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Conjugate Hib Vaccines and their Combinations: Present Success and Future Possibilities

HENRY SHINEFIELD, MD, STEVEN BLACK, MD

Kalser Permanente Pediatric Vaccine Study Center, Northern California, USA

Introduction

The introduction of conjugate *Haemophilus influenzae* type b (Hib) vaccines has had a dramatic impact on the incidence of Hib systemic disease. Following the demonstration of the effectiveness of these vaccines in two clinical trials in the United States of America, two different conjugate vaccines were licensed for use in the USA in late 1990 as infant immunogens: *Haemophilus* b conjugate vaccine – diphtheria CRM197 protein conjugate, (HbOC) (HibTITER, Lederle-Praxis Biologicals), and *Haemophilus* b conjugate vaccine – meningococcal protein conjugate (PRP-OMP) (PedvaxHib, Merck Sharp & Dohme). [8, 9, 75] Following administration of one of the conjugates – HbOC – in a Health Maintenance Organization (HMO) population, a single case of systemic Hib disease in an unvaccinated infant was seen in the entire year of 1992. This was a remarkable 97% fall in discase rate, that occurred in the Northern California Kaiser Permanente Medical Care Program (NC-KPMCP). The NCKPMCP has 2.5 million members and experienced an average of 70 cases annually in the less than five years age group from 1984 to 1988 [6].

Conjugate Hib vaccines

While current conjugate Hib vaccines are effective in reducing the incidence of systemic Hib diseases, it would be advantageous to combine these vaccines with other immunogens such as diphtheria, pertussis, tetanus (DPT) vaccines that are routinely administered to infants. This would reduce the number of injections that infants are given, minimizing the trauma to the infants receiving the vaccine, and would encourage parental and physician acceptance.

In the USA, the HbOC vaccine is normally given at two, four and six months of age, concurrently with DPT, followed by a booster of both vaccines at the age of 15 to 18 months. At present it is necessary to give the vaccines as two separate injections a teach of these visits. Parents may be reluctant to subject their infants to two injections at the same time, generating unnecessary return visits or reduced compliance with recommended vaccination schedules. The second vaccine is also associated with additional administration costs at each visit. It would be worthwhile to combine DPT with HbOC or other conjugate vaccines into a single preparation.

A number of Hib conjugate vaccine combinations have been used in clinical trials (Table 1).

TABLE 1
DPT/H/b combinations

1. DPT-HbOC:	No Interference noted Synergy noted in one study
2. DPT-PRP/D:	Decrease D anti-diphtheria and anti pertussis antibody
3. DPT-PRP/T:	Decrease anti-pertussis and anti-PRP antibody
4. Combinations with acellular pertussis/DT DTaP-HbOC:	No Interference noted

1. TETRAMUNE – Lederie-Praxis Biologicals – combined
2. No trademark – Connaught Laboratory Limited – combined
3. No trademark – Pasteur Merieux Co – mixture
4. DTaP-HbOC – Lederie-Praxis Biologicals – combined

The trial at NCKPMCP involved over 10,000 infants. Comparisons were made between infants aged two; four and six months, who received separate injections of HbOC and DPT in each thigh, and infants who received a single 0.5 ml injection of the combined product. Comparisons of local and systemic reactions, measurement of temperature elevation, emergency room visits and hospitalizations revealed no difference between the groups. In addition, there was no evidence that the combined vaccine was causally related to Sudden Infant Death Syndrome (Table 2). Infants were bled one month after their third injection. Immunologic results are presented in Table 3. These data are similar to results seen in HbOC recipients in similar studies, and also reflect antibody titer levels achieved by DPT recipients who participated in other published studies [10, 22].

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TABLE 2
Safety of HDPT in infancy: SIDS Surveillance October 1, 1990 – June 30, 1991, Northern California Kaiser Permanente Medical Care Program in Alameda, Contra Costa, Marin, San Francisco and San Mateo Counties.

