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Review

Overview of the development and current use of CRM_{197} conjugate vaccines for pediatric use

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ABSTRACT

Glycoconjugate vaccines have been proven safe and effective against various diseases in children. Although these vaccines have a history of effectiveness, there are still many unanswered questions to be addressed, including conjugate interference when multiple vaccines are administered at one time, expansion of serotype coverage, effectiveness in special populations, and issues relating to conjugate vaccine use in the developing world. This paper focuses on the use of CRM_{197} as a carrier protein, contrasting it to other carrier proteins used in single-antigen pediatric vaccines as well as identifying areas for future study.

Contents

1. Introduction

Since their introduction in the 1980s [1], glycoconjugate vaccines have demonstrated efficacy against bacterial pathogens affecting children worldwide, such as *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis*. Glycoconjugate vaccines are made by coupling the polysaccharide capsule portion of the organism to a carrier protein. This combination is more immunogenic than the saccharide alone and is also capable of inducing T-cell memory booster responses upon revaccination [2]. Conjugate vaccines have been developed using several protein carriers, one of which is CRM_{197}. This protein is a nontoxic mutant of the diphtheria toxin, with demonstrated immunogenicity in infants and young children. Because CRM_{197} is nontoxic, there is no need for detoxification involving formaldehyde or glutaraldehyde––a process shown to cause significant epitope modification [3]. This paper will focus on the carrier protein CRM_{197} and its use in single-antigen pediatric vaccines.

2. A history of effectiveness against multiple pathogens

The first CRM_{197} conjugate vaccine developed, HbOC (HibTITER®; Wyeth Pharmaceuticals, Philadelphia, PA, USA), protected infants against Hib-related disease.

In a prelicensure trial of approximately 60,000 children, the vaccine was found to be well tolerated, immunogenic, and associated with a 94% reduction of Hib-related disease in infants <18 months of age [4]. Further surveillance of 240,000 US children

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Table 1
Conjugate vaccines against disease caused by *Haemophilus influenzae* for use in pediatric populations.

Name	Manufacturer	Included serotypes	Current indicated ages	Carrier protein
PRP-T (ActHIB)	Sanofi Pasteur	b	2–18 months	Tetanus toxoid
PRP-OMP (PedvaxHIB)	Merck & Co., Inc.	b	2–71 months	Outer membrane protein of *N. meningitidis*
PRP-D (ProHIBIT)	Connaught Laboratories	b	18 months–5 years	Diphtheria toxoid
HbOC (HibTITER)	Wyeth Pharmaceuticals	b	2–71 months	CRM_{197}

Table 2
Conjugate vaccines against pneumococcal disease caused by *S. pneumoniae* for use in pediatric populations.

Name	Manufacturer	Included serotypes	Current indicated ages	Carrier protein
PCV7 (Prevnar)	Wyeth Pharmaceuticals	4, 6B, 9V, 14, 18C, 19F, 23F	2, 4, 6 months; booster at 12–15 months	CRM_{197}
PCV13 (Prevnar 13)	Wyeth Pharmaceuticals	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	2, 4, 6 months; booster at 12–15 months	CRM_{197}

vaccinated with HbOC found a near elimination of Hib-related disease in children 0–8 years of age over a period of 4 years and 8 months [5]. When compared with the previously licensed Hib vaccine conjugated to diphtheria toxoid (PRP-D; ProHIBIT®, Connaught Laboratories), HbOC demonstrated superior immunogenicity in children <6 months of age. Two other conjugate vaccines are also licensed in the United States—one conjugated to the outer membrane protein of *N. meningitidis* (PRP-OMP; PedvaxHIB®, Merck & Co, Inc., West Point, PA) and the other conjugated to tetanus toxoid (PRP-T; ActHIB®, Sanofi Pasteur, Lyon, France). These conjugate vaccines also demonstrated superior immunogenicity to PRP-D (Table 1) [6].

