000076386.52719.b3
91. Borrow R, Goldblatt D, Finn A, Southern J, Ashton L, Andrews N, Lal G, Riley C, Rahim R, Cartwright K, et al. Immunogenicity of, and immunologic memory to, a reduced primary schedule of meningococcal C-tetanus toxoid conjugate vaccine in infants in the United kingdom. Infect Immun 2003; 71:5549-55; PMID:14500473; http://dx.doi.org/10.1128/IAI.71.10.5549-5555.2003
92. Keyserling H, Papa T, Koranyi K, Ryall R, Bassily E, Bybel MJ, Sullivan K, Gilmet G, Reinhardt A. Safety, immunogenicity, and immune memory of a novel meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV-4) in healthy adolescents. Arch Pediatr Adolesc Med 2005; 159:907-13; PMID:16203934; http://dx.doi.org/10.1001/archpedi.159.10.907
93. Pichichero M, Papa T, Blatter M, Mitchell D, Kratz R, Sneed J, Bassily E, Casey J, Gilmet G. Immune memory in children previously vaccinated with an experimental quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine. Pediatr Infect Dis J 2006; 25:995-1000; PMID:17072120; http://dx.doi.org/10.1097/01.inf.0000243215.46312.4a
94. Pichichero ME, Sommerfelt AE, Steinhoff MC, Insel RA. Breast milk antibody to the capsular polysaccharide of Haemophilus influenzae type b. J Infect Dis 1980; 142:694-8; PMID:6970233; http://dx.doi.org/10.1093/infdis/142.5.694
95. Pichichero ME, Hall CB, Insel RA. A mucosal antibody response following systemic Haemophilus influenzae type B infection in children. J Clin Invest 1981; 67:1482-9; PMID:6971877; http://dx.doi.org/10.1172/JCI110178
96. Pichichero ME, Insel RA. Relationship between naturally occurring human mucosal and serum antibody to the capsular polysaccharide of Haemophilus influenzae type b. J Infect Dis 1982; 146:243-8; PMID:6980956; http://dx.doi.org/10.1093/infdis/146.2.243
97. Pichichero ME, Insel RA. Mucosal antibody response to parenteral vaccination with Haemophilus influenzae type b capsule. J Allergy Clin Immunol 1983; 72:481-6; PMID:6605372; http://dx.doi.org/10.1016/0091-6749(83)90585-7
98. Nieminen T, Käyhty H, Virolainen A, Eskola J. Circulating antibody secreting cell response to parenteral pneumococcal vaccines as an indicator of a salivary IgA antibody response. Vaccine 1998; 16:313-9; PMID:9607048; http://dx.doi.org/10.1016/S0264-410X(97)00162-X
99. Nieminen T, Eskola J, Käyhty H. Pneumococcal conjugate vaccination in adults: circulating antibody secreting cell response and humoral antibody responses in saliva and in serum. Vaccine 1998; 16:630-6; PMID:9569475; http://dx.doi.org/10.1016/S0264-410X(97)00235-1
100. Nieminen T, Käyhty H, Leroy O, Eskola J. Pneumococcal conjugate vaccination in toddlers: mucosal antibody response measured as circulating antibody-secreting cells and as salivary antibodies. Pediatr Infect Dis J 1999; 18:764-72; PMID:10493335; http://dx.doi.org/10.1097/00006454-199909000-00005
101. Korkeila M, Lehtonen H, Ahman H, Leroy O, Eskola J, Käyhty H. Salivary anti-capsular antibodies in infants and children immunised with Streptococcus pneumoniae capsular polysaccharides conjugated to diphtheria or tetanus toxoid. Vaccine 2000; 18:1218-26; PMID:10649623; http://dx.doi.org/10.1016/S0264-410X(99)00393-X

102. Choo S, Zhang Q, Seymour L, Akhtar S, Finn A. Primary and booster salivary antibody responses to a 7-valent pneumococcal conjugate vaccine in infants. J Infect Dis 2000; 182:1260-3; PMID:10979930; http://dx.doi.org/10.1086/315834
103. Nurkka A, Ahman H, Korkeila M, Jäntti V, Käyhty H, Eskola J. Serum and salivary anti-capsular antibodies in infants and children immunized with the heptavalent pneumococcal conjugate vaccine. Pediatr Infect Dis J 2001; 20:25-33; PMID:11176563; http://dx.doi.org/10.1097/00006454-200101000-00006
104. Nurkka A, Ahman H, Yaich M, Eskola J, Käyhty H. Serum and salivary anti-capsular antibodies in infants and children vaccinated with octavalent pneumococcal conjugate vaccines, PncD and PncT. Vaccine 2001; 20:194-201; PMID:11567764; http://dx.doi.org/10.1016/S0264-410X(01)00250-X
105. Finn A, Zhang Q, Seymour L, Fasching C, Pettitt E, Janoff EN. Induction of functional secretory IgA responses in breast milk, by pneumococcal capsular polysaccharides. J Infect Dis 2002; 186:1422-9; PMID:12404157; http://dx.doi.org/10.1086/344356
106. Takala AK, Eskola J, Leinonen M, Käyhty H, Nissinen A, Pekkanen E, Mäkelä PH. Reduction of oropharyngeal carriage of Haemophilus influenzae type b (Hib) in children immunized with an Hib conjugate vaccine. J Infect Dis 1991; 164:982-6; PMID:1940479; http://dx.doi.org/10.1093/infdis/164.5.982
107. Kauppi-Korkeila M, van Alphen L, Madore D, Saarinen L, Käyhty H. Mechanism of antibody-mediated reduction of nasopharyngeal colonization by Haemophilus influenzae type b studied in an infant rat model. J Infect Dis 1996; 174:1337-40; PMID:8940229; http://dx.doi.org/10.1093/infdis/174.6.1337
108. Takala AK, Santosham M, Almeido-Hill J, Wolff M, Newcomer W, Reid R, Käyhty H, Esko E, Mäkelä PH. Vaccination with Haemophilus influenzae type b meningococcal protein conjugate vaccine reduces oropharyngeal carriage of Haemophilus influenzae type b among American Indian children. Pediatr Infect Dis J 1993; 12:593-9; PMID:8346004; http://dx.doi.org/10.1097/00006454-199307000-00010
109. Fernandez J, Levine OS, Sanchez J, Balter S, LaClaire L, Feris J, Romero-Steiner S. Prevention of Haemophilus influenzae type b colonization by vaccination: correlation with serum anti-capsular IgG concentration. J Infect Dis 2000; 182:1553-6; PMID:11023481; http://dx.doi.org/10.1086/315870
110. Heath PT, McVernon J. The UK Hib vaccine experience. Arch Dis Child 2002; 86:396-9; PMID:12023165; http://dx.doi.org/10.1136/adc.86.6.396
111. Moulton LH, Chung S, Croll J, Reid R, Weatherholtz RC, Santosham M. Estimation of the indirect effect of Haemophilus influenzae type b conjugate vaccine in an American Indian population. Int J Epidemiol 2000; 29:753-6; PMID:10922355; http://dx.doi.org/10.1093/ije/29.4.753
112. Käyhty H, Peltola H, Karanko V, Mäkelä PH. The protective level of serum antibodies to the capsular polysaccharide of Haemophilus influenzae type b. J Infect Dis 1983; 147:1100; PMID:6602191; http://dx.doi.org/10.1093/infdis/147.6.1100
113. Dagan R, Givon-Lavi N, Fraser D, Lipsitch M, Siber GR, Kohberger R. Serum serotype-specific pneumococcal anticapsular immunoglobulin g concentrations after immunization with a 9-valent conjugate pneumococcal vaccine correlate with nasopharyngeal acquisition of pneumococcus. J Infect Dis 2005; 192:367-76; PMID:15995949; http://dx.doi.org/10.1086/431679
114. Dagan R, Melamed R, Muallem M, Piglansky L, Greenberg D, Abramson O, Mendelman PM, Bohidar N, Yagupsky P. Reduction of nasopharyngeal carriage of pneumococci during the second year of life by a heptavalent conjugate pneumococcal vaccine. J Infect Dis 1996; 174:1271-8; PMID:8940218; http://dx.doi.org/10.1093/infdis/174.6.1271