Population	Number of SIDS cases	Person-years	Rate/1000 py	95% C.L.
HDPT recipients	6	3,887	1,5	0,6-3,4
Kaiser five counties	13	5,390	2,4	1,3-4,1
Five counties reporting	74	33,900	2,2	1,7-2,7

1) SIDS cases in HDPT reciplents identified by county reporting within the five couties above as well as passive reporting by study nurses in other counties
2) Interval batween vaccine and SIDS in HDPT recipients: 1.14.26.28.42 and 68 days
3) Person-time denominator estimated for five counties from estimates of binhs from each county for each quartar Person-time for Kaiser infants in the five countiee estimated from Total number of births at these medical centers during the observation period less follow-up accrued for HDPT infants
4) Poisson confidence interval

A similar study was carried out by a group of investigators in New York state [64]. This study involved approximately 150 infants who again were given vaccines, either combined or as separate HbOC and DPT injections, at the age of two, four and six months. In this study, the emphasis was on immunogenicity rather than safety. Antibody levels were assessed prior to each injection and approximately one month after the third injection.

The reason for this reaction was unexplained. It is of interest that other data also suggest that DPT given simultaneously with HibTITER in separate injections, represents a greater immunogenic potencial for PRP antibody production in infants than when PRP is given alone [69]. However, this observation of synergy cannot be extended to all combinations of conjugate Hib vaccines with DPT.

TABLE 3
Summary of HDPT immunology

Antigone	N	GMT	95% C.L
$HbOC_1$	123	8.20	6.12 - 10.89
$Tetanus_2$	120	7.52	6.56 - 8.63
$Diphtheria_3$	112	0.92	0.67 - 1.26
$Pertussis_4$	108	110.10	78.00 - 155.60

1) Percentage of children with antibody titers greater than 1 ug/ml = = 89%
2) Elisa assay
3) Vero cell assay
4) Pertussis agglutinin assay

TABLE 4
Comparison of immunogenicity in toddlers of DTaP/HbOC combined and DTaP and HbOC given as separate injections,

Combined	PRP (Mcg/ml)	Dipth (1U/ml)	T?? (Eu/ml)	PT (Eu/ml)	Pert FHA (Eu/ml)	??? (Eu/ml)
N_2	273	230	293	233	233	233
GMT_3	37	9	17	118	68	134
95% C.I.	[31,44]	[8,11]	[16,19]	[102,137]	[58,79]	[112,159]
Separate						
N_2	78	68	90	68	68	68
GMT_3	48	8	15	114	56	123
95% C.I.	[34,69]	[6,10]	[13,18]	[79,163]	[41,77]	[87,175]

1) All subjects primed with DPT and HbOC given as separate injections et 2,4 and 6 months of age.
2) Number of children
3) Geomatric mean tiler

A similar phenomenon of interference was seen when the *Haemophilus* b conjugate vaccine – tetanus toxoid conjugate, (PRP/T) (ActHIB, Pasteur-Merieux-Connaught) was administered with the DPT vaccine [18]. In this study one of three regimens was given to study participants at the age of two, four and six months. Group 1 received DPT mixed in the same syringe as PRPT/T; Group 2 received DPT and PRP/T given at separate injection sites and Group 3 received DPT with-out PRP/T. Serum anti-diphtheria toxoid and anti-tetanus toxoid antibodies were similar in all patients. However, concurrent administration of PRP/Tvaccine with DPT vaccine, either in the same syringe or at different sites, interfered with anti-

-pertussis responses to the primary series of immunizations. While there is evidence that absorption of PRP/T to an aluminum hydroxide adjuvant may reduce responses to both PRP and tetanus toxoid components of the conjugate vaccines, [17] this physical interaction between vaccines cannot explain the depression of anti-pertussis responses in the group that received DPT and PRP/T vaccines at separate sites. Depression of anti-PRP antibody has also been noted when PRPT / Tand DPT aregiven as a combined vaccine [28]. Despite clear demonstration of immunologic interference in these studies, antibody levels obtained are still within what are considered protective levels. Therefre the clinical significance of these data is unclear. The biological basis for these observations also remains unexplained.