Another example of a CRM_{197} conjugate vaccine is PCV13 (Prevnar 13™, Wyeth Pharmaceuticals), a 13-valent vaccine against invasive pneumococcal disease (IPD) caused by *S. pneumoniae*. This vaccine was recently approved in the United States and the European Union and was developed as a replacement for the 7-valent vaccine, PCV7 (Prevnar®, Wyeth Pharmaceuticals). Clinical trials were designed to assess noninferiority of PCV13 to PCV7 and the effectiveness of the vaccine against IPD was inferred from comparative studies to PCV7. Prior to approval, noninferiority of PCV13 was demonstrated in a randomized, double-blind, controlled trial using 2 groups of 2-month-old infants that were balanced for age, race, and ethnicity. Responses to the 7 serotypes contained in PCV7 were compared directly, whereas the responses to the 6 additional serotypes contained in PCV13 were compared to the lowest response observed among the PCV7 serotypes in children immunized with PCV7 (Table 2) [7].

A large-scale study at Kaiser Permanente Study Center in California involving approximately 38,000 children demonstrated vaccine efficacy of 94% against IPD caused by the 7 serotypes contained in PCV7 [8]. Subsequent surveillance found a considerable decline in the incidence of IPD in children less than 5 years of age from 2000 to 2005 [9].

According to recent surveillance completed in Canada, children in the 6–23-month age group have experienced 86% and 77% decreases in IPD rates caused by the 7 serotypes in PCV7 and all serotypes, respectively. A reduction in IPD incidence in 2–4-, 16–64-, and 65–84-year age groups was also observed, providing evidence that PCV7 provides indirect herd immunity in addition to direct protection of immunized children [10]. These results are similar to past surveillance [11,12].

In the late 1990s, 2 CRM_{197} conjugate vaccines (Meningitec®, Wyeth Pharmaceuticals; Menjugate®, Novartis Vaccines, Siena, Italy) were developed against meningococcal disease caused by serotype C. Owing to a great immediate need, these vaccines were licensed in several European countries based solely on immunogenicity data. Subsequent surveillance found the persistence of protection to be short-lived when the vaccine was administered at 2, 3, and 4 months of age [13], prompting the addition of a booster dose to the immunization schedule. Surveillance has shown a decrease in the incidence in meningococcal disease caused by serotype C in all age groups, consistent with herd immunity [14–16].

A quadrivalent vaccine against meningococcal serotypes A, C, W-135, and Y conjugated to CRM_{197} (Menveo®, Novartis Vaccines) recently was approved for use in the United States and the European Union. The previously licensed quadrivalent meningococcal vaccine (Menactra®, Sanofi Pasteur) is conjugated to diphtheria toxoid and is not immunogenic in infants. It is interesting to note that this is similar to Hib-DT. Phase II and Phase III studies of Menveo have demonstrated immunogenicity in infants [17,18]. Thus, use of the CRM_{197} conjugate has facilitated the development of a vaccine that is reliably immunogenic in infants. This is very important given that infants have the greatest risk for contracting meningococcal disease [19]. Additionally, although approximately 50% of meningococcal disease in infants <6 months of age is caused by serotype B, which is not included in the quadrivalent vaccines, the incidences of serotypes C, Y, and W-135 are higher in infancy than in any other age group (Table 3) [20,21].

3. Unanswered questions

Although the success and effectiveness of CRM_{197} conjugate vaccines have been demonstrated, there are still questions regarding these vaccines.

3.1. Conjugate interference

The administration of multiple conjugate vaccines using the same carrier protein is thought to produce an interference effect. One of the first studies to explore this phenomenon demonstrated a dose-related decrease in immune response in children administered a pneumococcal vaccine concomitant with a Hib vaccine, each

Table 3
Conjugate vaccines against disease caused by *N. meningitidis* for use in pediatric populations.

Name	Manufacturer	Included serotypes	Current indicated ages	Carrier protein
Meningitec	Wyeth Pharmaceuticals	C	>2 months	CRM_{197}
Menjugate	Novartis Vaccines	C	>2 months	CRM_{197}
MSV4	Sanofi Pasteur	A, C, W-135, Y	2–55 years	Diphtheria toxoid
Menveo	Novartis Vaccines	A, C, W-135, Y	11–55 years	CRM_{197}