115. Millar EV, O'Brien KL, Bronsdon MA, Madore D, Hackell JG, Reid R, Santosham M. Anticapsular serum antibody concentration and protection against pneumococcal colonization among children vaccinated with 7-valent pneumococcal conjugate vaccine. Clin Infect Dis 2007; 44:1173-9; PMID:17407035; http://dx.doi.org/10.1086/513199
116. Dagan R, Muallem M, Melamed R, Leroy O, Yagupsky P. Reduction of pneumococcal nasopharyngeal carriage in early infancy after immunization with tetravalent pneumococcal vaccines conjugated to either tetanus toxoid or diphtheria toxoid. Pediatr Infect Dis J 1997; 16:1060-4; PMID:9384340; http://dx.doi.org/10.1097/00006454-199711000-00011
117. Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999; 180:1171-6; PMID:10479145; http://dx.doi.org/10.1086/315009
118. Dagan R, Givon-Lavi N, Zamir O, Sikuler-Cohen M, Guy L, Janco J, Yagupsky P, Fraser D. Reduction of nasopharyngeal carriage of Streptococcus pneumoniae after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. J Infect Dis 2002; 185:927-36; PMID:11920317; http://dx.doi.org/10.1086/339525
119. Givon-Lavi N, Fraser D, Dagan R. Vaccination of day-care center attendees reduces carriage of Streptococcus pneumoniae among their younger siblings. Pediatr Infect Dis J 2003; 22:524-32; PMID:12799509; http://dx.doi.org/10.1097/01.inf.0000069760.65826.f2
120. Dagan R, Givon-Lavi N, Zamir O, Fraser D. Effect of a nonavalent conjugate vaccine on carriage of antibiotic-resistant Streptococcus pneumoniae in day-care centers. Pediatr Infect Dis J 2003; 22:532-40; PMID:12799510; http://dx.doi.org/10.1097/01.inf.0000069761.11093.c3
121. Moore MR, Hyde TB, Hennessy TW, Parks DJ, Reasonover AL, Harker-Jones M, Gove J, Bruden DL, Rudolph K, Parkinson A, et al. Impact of a conjugate vaccine on community-wide carriage of nonsusceptible Streptococcus pneumoniae in Alaska. J Infect Dis 2004; 190:2031-8; PMID:15529269; http://dx.doi.org/10.1086/425422
122. Ghaffar F, Barton T, Lozano J, Muniz LS, Hicks P, Gan V, Ahmad N, McCracken GH Jr. Effect of the 7-valent pneumococcal conjugate vaccine on nasopharyngeal colonization by Streptococcus pneumoniae in the first 2 years of life. Clin Infect Dis 2004; 39:930-8; PMID:15472842; http://dx.doi.org/10.1086/423379
123. Pelton SI, Loughlin AM, Marchant CD. Seven valent pneumococcal conjugate vaccine immunization in two Boston communities: changes in serotypes and antimicrobial susceptibility among Streptococcus pneumoniae isolates. Pediatr Infect Dis J 2004; 23:1015-22; PMID:15545856; http://dx.doi.org/10.1097/01.inf.0000143645.58215.f0
124. Huang SS, Platt R, Rifas-Shiman SL, Pelton SI, Goldmann D, Finkelstein JA. Post-PCV7 changes in colonizing pneumococcal serotypes in 16 Massachusetts communities, 2001 and 2004. Pediatrics 2005; 116:e408-13; PMID:16140686; http://dx.doi.org/10.1542/peds.2004-2338
125. Jones VF, Harrison C, Stout GG, Hopkins J. Nasopharyngeal colonization with heptavalent pneumococcal conjugate vaccine serotypes of Streptococcus pneumoniae with prolonged vaccine dosing intervals. Pediatr Infect Dis J 2005; 24:969-73; PMID:16282931; http://dx.doi.org/10.1097/01.inf.0000187030.83080.8a
126. Hammitt LL, Bruden DL, Butler JC, Baggett HC, Hurlburt DA, Reasonover A, Hennessy TW. Indirect effect of conjugate vaccine on adult carriage of Streptococcus pneumoniae: an explanation of trends in invasive pneumococcal disease. J Infect Dis 2006; 193:1487-94; PMID:16652275; http://dx.doi.org/10.1086/503805
127. Cohen R, Levy C, de La Rocque F, Gelbert N, Wollner A, Fritzell B, Bonnet E, Tetelboum R, Varon E. Impact of pneumococcal conjugate vaccine and of reduction of antibiotic use on nasopharyngeal carriage of nonsusceptible pneumococci in children with acute otitis media. Pediatr Infect Dis J 2006; 25:1001-7; PMID:17072121; http://dx.doi.org/10.1097/01.inf.0000243163.85163.a8
128. Dunais B, Bruno P, Carsenti-Dellamonica H, Touboul P, Dellamonica P, Pradier C. Trends in nasopharyngeal carriage of Streptococcus pneumoniae among children attending daycare centers in southeastern France from 1999 to 2006. Pediatr Infect Dis J 2008; 27:1033-5; PMID:18955896; http://dx.doi.org/10.1097/INF.0b013e31817bb8cf
129. Millar EV, Watt JP, Bronsdon MA, Dallas J, Reid R, Santosham M, O'Brien KL. Indirect effect of 7-valent pneumococcal conjugate vaccine on pneumococcal colonization among unvaccinated household members. Clin Infect Dis 2008; 47:989-96; PMID:18781875; http://dx.doi.org/10.1086/591966
130. Cheung YB, Zaman SM, Nsekpong ED, Van Beneden CA, Adegbola RA, Greenwood B, Cutts FT. Nasopharyngeal carriage of Streptococcus pneumoniae in Gambian children who participated in a 9-valent pneumococcal conjugate vaccine trial and in their younger siblings. Pediatr Infect Dis J 2009; 28:990-5; PMID:19536041; http://dx.doi.org/10.1097/INF.0b013e3181a78185
131. Huang SS, Hinrichsen VL, Stevenson AE, Rifas-Shiman SL, Kleinman K, Pelton SI, Lipsitch M, Hanage WP, Lee GM, Finkelstein JA. Continued impact of pneumococcal conjugate vaccine on carriage in young children. Pediatrics 2009; 124:e1-11; PMID:19564254; http://dx.doi.org/10.1542/peds.2008-3099
132. Spijkerman J, van Gils EJ, Veenhoven RH, Hak E, Yzerman EP, van der Ende A, Wijmenga-Monsuur AJ, van den Dobbelsteen GP, Sanders EA. Carriage of Streptococcus pneumoniae 3 years after start of vaccination program, the Netherlands. Emerg Infect Dis 2011; 17:584-91; PMID:21470445
133. Haber M, Barskey A, Baughman W, Barker L, Whitney CG, Shaw KM, Orenstein W, Stephens DS. Herd immunity and pneumococcal conjugate vaccine: a quantitative model. Vaccine 2007; 25:5390-8; PMID:17583392; http://dx.doi.org/10.1016/j.vaccine.2007.04.088
134. Cohen R, Levy C, Bingen E, Koskas M, Nave I, Varon E. Impact of 13-valent pneumococcal conjugate vaccine on pneumococcal nasopharyngeal carriage in children with acute otitis media. Pediatr Infect Dis J 2012; 31:297-301; PMID:22330166; http://dx.doi.org/10.1097/INF.0b013e318247ef84
135. De Wals P, Deceuninck G, Boulianne N, De Serres G. Effectiveness of a mass immunization campaign using serogroup C meningococcal conjugate vaccine. JAMA 2004; 292:2491-4; PMID:15562128; http://dx.doi.org/10.1001/jama.292.20.2491
136. Trotter CL, Andrews NJ, Kaczmarski EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 2004; 364:365-7; PMID:15276396; http://dx.doi.org/10.1016/S0140-6736(04)16725-1

137. Ramsay ME, Andrews NJ, Trotter CL, Kaczmarski EB, Miller E. Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis. BMJ 2003; 326:365-6; PMID:12586669; http://dx.doi.org/10.1136/bmj.326.7385.365
138. Maiden MC, Stuart JM; UK Meningococcal Carraige Group. Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. Lancet 2002; 359:1829-31; PMID:12044380; http://dx.doi.org/10.1016/S0140-6736(02)08679-8
139. Prymula R, Hanovcova I, Splino M, Kriz P, Motlova J, Lebedova V, Lommel P, Kaliskova E, Pascal T, Borys D, et al. Impact of the 10-valent pneumococcal non-typeable Haemophilus influenzae Protein D conjugate vaccine (PHiD-CV) on bacterial nasopharyngeal carriage. Vaccine 2011; 29:1959-67; PMID:21215830; http://dx.doi.org/10.1016/j.vaccine.2010.12.086