An acellular pertussis / disphtheria / tetanus vaccine (DTaP, Lederle-Praxis Biologicals) combined with HbOC has also been studied [80]. This study was a randomized, open-label, multicenter trial in about 400 children in the NCKPMCP. In this study, children aged 18 months plus or minus three months, who received three routine doses of comercial DPT plus three doses of HbOC separated and concurrently in infancy, were randomized to receive one of three doses of DTaP plus HbOC combined or one dose of DTaP and HbOC administered concurrently in separate syringes. Serum was tested fr antibodies prior bo, and approximately one month after, vaccination in 393 children.

Local and systemic reactions and temperatures within three days post vaccine administration were provided by each child's parent or guardian on a symptom report form. The results demonstrated that the combined DTaP/HbC vaccine was both safe and immunogenic (Table 4). There was no significant difference in reactin rate or antibody formation noted from DTaP and HbOC administered separately and concurrently.

TABLE 5
Financial savings in USA with use of Hib conjugate vaccine

- Average cost per case of Hib Disease = $50,000,
- Prior to vaccine usa, NCKPMCP, observed en average of 70 cases per year for total cost of 3.5 million.
- 1992 NCKPMCP Hib cost (97% reduction of disease) $50,000.
- Vaccine cost for NCKPMCP birth cohort of 35,000/ year is $2.1 million.
- Oversall savings with vaccine program within NCKPMCP is therefore more than $1.35 million.
- USA overall savings, in 1992 more than $500,000,000.

1) Hay JW & RS. Ped 1987; 80: 319-329. Hay JW & Daum RS. Pediatr Infect Dis J. 1990; 9: 245-252. (1985 cost per case)
2) Northom California Kaiser Permanente Medical Care Program
3) Based on 4,000,000 births/year & 90% reduction in disease

Comment

The use of a conjugate Hib vaccine has virtually eliminated Hib disease in the NCKPMCP population of 2,5 million subscribers. This mimics the effects of conjugate vaccines seen in Finland [27] and presages what is taking place in the entire US population.

To date, about 38,000,000 doses of Hib conjugate vaccine have been distributed (35,000,000 HbOC; 3,000,000 PRP-OMP in the USA). The reported incidence of Hib disease in the USA as of December 31, 1992 has fallen from approximately 18,000 cases per year to less than 1,300 cases in 1992 [59]. This dramatic drop in disease rate has also resulted in significant medical care cost savings as demonstrated in Table 5.

This reduction in disease clearly demonstrates how one aspect of preventive medicine, namely the use of vaccine, can both improve the health and welfare of children and simultaneously result in considerable medical cost savings.

The continued success of this program depends on the continued use of conjugate Hib vaccine. In essence, it is important to get the vaccine to the target infant population. There are many barriers in programs devised to achieve high vaccination rates in infantes. It is rcasonable to assume that combining antigens, necessitating fewer injections for infant protection, will improve vaccination rates. What is also aparent in the data collected to date on combinations of conjugate vaccines with other immunogens, is the fact that each combination of antigens is an entity unto itself. The immunological response of such mixtures can not accurateeely be predicted.

It is also important to emphasize that while no problem has been uncovered to date regarding the safety of antigen combinations, the safety of these products cannot be assumed. It must be established by careful clinical trials.

Conclusion

It is obvious that medical personnel who care for infants and children are participating in an exciting era of preventive medicine. As vaccine development progresses and a variety of antigens, adjuvants and vaccine combinations are proposed for clínical use, at least two points must be kept in mind. First, it would be worthwile to have available an experimental in vivo model which will predict clinical safety and efficacy. While such techniques have not been developed as yet, an approach to the problem has been initiated [83]. Secondly, just as sophistication in vaccine development is progressing, the ability to rapidly collect, collect and understand large amounts of safety and immunologic data is also becoming more and more proficient. The presence of large catchment areas with accurate databases permits pre-FDA licensure testing and post-FDA licensure surveillance with an ever increasing number of subjects. Such large-scale clinical observations will help to assure safety and efficacy prior to licensure, while post-FDA licensure data analysis may reveal previously undetected and rare adverse reactions related to specific vaccinations early on. These types of studies now can and should be carried out.

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Correspondência: Henry R. Shinefield
Kaiser Permanente Vaccine
Study Center
2200 O'Farrel Street
San Francisco, CA 94175