140. van den Bergh MR, Spijkerman J, Swinnen KM, François NA, Pascal TG, Borys D, Schuerman L, Ijzerman EP, Bruin JP, van der Ende A, et al. Effects of the 10-valent pneumococcal nontypeable Haemophilus influenzae protein D-conjugate vaccine on nasopharyngeal bacterial colonization in young children: a randomized controlled trial. Clin Infect Dis 2013; 56:e30-9; PMID:23118268; http://dx.doi.org/10.1093/cid/cis922
141. Schlesinger Y, Granoff DM; The Vaccine Study Group. Avidity and bactericidal activity of antibody elicited by different Haemophilus influenzae type b conjugate vaccines. JAMA 1992; 267:1489-94; PMID:1538539; http://dx.doi.org/10.1001/jama.1992.03480110065035
142. Lucas AH, Granoff DM. Functional differences in idiotypically defined IgG1 anti-polysaccharide antibodies elicited by vaccination with Haemophilus influenzae type B polysaccharide-protein conjugates. J Immunol 1995; 154:4195-202; PMID:7706754
143. Granoff DM, Harris SL. Protective activity of group C anticapsular antibodies elicited in two-year-olds by an investigational quadrivalent Neisseria meningitidis-diphtheria toxoid conjugate vaccine. Pediatr Infect Dis J 2004; 23:490-7; PMID:15194828; http://dx.doi.org/10.1097/01.inf.0000129686.12470.e6
144. Siskind GW, Benacerraf B. Cell selection by antigen in the immune response. Adv Immunol 1969; 10:1-50; PMID:4900673; http://dx.doi.org/10.1016/S0065-2776(08)60414-9
145. Denoël PA, Goldblatt D, de Vleeschauwer I, Jacquet JM, Pichichero ME, Poolman JT. Quality of the Haemophilus influenzae type b (Hib) antibody response induced by diphtheria-tetanus-acellular pertussis/Hib combination vaccines. Clin Vaccine Immunol 2007; 14:1362-9; PMID:17699836; http://dx.doi.org/10.1128/CVI.00154-07
146. Usinger WR, Lucas AH. Avidity as a determinant of the protective efficacy of human antibodies to pneumococcal capsular polysaccharides. Infect Immun 1999; 67:2366-70; PMID:10225896
147. Anttila M, Eskola J, Ahman H, Käyhty H. Differences in the avidity of antibodies evoked by four different pneumococcal conjugate vaccines in early childhood. Vaccine 1999; 17:1970-7; PMID:10217596; http://dx.doi.org/10.1016/S0264-410X(98)00458-7
148. Ekström N, Väkeväinen M, Verho J, Kilpi T, Käyhty H. Functional antibodies elicited by two heptavalent pneumococcal conjugate vaccines in the Finnish Otitis Media Vaccine Trial. Infect Immun 2007; 75:1794-800; PMID:17261612; http://dx.doi.org/10.1128/IAI.01673-06
149. Fairley CK, Begg N, Borrow R, Fox AJ, Jones DM, Cartwright K. Conjugate meningococcal serogroup A and C vaccine: reactogenicity and immunogenicity in United Kingdom infants. J Infect Dis 1996; 174:1360-3; PMID:8940235; http://dx.doi.org/10.1093/infdis/174.6.1360
150. Campagne G, Garba A, Fabre P, Schuchat A, Ryall R, Boulanger D, Bybel M, Carlone G, Briantais P, Ivanoff B, et al. Safety and immunogenicity of three doses of a Neisseria meningitidis A + C diphtheria conjugate vaccine in infants from Niger. Pediatr Infect Dis J 2000; 19:144-50; PMID:10694002; http://dx.doi.org/10.1097/00006454-200002000-00013
151. Miller E, Salisbury D, Ramsay M. Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. Vaccine 2001; 20(Suppl 1):S58-67; PMID:11587814; http://dx.doi.org/10.1016/S0264-410X(01)00299-7
152. Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. Lancet 2001; 357:195-6; PMID:11213098; http://dx.doi.org/10.1016/S0140-6736(00)03594-7
153. Zhang Q, Lakshman R, Burkinshaw R, Choo S, Everard J, Akhtar S, Finn A. Primary and booster mucosal immune responses to meningococcal group A and C conjugate and polysaccharide vaccines administered to university students in the United Kingdom. Infect Immun 2001; 69:4337-41; PMID:11401971; http://dx.doi.org/10.1128/IAI.69.7.4337-4341.2001
154. Rennels MB, Edwards KM, Keyserling HL, Reisinger K, Blatter MM, Quataert SA, Madore DV, Chang I, Malinoski FJ, Hackell JG, et al. Safety and immunogenicity of four doses of Neisseria meningitidis group C vaccine conjugated to CRM197 in United States infants. Pediatr Infect Dis J 2001; 20:153-9; PMID:11224833; http://dx.doi.org/10.1097/00006454-200102000-00007
155. Joseph H, Ryall R, Bybel M, Papa T, MacLennan J, Buttery J, Borrow R. Immunogenicity and immunological priming of the serogroup a portion of a bivalent meningococcal A/C conjugate vaccine in 2-year-old children. J Infect Dis 2003; 187:1142-6; PMID:12660929; http://dx.doi.org/10.1086/368358
156. De Wals P, Deceuninck G, De Serres G, Boivin JF, Duval B, Remis R, Massé R. Effectiveness of serogroup C meningococcal polysaccharide vaccine: results from a case-control study in Quebec. Clin Infect Dis 2005; 40:1116-22; PMID:15791510; http://dx.doi.org/10.1086/428729
157. Gray SJ, Trotter CL, Ramsay ME, Guiver M, Fox AJ, Borrow R, Mallard RH, Kaczmarski EB; Meningococcal Reference Unit. Epidemiology of meningococcal disease in England and Wales 1993/94 to 2003/04: contribution and experiences of the Meningococcal Reference Unit. J Med Microbiol 2006; 55:887-96; PMID:16772416; http://dx.doi.org/10.1099/jmm.0.46288-0
158. de Greeff SC, de Melker HE, Spanjaard L, Schouls LM, van Derende A. Protection from routine vaccination at the age of 14 months with meningococcal serogroup C conjugate vaccine in the Netherlands. Pediatr Infect Dis J 2006; 25:79-80; PMID:16395110; http://dx.doi.org/10.1097/01.inf.0000195594.41449.c6
159. Snape MD, Kelly DF, Salt P, Green S, Snowden C, Diggle L, Borkowski A, Yu LM, Moxon ER, Pollard AJ. Serogroup C meningococcal glycoconjugate vaccine in adolescents: persistence of bactericidal antibodies and kinetics of the immune response to a booster vaccine more than 3 years after immunization. Clin Infect Dis 2006; 43:1387-94; PMID:17083009; http://dx.doi.org/10.1086/508776
160. Trotter CL, Chandra M, Cano R, Larrauri A, Ramsay ME, Brehony C, Jolley KA, Maiden MC, Heuberger S, Frosch M. A surveillance network for meningococcal disease in Europe. FEMS Microbiol Rev 2007; 31:27-36; PMID:17168995; http://dx.doi.org/10.1111/j.1574-6976.2006.00060.x
161. Kshirsagar N, Mur N, Thatte U, Gogtay N, Viviani S, Préziosi MP, Elie C, Findlow H, Carlone G, Borrow R, et al. Safety, immunogenicity, and antibody persistence of a new meningococcal group A conjugate vaccine in healthy Indian adults. Vaccine 2007; 25(Suppl 1):A101-7; PMID:17532101; http://dx.doi.org/10.1016/j.vaccine.2007.04.050
162. Maiden MC, Ibarz-Pavón AB, Urwin R, Gray SJ, Andrews NJ, Clarke SC, Walker AM, Evans MR, Kroll JS, Neal KR, et al. Impact of meningococcal serogroup C conjugate vaccines on carriage and herd immunity. J Infect Dis 2008; 197:737-43; PMID:18271745; http://dx.doi.org/10.1086/527401
163. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R; Canadian Immunization Monitoring Program, Active (IMPACT). The impact of childhood meningococcal serogroup C conjugate vaccine programs in Canada. Pediatr Infect Dis J 2009; 28:220-4; PMID:19209096; http://dx.doi.org/10.1097/INF.0b013e31819040e7
164. De Wals P, Deceuninck G, Lefebvre B, Boulianne N, De Serres G. Effectiveness of serogroup C meningococcal conjugate vaccine: a 7-year follow-up in Quebec, Canada. Pediatr Infect Dis J 2011; 30:566-9; PMID:21326136; http://dx.doi.org/10.1097/INF.0b013e31820e8638
165. O'Brien KL, Steinhoff MC, Edwards K, Keyserling H, Thoms ML, Madore D. Immunologic priming of young children by pneumococcal glycoprotein conjugate, but not polysaccharide, vaccines. Pediatr Infect Dis J 1996; 15:425-30; PMID:8724065; http://dx.doi.org/10.1097/00006454-199605000-00009
166. Shelly MA, Jacoby H, Riley GJ, Graves BT, Pichichero M, Treanor JJ. Comparison of pneumococcal polysaccharide and CRM197-conjugated pneumococcal oligosaccharide vaccines in young and elderly adults. Infect Immun 1997; 65:242-7; PMID:8975918
167. Pichichero ME, Shelly MA, Treanor JJ. Evaluation of a pentavalent conjugated pneumococcal vaccine in toddlers. Pediatr Infect Dis J 1997; 16:72-4; PMID:9002106; http://dx.doi.org/10.1097/00006454-199701000-00016
168. Pichichero ME, Porcelli S, Treanor J, Anderson P. Serum antibody responses of weanling mice and two-year-old children to pneumococcal-type 6A-protein conjugate vaccines of differing saccharide chain lengths. Vaccine 1998; 16:83-91; PMID:9607014; http://dx.doi.org/10.1016/S0264-410X(97)00146-1
169. Käyhty H, Ahman H, Rönnberg PR, Tillikainen R, Eskola J. Pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine is immunogenic in infants and children. J Infect Dis 1995; 172:1273-8; PMID:7594664; http://dx.doi.org/10.1093/infdis/172.5.1273
170. Ahman H, Käyhty H, Tamminen P, Vuorela A, Malinoski F, Eskola J. Pentavalent pneumococcal oligosaccharide conjugate vaccine PncCRM is well-tolerated and able to induce an antibody response in infants. Pediatr Infect Dis J 1996; 15:134-9; PMID:8822286; http://dx.doi.org/10.1097/00006454-199602000-00009
171. Daum RS, Hogerman D, Rennels MB, Bewley K, Malinoski F, Rothstein E, Reisinger K, Block S, Keyserling H, Steinhoff M. Infant immunization with pneumococcal CRM197 vaccines: effect of saccharide size on immunogenicity and interactions with simultaneously administered vaccines. J Infect Dis 1997; 176:445-55; PMID:9237711; http://dx.doi.org/10.1086/514063
172. Shinefield HR, Black S, Ray P, Chang I, Lewis N, Fireman B, Hackell J, Paradiso PR, Siber G, Kohberger R, et al. Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers. Pediatr Infect Dis J 1999; 18:757-63; PMID:10493334; http://dx.doi.org/10.1097/00006454-199909000-00004

173. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, Elvin L, Ensor KM, Hackell J, Siber G, et al.; Northern California Kaiser Permanente Vaccine Study Center Group. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; 19:187-95; PMID:10749457; http://dx.doi.org/10.1097/00006454-200003000-00003
174. Choo S, Seymour L, Morris R, Quataert S, Lockhart S, Cartwright K, Finn A. Immunogenicity and reactogenicity of a pneumococcal conjugate vaccine administered combined with a haemophilus influenzae type B conjugate vaccine in United Kingdom infants. Pediatr Infect Dis J 2000; 19:854-62; PMID:11001109; http://dx.doi.org/10.1097/00006454-200009000-00009
175. Schmitt HJ, Faber J, Lorenz I, Schmöle-Thoma B, Ahlers N. The safety, reactogenicity and immunogenicity of a 7-valent pneumococcal conjugate vaccine (7VPnC) concurrently administered with a combination DTaP-IPV-Hib vaccine. Vaccine 2003; 21:3653-62; PMID:12922095; http://dx.doi.org/10.1016/S0264-410X(03)00389-X
176. Käyhty H, Ahman H, Eriksson K, Sörberg M, Nilsson L. Immunogenicity and tolerability of a heptavalent pneumococcal conjugate vaccine administered at 3, 5 and 12 months of age. Pediatr Infect Dis J 2005; 24:108-14; PMID:15702037; http://dx.doi.org/10.1097/01.inf.0000151022.92222.be
177. Bryant KA, Block SL, Baker SA, Gruber WC, Scott DA; PCV13 Infant Study Group. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. Pediatrics 2010; 125:866-75; PMID:20435707; http://dx.doi.org/10.1542/peds.2009-1405
178. Kieninger DM, Kueper K, Steul K, Juergens C, Ahlers N, Baker S, Jansen KU, Devlin C, Gruber WC, Emini EA, et al.; 006 study group. Safety, tolerability, and immunologic noninferiority of a 13-valent pneumococcal conjugate vaccine compared to a 7-valent pneumococcal conjugate vaccine given with routine pediatric vaccinations in Germany. Vaccine 2010; 28:4192-203; PMID:20417262; http://dx.doi.org/10.1016/j.vaccine.2010.04.008
179. Esposito S, Tansey S, Thompson A, Razmpour A, Liang J, Jones TR, Ferrera G, Maida A, Bona G, Sabatini C, et al. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine compared to those of a 7-valent pneumococcal conjugate vaccine given as a three-dose series with routine vaccines in healthy infants and toddlers. Clin Vaccine Immunol 2010; 17:1017-26; PMID:20427630; http://dx.doi.org/10.1128/CVI.00062-10
180. Yeh SH, Gurtman A, Hurley DC, Block SL, Schwartz RH, Patterson S, Jansen KU, Love J, Gruber WC, Emini EA, et al.; 004 Study Group. Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in infants and toddlers. Pediatrics 2010; 126:e493-505; PMID:20732948; http://dx.doi.org/10.1542/peds.2009-3027
181. Snape MD, Klinger CL, Daniels ED, John TM, Layton H, Rollinson L, Pestridge S, Dymond S, Galiza E, Tansey S, et al. Immunogenicity and reactogenicity of a 13-valent-pneumococcal conjugate vaccine administered at 2, 4, and 12 months of age: a double-blind randomized active-controlled trial. Pediatr Infect Dis J 2010; 29:e80-90; PMID:21155091; http://dx.doi.org/10.1097/INF.0b013e3181faa6be
182. Vanderkooi OG, Scheifele DW, Girgenti D, Halperin SA, Patterson SD, Gruber WC, Emini EA, Scott DA, Kellner JD; Canadian PCV13 Study Group. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine in healthy infants and toddlers given with routine pediatric vaccinations in Canada. Pediatr Infect Dis J 2012; 31:72-7; PMID:21960186; http://dx.doi.org/10.1097/INF.0b013e318233049d
183. Huang LM, Lin TY, Juergens C. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine given with routine pediatric vaccines in Taiwan. Vaccine 2012; 30:2054-9; PMID:22198517; http://dx.doi.org/10.1016/j.vaccine.2011.12.054
184. Amdekar YK, Lalwani SK, Bavdekar A, Balasubramanian S, Chhatwal J, Bhat SR, Verghese VP, Tansey SP, Gadgil D, Jiang Q, et al. Immunogenicity and Safety of a 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants and Toddlers Given With Routine Vaccines in India. Pediatr Infect Dis J 2013; 32:509-16; PMID:23190777; http://dx.doi.org/10.1097/INF.0b013e31827b478d
185. Black SB, Shinefield HR, Hansen J, Elvin L, Laufer D, Malinoski F. Postlicensure evaluation of the effectiveness of seven valent pneumococcal conjugate vaccine. Pediatr Infect Dis J 2001; 20:1105-7; PMID:11740313; http://dx.doi.org/10.1097/00006454-200112000-00002
186. Black SB, Shinefield HR, Ling S, Hansen J, Fireman B, Spring D, Noyes J, Lewis E, Ray P, Lee J, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. Pediatr Infect Dis J 2002; 21:810-5; PMID:12352800; http://dx.doi.org/10.1097/00006454-200209000-00005
187. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, Reingold A, Cieslak PR, Pilishvili T, Jackson D, et al.; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003; 348:1737-46; PMID:12724479; http://dx.doi.org/10.1056/NEJMoa022823
188. Black S, Shinefield H, Baxter R, Austrian R, Bracken L, Hansen J, Lewis E, Fireman B. Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in Northern California Kaiser Permanente. Pediatr Infect Dis J 2004; 23:485-9; PMID:15194827; http://dx.doi.org/10.1097/01.inf.0000129685.04847.94
189. Whitney CG, Pilishvili T, Farley MM, Schaffner W, Craig AS, Lynfield R, Nyquist AC, Gershman KA, Vazquez M, Bennett NM, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet 2006; 368:1495-502; PMID:17071283; http://dx.doi.org/10.1016/S0140-6736(06)69637-2
190. Sharma D, Baughman W, Holst A, Thomas S, Jackson D, da Gloria Carvalho M, Beall B, Satola S, Jerris R, Jain S, et al. Pneumococcal carriage and invasive disease in children before introduction of the 13-valent conjugate vaccine: comparison with the era before 7-valent conjugate vaccine. Pediatr Infect Dis J 2013; 32:e45-53; PMID:23080290; http://dx.doi.org/10.1097/INF.0b013e3182788fdd
191. Snape MD, Perrett KP, Ford KJ, John TM, Pace D, Yu LM, Langley JM, McNeil S, Dull PM, Ceddia F, et al. Immunogenicity of a tetravalent meningococcal glycoconjugate vaccine in infants: a randomized controlled trial. JAMA 2008; 299:173-84; PMID:18182599; http://dx.doi.org/10.1001/jama.2007.29-c
192. Jackson LA, Baxter R, Reisinger K, Karsten A, Shah J, Bedell L, Dull PM; V59P13 Study Group. Phase III comparison of an investigational quadrivalent meningococcal conjugate vaccine with the licensed meningococcal ACWY conjugate vaccine in adolescents. Clin Infect Dis 2009; 49:e1-10; PMID:19476428; http://dx.doi.org/10.1086/599117
193. Perrett KP, Snape MD, Ford KJ, John TM, Yu LM, Langley JM, McNeil S, Dull PM, Ceddia F, Anemona A, et al. Immunogenicity and immune memory of a nonadjuvanted quadrivalent meningococcal glycoconjugate vaccine in infants. Pediatr Infect Dis J 2009; 28:186-93; PMID:19209097; http://dx.doi.org/10.1097/INF.0b013e31818e037d
194. Jackson LA, Jacobson RM, Reisinger KS, Anemona A, Danzig LE, Dull PM. A randomized trial to determine the tolerability and immunogenicity of a quadrivalent meningococcal glycoconjugate vaccine in healthy adolescents. Pediatr Infect Dis J 2009; 28:86-91; PMID:19116603; http://dx.doi.org/10.1097/INF.0b013e31818a0237
195. Halperin SA, Diaz-Mitoma F, Dull P, Anemona A, Ceddia F. Safety and immunogenicity of an investigational quadrivalent meningococcal conjugate vaccine after one or two doses given to infants and toddlers. Eur J Clin Microbiol Infect Dis 2010; 29:259-67; PMID:20033465; http://dx.doi.org/10.1007/s10096-009-0848-8
196. Black S, Klein NP, Shah J, Bedell L, Karsten A, Dull PM. Immunogenicity and tolerability of a quadrivalent meningococcal glycoconjugate vaccine in children 2-10 years of age. Vaccine 2010; 28:657-63; PMID:19895922; http://dx.doi.org/10.1016/j.vaccine.2009.10.104
197. Arguedas A, Soley C, Loaiza C, Rincon G, Guevara S, Perez A, Porras W, Alvarado O, Aguilar L, Abdelnour A, et al. Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines. Vaccine 2010; 28:3171-9; PMID:20189491; http://dx.doi.org/10.1016/j.vaccine.2010.02.045
198. Gasparini R, Conversano M, Bona G, Gabutti G, Anemona A, Dull PM, Ceddia F. Randomized trial on the safety, tolerability, and immunogenicity of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, administered concomitantly with a combined tetanus, reduced diphtheria, and acellular pertussis vaccine in adolescents and young adults. Clin Vaccine Immunol 2010; 17:537-44; PMID:20164251; http://dx.doi.org/10.1128/CVI.00436-09
199. Klein NP, Reisinger KS, Johnston W, Odrljin T, Gill CJ, Bedell L, Dull P. Safety and immunogenicity of a novel quadrivalent meningococcal CRM-conjugate vaccine given concomitantly with routine vaccinations in infants. Pediatr Infect Dis J 2012; 31:64-71; PMID:22094635; http://dx.doi.org/10.1097/INF.0b013e31823dce5c
200. Rennels M, King J Jr., Ryall R, Papa T, Froeschle J. Dosage escalation, safety and immunogenicity study of four dosages of a tetravalent meninogococcal polysaccharide diphtheria toxoid conjugate vaccine in infants. Pediatr Infect Dis J 2004; 23:429-35; PMID:15131466; http://dx.doi.org/10.1097/01.inf.0000126297.28952.f8
201. Granoff DM, Morgan A, Welsch JA. Persistence of group C anticapsular antibodies two to three years after immunization with an investigational quadrivalent Neisseria meningitidis-diphtheria toxoid conjugate vaccine. Pediatr Infect Dis J 2005; 24:132-6; PMID:15702041; http://dx.doi.org/10.1097/01.inf.0000151035.64356.f8
202. Pichichero M, Casey J, Blatter M, Rothstein E, Ryall R, Bybel M, Gilmet G, Papa T. Comparative trial of the safety and immunogenicity of quadrivalent (A, C, Y, W-135) meningococcal polysaccharide-diphtheria conjugate vaccine versus quadrivalent polysaccharide vaccine in two- to ten-year-old children. Pediatr Infect Dis J 2005; 24:57-62; PMID:15665711; http://dx.doi.org/10.1097/01.inf.0000148928.10057.86

203. Macneil JR, Cohn AC, Zell ER, Schmink S, Miller E, Clark T, Messonnier NE; Active Bacterial Core surveillance (ABCs) Team and MeningNet Surveillance Partners. Early estimate of the effectiveness of quadrivalent meningococcal conjugate vaccine. Pediatr Infect Dis J 2011; 30:451-5; PMID:21206392
204. Pina LM, Bassily E, Machmer A, Hou V, Reinhardt A. Safety and immunogenicity of a quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine in infants and toddlers: three multicenter phase III studies. Pediatr Infect Dis J 2012; 31:1173-83; PMID:22814965; http://dx.doi.org/10.1097/INF.0b013e318268dfe4
205. Campbell JD, Edelman R, King JC Jr., Papa T, Ryall R, Rennels MB. Safety, reactogenicity, and immunogenicity of a tetravalent meningococcal polysaccharide-diphtheria toxoid conjugate vaccine given to healthy adults. J Infect Dis 2002; 186:1848-51; PMID:12447774; http://dx.doi.org/10.1086/345763
206. Knuf M, Kieninger-Baum D, Habermehl P, Muttonen P, Maurer H, Vink P, Poolman J, Boutriau D. A dose-range study assessing immunogenicity and safety of one dose of a new candidate meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate (MenACWY-TT) vaccine administered in the second year of life and in young children. Vaccine 2010; 28:744-53; PMID:19887137; http://dx.doi.org/10.1016/j.vaccine.2009.10.064
207. Ostergaard L, Lebacq E, Poolman J, Maechler G, Boutriau D. Immunogenicity, reactogenicity and persistence of meningococcal A, C, W-135 and Y-tetanus toxoid candidate conjugate (MenACWY-TT) vaccine formulations in adolescents aged 15-25 years. Vaccine 2009; 27:161-8; PMID:18834910; http://dx.doi.org/10.1016/j.vaccine.2008.08.075
208. Vesikari T, Forstén A, Boutriau D, Bianco V, Van der Wielen M, Miller JM. A randomized study to assess the immunogenicity, antibody persistence and safety of a tetravalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine in children aged 2-10 years. Hum Vaccin Immunother 2012; 8:1882-91; PMID:23032168; http://dx.doi.org/10.4161/hv.22165
209. Vesikari T, Karvonen A, Bianco V, Van der Wielen M, Miller J. Tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine is well tolerated and immunogenic when co-administered with measles-mumps-rubella-varicella vaccine during the second year of life: An open, randomized controlled trial. Vaccine 2011; 29:4274-84; PMID:21443965; http://dx.doi.org/10.1016/j.vaccine.2011.03.043
210. Memish ZA, Dbaibo G, Montellano M, Verghese VP, Jain H, Dubey AP, Bianco V, Van der Wielen M, Gatchalian S, Miller JM. Immunogenicity of a single dose of tetravalent meningococcal serogroups A, C, W-135, and Y conjugate vaccine administered to 2- to 10-year-olds is noninferior to a licensed-ACWY polysaccharide vaccine with an acceptable safety profile. Pediatr Infect Dis J 2011; 30:e56-62; PMID:21278617; http://dx.doi.org/10.1097/INF.0b013e31820e6e02
211. Baxter R, Baine Y, Ensor K, Bianco V, Friedland LR, Miller JM. Immunogenicity and safety of an investigational quadrivalent meningococcal ACWY tetanus toxoid conjugate vaccine in healthy adolescents and young adults 10 to 25 years of age. Pediatr Infect Dis J 2011; 30:e41-8; PMID:21200360; http://dx.doi.org/10.1097/INF.0b013e3182054ab9
212. Bermal N, Huang LM, Dubey AP, Jain H, Bavdekar A, Lin TY, Bianco V, Baine Y, Miller JM. Safety and immunogenicity of a tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine in adolescents and adults. Hum Vaccin 2011; 7:239-47; PMID:21343698; http://dx.doi.org/10.4161/hv.7.2.14068
213. Dbaibo G, Macalalad N, Aplasca-De Los Reyes MR, Dimaano E, Bianco V, Baine Y, Miller J. The immunogenicity and safety of an investigational meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (ACWY-TT) compared with a licensed meningococcal tetravalent polysaccharide vaccine: a randomized, controlled non-inferiority study. Hum Vaccin Immunother 2012; 8:873-80; PMID:22485050; http://dx.doi.org/10.4161/hv.20211
214. Marshall GS, Marchant CD, Blatter M, Friedland LR, Aris E, Miller JM. Co-administration of a novel Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine does not interfere with the immune response to antigens contained in infant vaccines routinely used in the United States. Hum Vaccin 2011; 7:258-64; PMID:21307655; http://dx.doi.org/10.4161/hv.7.2.14170
215. Nolan T, Richmond P, Marshall H, McVernon J, Alexander K, Mesaros N, Aris E, Miller J, Poolman J, Boutriau D. Immunogenicity and safety of an investigational combined haemophilus influenzae type B-Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine. Pediatr Infect Dis J 2011; 30:190-6; PMID:20948453; http://dx.doi.org/10.1097/INF.0b013e3181fcb2bf
216. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, Takala A, Käyhty H, Karma P, Kohberger R, et al.; Finnish Otitis Media Study Group. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001; 344:403-9; PMID:11172176; http://dx.doi.org/10.1056/NEJM200102083440602
217. O'Brien KL, Moulton LH, Reid R, Weatherholtz R, Oski J, Brown L, Kumar G, Parkinson A, Hu D, Hackell J, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. Lancet 2003; 362:355-61; PMID:12907008; http://dx.doi.org/10.1016/S0140-6736(03)14022-6
218. Kilpi T, Ahman H, Jokinen J, Lankinen KS, Palmu A, Savolainen H, Grönholm M, Leinonen M, Hovi T, Eskola J, et al.; Finnish Otitis Media Study Group. Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children: randomized, controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine in 1666 children. Clin Infect Dis 2003; 37:1155-64; PMID:14557958; http://dx.doi.org/10.1086/378744
219. Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E, Kohl I, Lommel P, Poolman J, Prieels JP, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable Haemophilus influenzae: a randomised double-blind efficacy study. Lancet 2006; 367:740-8; PMID:16517274; http://dx.doi.org/10.1016/S0140-6736(06)68304-9
220. Prymula R, Chlibek R, Splino M, Kaliskova E, Kohl I, Lommel P, Schuerman L. Safety of the 11-valent pneumococcal vaccine conjugated to non-typeable Haemophilus influenzae-derived protein D in the first 2 years of life and immunogenicity of the co-administered hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio virus, Haemophilus influenzae type b and control hepatitis A vaccines. Vaccine 2008; 26:4563-70; PMID:18602724; http://dx.doi.org/10.1016/j.vaccine.2008.05.080
221. Knuf M, Szenborn L, Moro M, Petit C, Bermal N, Bernard L, Dieussaert I, Schuerman L. Immunogenicity of routinely used childhood vaccines when coadministered with the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV). Pediatr Infect Dis J 2009; 28(Suppl):S97-108; PMID:19325452; http://dx.doi.org/10.1097/INF.0b013e318199f61b
222. Palmu AA, Jokinen J, Borys D, Nieminen H, Ruokokoski E, Siira L, Puumalainen T, Lommel P, Hezareh M, Moreira M, et al. Effectiveness of the ten-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: a cluster randomised trial. Lancet 2013; 381:214-22; PMID:23158882; http://dx.doi.org/10.1016/S0140-6736(12)61854-6
223. Wuorimaa T, Dagan R, Eskola J, Janco J, Ahman H, Leroy O, Käyhty H. Tolerability and immunogenicity of an eleven-valent pneumococcal conjugate vaccine in healthy toddlers. Pediatr Infect Dis J 2001; 20:272-7; PMID:11303829; http://dx.doi.org/10.1097/00006454-200103000-00011
224. Wuorimaa T, Dagan R, Väkeväinen M, Bailleux F, Haikala R, Yaich M, Eskola J, Käyhty H. Avidity and subclasses of IgG after immunization of infants with an 11-valent pneumococcal conjugate vaccine with or without aluminum adjuvant. J Infect Dis 2001; 184:1211-5; PMID:11598848; http://dx.doi.org/10.1086/323648
225. Puumalainen T, Zeta-Capeding MR, Käyhty H, Lucero MG, Auranen K, Leroy O, Nohynek H. Antibody response to an eleven valent diphtheria- and tetanus-conjugated pneumococcal conjugate vaccine in Filipino infants. Pediatr Infect Dis J 2002; 21:309-14; PMID:12075762; http://dx.doi.org/10.1097/00006454-200204000-00010
226. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N; Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003; 349:1341-8; PMID:14523142; http://dx.doi.org/10.1056/NEJMoa035060
227. Puumalainen T, Dagan R, Wuorimaa T, Zeta-Capeding R, Lucero M, Ollgren J, Käyhty H, Nohynek H. Greater antibody responses to an eleven valent mixed carrier diphtheria- or tetanus-conjugated pneumococcal vaccine in Filipino than in Finnish or Israeli infants. Pediatr Infect Dis J 2003; 22:141-9; PMID:12586978; http://dx.doi.org/10.1097/01.inf.0000050459.74134.d5
228. Puumalainen T, Ekström N, Zeta-Capeding R, Ollgren J, Jousimies K, Lucero M, Nohynek H, Käyhty H. Functional antibodies elicited by an 11-valent diphtheria-tetanus toxoid-conjugated pneumococcal vaccine. J Infect Dis 2003; 187:1704-8; PMID:12751027; http://dx.doi.org/10.1086/375242
229. Dagan R, Goldblatt D, Maleckar JR, Yaïch M, Eskola J. Reduction of antibody response to an 11-valent pneumococcal vaccine coadministered with a vaccine containing acellular pertussis components. Infect Immun 2004; 72:5383-91; PMID:15322036; http://dx.doi.org/10.1128/IAI.72.9.5383-5391.2004
230. Lucero MG, Puumalainen T, Ugpo JM, Williams G, Käyhty H, Nohynek H. Similar antibody concentrations in Filipino infants at age 9 months, after 1 or 3 doses of an adjuvanted, 11-valent pneumococcal diphtheria/tetanus-conjugated vaccine: a randomized controlled trial. J Infect Dis 2004; 189:2077-84; PMID:15143476; http://dx.doi.org/10.1086/420849
231. Dagan R, Kayhty H, Wuorimaa T, Yaich M, Bailleux F, Zamir O, Eskola J. Tolerability and immunogenicity of an eleven valent mixed carrier Streptococcus pneumoniae capsular polysaccharide-diphtheria toxoid or tetanus protein conjugate vaccine in Finnish and Israeli infants. Pediatr Infect Dis J 2004; 23:91-8; PMID:14872172; http://dx.doi.org/10.1097/01.inf.0000109221.50972.53

232. Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, Oluwalana C, Vaughan A, Obaro SK, Leach A, et al.; Gambian Pneumococcal Vaccine Trial Group. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet 2005; 365:1139-46; PMID:15794968; http://dx.doi.org/10.1016/S0140-6736(05)71876-6
233. Vesikari T, Wysocki J, Chevallier B, Karvonen A, Czajka H, Arsène JP, Lommel P, Dieussaert I, Schuerman L. Immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) compared to the licensed 7vCRM vaccine. Pediatr Infect Dis J 2009; 28(Suppl):S66-76; PMID:19325449; http://dx.doi.org/10.1097/INF.0b013e318199f8ef
234. Chan CY, Molrine DC, George S, Tarbell NJ, Mauch P, Diller L, Shamberger RC, Phillips NR, Goorin A, Ambrosino DM. Pneumococcal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treatment of Hodgkin's disease. J Infect Dis 1996; 173:256-8; PMID:8537671; http://dx.doi.org/10.1093/infdis/173.1.256
235. Leach A, Ceesay SJ, Banya WA, Greenwood BM. Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants. Pediatr Infect Dis J 1996; 15:333-9; PMID:8866803; http://dx.doi.org/10.1097/00006454-199604000-00010
236. King JC Jr., Vink PE, Farley JJ, Smilie M, Parks M, Lichenstein R. Safety and immunogenicity of three doses of a five-valent pneumococcal conjugate vaccine in children younger than two years with and without human immunodeficiency virus infection. Pediatrics 1997; 99:575-80; PMID:9093301; http://dx.doi.org/10.1542/peds.99.4.575
237. Sorensen RU, Leiva LE, Giangrosso PA, Butler B, Javier FC 3rd, Sacerdote DM, Bradford N, Moore C. Response to a heptavalent conjugate Streptococcus pneumoniae vaccine in children with recurrent infections who are unresponsive to the polysaccharide vaccine. Pediatr Infect Dis J 1998; 17:685-91; PMID:9726341; http://dx.doi.org/10.1097/00006454-199808000-00005
238. Miernyk KM, Parkinson AJ, Rudolph KM, Petersen KM, Bulkow LR, Greenberg DP, Ward JI, Brenneman G, Reid R, Santosham M. Immunogenicity of a heptavalent pneumococcal conjugate vaccine in Apache and Navajo Indian, Alaska native, and non-native American children aged <2 years. Clin Infect Dis 2000; 31:34-41; PMID:10913393; http://dx.doi.org/10.1086/313907
239. Obaro SK, Adegbola RA, Chang I, Banya WA, Jaffar S, Mcadam KW, Greenwood BM. Safety and immunogenicity of a nonavalent pneumococcal vaccine conjugated to CRM197 administered simultaneously but in a separate syringe with diphtheria, tetanus and pertussis vaccines in Gambian infants. Pediatr Infect Dis J 2000; 19:463-9; PMID:10819345; http://dx.doi.org/10.1097/00006454-200005000-00014
240. Obaro SK, Enwere GC, Deloria M, Jaffar S, Goldblatt D, Brainsby K, Hallander H, McInnes P, Greenwood BM, McAdam KP. Safety and immunogenicity of pneumococcal conjugate vaccine in combination with diphtheria, tetanus toxoid, pertussis and Haemophilus influenzae type b conjugate vaccine. Pediatr Infect Dis J 2002; 21:940-7; PMID:12394817; http://dx.doi.org/10.1097/00006454-200210000-00011
241. Huebner RE, Mbelle N, Forrest B, Madore DV, Klugman KP. Immunogenicity after one, two or three doses and impact on the antibody response to coadministered antigens of a nonavalent pneumococcal conjugate vaccine in infants of Soweto, South Africa. Pediatr Infect Dis J 2002; 21:1004-7; PMID:12442020; http://dx.doi.org/10.1097/00006454-200211000-00006
242. Kumar D, Rotstein C, Miyata G, Arlen D, Humar A. Randomized, double-blind, controlled trial of pneumococcal vaccination in renal transplant recipients. J Infect Dis 2003; 187:1639-45; PMID:12721944; http://dx.doi.org/10.1086/374784
243. Nachman S, Kim S, King J, Abrams EJ, Margolis D, Petru A, Shearer W, Smith E, Moye J, Blanchard S, et al.; Pediatric AIDS Clinical Trials Group Study 292 Team. Safety and immunogenicity of a heptavalent pneumococcal conjugate vaccine in infants with human immunodeficiency virus type 1 infection. Pediatrics 2003; 112:66-73; PMID:12837869; http://dx.doi.org/10.1542/peds.112.1.66
244. Madhi SA, Klugman KP, Kuwanda L, Cutland C, Käyhty H, Adrian P. Quantitative and qualitative anamnestic immune responses to pneumococcal conjugate vaccine in HIV-infected and HIV-uninfected children 5 years after vaccination. J Infect Dis 2009; 199:1168-76; PMID:19265481; http://dx.doi.org/10.1086/597388
245. Cordonnier C, Labopin M, Chesnel V, Ribaud P, De La Camara R, Martino R, Ullmann AJ, Parkkali T, Locasciulli A, Yakouben K, et al.; Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Randomized study of early versus late immunization with pneumococcal conjugate vaccine after allogeneic stem cell transplantation. Clin Infect Dis 2009; 48:1392-401; PMID:19368505; http://dx.doi.org/10.1086/598324
246. Anderson EL, Bowers T, Mink CM, Kennedy DJ, Belshe RB, Harakeh H, Pais L, Holder P, Carlone GM. Safety and immunogenicity of meningococcal A and C polysaccharide conjugate vaccine in adults. Infect Immun 1994; 62:3391-5; PMID:8039909
247. Harris SL, Finn A, Granoff DM. Disparity in functional activity between serum anticapsular antibodies induced in adults by immunization with an investigational group A and C Neisseria meningitidis-diphtheria toxoid conjugate vaccine and by a polysaccharide vaccine. Infect Immun 2003; 71:3402-8; PMID:12761124; http://dx.doi.org/10.1128/IAI.71.6.3402-3408.2003
248. Musher DM, Rueda AM, Nahm MH, Graviss EA, Rodriguez-Barradas MC. Initial and subsequent response to pneumococcal polysaccharide and protein-conjugate vaccines administered sequentially to adults who have recovered from pneumococcal pneumonia. J Infect Dis 2008; 198:1019-27; PMID:18710324; http://dx.doi.org/10.1086/591629
249. Reisinger KS, Baxter R, Block SL, Shah J, Bedell L, Dull PM. Quadrivalent meningococcal vaccination of adults: phase III comparison of an investigational conjugate vaccine, MenACWY-CRM, with the licensed vaccine, Menactra. Clin Vaccine Immunol 2009; 16:1810-5; PMID:19812260; http://dx.doi.org/10.1128/CVI.00207-09
250. Miernyk KM, Butler JC, Bulkow LR, Singleton RJ, Hennessy TW, Dentinger CM, Peters HV, Knutsen B, Hickel J, Parkinson AJ. Immunogenicity and reactogenicity of pneumococcal polysaccharide and conjugate vaccines in alaska native adults 55-70 years of age. Clin Infect Dis 2009; 49:241-8; PMID:19522655; http://dx.doi.org/10.1086/599824
251. Stamboulian D, Lopardo G, Lopez P, Cortes-Barbosa C, Valencia A, Bedell L, Karsten A, Dull PM. Safety and immunogenicity of an investigational quadrivalent meningococcal CRM(197) conjugate vaccine, MenACWY-CRM, compared with licensed vaccines in adults in Latin America. Int J Infect Dis 2010; 14:e868-75; PMID:20655261; http://dx.doi.org/10.1016/j.ijid.2010.03.017
252. Lazarus R, Clutterbuck E, Yu LM, Bowman J, Bateman EA, Diggle L, Angus B, Peto TE, Beverley PC, Mant D, et al. A randomized study comparing combined pneumococcal conjugate and polysaccharide vaccination schedules in adults. Clin Infect Dis 2011; 52:736-42; PMID:21367726; http://dx.doi.org/10.1093/cid/cir003
253. Schutze MP, Leclerc C, Vogel FR, Chedid L. Epitopic suppression in synthetic vaccine models: analysis of the effector mechanisms. Cell Immunol 1987; 104:79-90; PMID:2433056; http://dx.doi.org/10.1016/0008-8749(87)90008-6
254. Herzenberg LA, Tokuhisa T, Herzenberg LA. Carrier-priming leads to hapten-specific suppression. Nature 1980; 285:664-7; PMID:6967189; http://dx.doi.org/10.1038/285664a0
255. Schutze MP, Deriaud E, Przewlocki G, LeClerc C. Carrier-induced epitopic suppression is initiated through clonal dominance. J Immunol 1989; 142:2635-40; PMID:2467933
256. Barington T, Kristensen K, Henrichsen J, Heilmann C. Influence of prevaccination immunity on the human B-lymphocyte response to a Haemophilus influenzae type b conjugate vaccine. Infect Immun 1991; 59:1057-64; PMID:1997409
257. Barington T, Skettrup M, Juul L, Heilmann C. Non-epitope-specific suppression of the antibody response to Haemophilus influenzae type b conjugate vaccines by preimmunization with vaccine components. Infect Immun 1993; 61:432-8; PMID:7678586
258. Dagan R, Eskola J, Leclerc C, Leroy O. Reduced response to multiple vaccines sharing common protein epitopes that are administered simultaneously to infants. Infect Immun 1998; 66:2093-8; PMID:9573094
259. Renjifo X, Wolf S, Pastoret PP, Bazin H, Urbain J, Leo O, Moser M. Carrier-induced, hapten-specific suppression: a problem of antigen presentation? J Immunol 1998; 161:702-6; PMID:9670945
260. Fattom A, Cho YH, Chu C, Fuller S, Fries L, Naso R. Epitopic overload at the site of injection may result in suppression of the immune response to combined capsular polysaccharide conjugate vaccines. Vaccine 1999; 17:126-33; PMID:9987146; http://dx.doi.org/10.1016/S0264-410X(98)00162-5
261. Rennels MB, Englund JA, Bernstein DI, Losonsky GA, Anderson EL, Pichichero ME, Munoz FM, Wolff MC. Diminution of the anti-polyribosylribitol phosphate response to a combined diphtheria-tetanus-acellular pertussis/Haemophilus influenzae type b vaccine by concurrent inactivated poliovirus vaccination. Pediatr Infect Dis J 2000; 19:417-23; PMID:10819337; http://dx.doi.org/10.1097/00006454-200005000-00006
262. Lin TY, Wang YH, Chang LY, Chiu CH, Huang YC, Tang H, Bock HL. Safety and immunogenicity of a diphtheria, tetanus, and acellular pertussis-inactivated poliovirus vaccine/Haemophilus influenzae type B combination vaccine administered to Taiwanese infants at 2, 4, and 6 months of age. Chang Gung Med J 2003; 26:315-22; PMID:12934847
263. Carlsson RM, Claesson BA, Selstam U, Fagerlund E, Granström M, Blondeau C, Hoffenbach A. Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-Haemophilus influenzae type b vaccine administered at 2-4-6-13 or 3-5-12 months of age. Pediatr Infect Dis J 1998; 17:1026-33; PMID:9849987; http://dx.doi.org/10.1097/00006454-199811000-00013
264. Gold R, Scheifele D, Barreto L, Wiltsey S, Bjornson G, Meekison W, Guasparini R, Medd L. Safety and immunogenicity of Haemophilus influenzae vaccine (tetanus toxoid conjugate) administered concurrently or combined with diphtheria and tetanus toxoids, pertussis vaccine and inactivated poliomyelitis vaccine to healthy infants at two, four and six months of age. Pediatr Infect Dis J 1994; 13:348-55; PMID:8072815; http://dx.doi.org/10.1097/00006454-199405000-00004

265. Jones IG, Tyrrell H, Hill A, Horobin JM, Taylor B. Randomised controlled trial of combined diphtheria, tetanus, whole-cell pertussis vaccine administered in the same syringe and separately with Haemophilus influenzae type b vaccine at two, three and four months of age. Vaccine 1998; 16:109-13; PMID:9607017; http://dx.doi.org/10.1016/S0264-410X(97)00161-8
266. Burrage M, Robinson A, Borrow R, Andrews N, Southern J, Findlow J, Martin S, Thornton C, Goldblatt D, Corbel M, et al. Effect of vaccination with carrier protein on response to meningococcal C conjugate vaccines and value of different immunoassays as predictors of protection. Infect Immun 2002; 70:4946-54; PMID:12183540; http://dx.doi.org/10.1128/IAI.70.9.4946-4954.2002
267. Trotter CL, Ramsay ME, Slack MP. Rising incidence of Haemophilus influenzae type b disease in England and Wales indicates a need for a second catch-up vaccination campaign. Commun Dis Public Health 2003; 6:55-8; PMID:12736974
268. Swartley JS, Marfin AA, Edupuganti S, Liu LJ, Cieslak P, Perkins B, Wenger JD, Stephens DS. Capsule switching of Neisseria meningitidis. Proc Natl Acad Sci U S A 1997; 94:271-6; PMID:8990198; http://dx.doi.org/10.1073/pnas.94.1.271
269. Ko KS, Baek JY, Song JH. Capsular gene sequences and genotypes of 'serotype 6E' Streptococcus pneumoniae isolates. J Clin Microbiol 2013; PMID:23824778; http://dx.doi.org/10.1128/JCM.01645-13
270. Richter SS, Heilmann KP, Dohrn CL, Riahi F, Diekema DJ, Doern GV. Pneumococcal serotypes before and after introduction of conjugate vaccines, United States, 1999-2011(1.). Emerg Infect Dis 2013; 19:1074-83; PMID:23763847; http://dx.doi.org/10.3201/eid1907.121830
271. Moffitt KL, Malley R. Next generation pneumococcal vaccines. Curr Opin Immunol 2011; 23:407-13; PMID:21514128; http://dx.doi.org/10.1016/j.coi.2011.04.002
272. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. Lancet 2011; 378:1962-73; PMID:21492929; http://dx.doi.org/10.1016/S0140-6736(10)62225-8
273. Beall BW, Gertz RE, Hulkower RL, Whitney CG, Moore MR, Brueggemann AB. Shifting genetic structure of invasive serotype 19A pneumococci in the United States. J Infect Dis 2011; 203:1360-8; PMID:21398395; http://dx.doi.org/10.1093/infdis/jir052
274. Pichichero ME, Casey JR. Emergence of a multiresistant serotype 19A pneumococcal strain not included in the 7-valent conjugate vaccine as an otopathogen in children. JAMA 2007; 298:1772-8; PMID:17940232; http://dx.doi.org/10.1001/jama.298.15.1772
275. Blum MD, Dagan R, Mendelman PM, Pinsk V, Giordani M, Li S, Bohidar N, McNeely TB. A comparison of multiple regimens of pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine and pneumococcal polysaccharide vaccine in toddlers. Vaccine 2000; 18:2359-67; PMID:10738092; http://dx.doi.org/10.1016/S0264-410X(00)00021-9
276. Zangwill KM, Greenberg DP, Chiu CY, Mendelman P, Wong VK, Chang SJ, Partridge S, Ward JI. Safety and immunogenicity of a heptavalent pneumococcal conjugate vaccine in infants. Vaccine 2003; 21:1894-900; PMID:12706674; http://dx.doi.org/10.1016/S0264-410X(03)00013-6