VIRGINIA
EPIDEMIOLOGY BULLETIN

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Editor: Carl W. Armstrong, M.D., F.A.C.P.

October, 1992 Volume 92, Number 10

Haemophilus influenzae type b Meningitis in Virginia

Declining Incidence Due to Hib Immunization

Recent Trends

A review of the number of cases of *Haemophilus influenzae* type b (Hib) meningitis in children ≤5 years of age reported in Virginia from January 1982 through June 1992 demonstrates a large decrease in reports in recent years (Figure 1). This decline has occurred since 1985 when the first *H. influenzae* vaccines came on the market. In 1992, only 7 cases had been reported through June.

Approximately 75% of the cases reported during the past ten years occurred in children less than 15 months of age with the highest incidence among children ≤1 year of age (Figure 2); most cases occurring in the second half of the first year of life. The incidence in whites and nonwhites was almost identical (16.5 vs. 17.0 per 100,000 per year, respectively).

As shown in Figure 3, the months of November through April had the highest incidence of reported cases for all reporting years combined. As expected, the majority of reported cases came from the large population centers around the state; Norfolk, Virginia Beach and Fairfax County accounted for over 25% of the reported cases during the period studied. Calculated incidence rates are shown on the accompanying map (Figure 4.).

Figure 1. *H. influenzae* Meningitis Cases Reported in Children ≤5 Years of Age, Virginia, January 1982-June 1992

Note: Total for 1992 is projected based on first six months.

In This Issue:

Historical Perspective

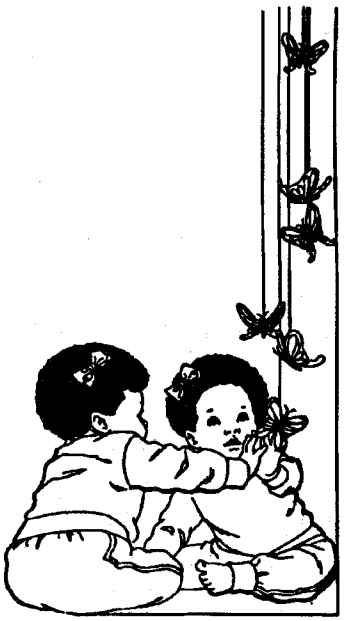
Infections caused by Hib pose a serious health threat to infants and children. This encapsulated organism is the leading cause of bacterial meningitis in children three months to five years of age, accounting for nearly 12,000 cases in 1990. The mortality rate for Hib meningitis is 5%, and 20-30% of survivors suffer serious morbidity in the form of neurologic sequelae.[1] Other invasive diseases in children that may be attributable to Hib include septicemia, pneumonia, epiglottitis, cellulitis, arthritis, osteomyelitis, and pericarditis. The primary mode of transmission of *H. influenzae* is by respiratory droplet spread. Nontypable (unencapsulated) stains of *H. influenzae* are a major cause of otitis media, sinusitis, and respiratory mucosal infection but rarely result in bacteremia. Approximately 79% of all Hib cases occur in infants younger than 15 months, with a peak incidence between 6 and 12 months.[2]

The species *H. influenzae* was initially described in 1892 by Pfeiffer, who discovered the presence of the organism in the sputum of patients with "influenza" and proposed a causal association between this bacterial species and the clinical syndrome known as influenza. In the 1930s, Pittman showed that *H. influenzae* could be isolated in encapsulated and unencapsulated forms, identified six capsular types which were named types a to f, observed that virtually all *H. influenzae* isolates from cerebrospinal fluid and blood were of the capsular type b and demonstrated that horse anti-

type b serum conferred type-specific protection against lethal systemic infection in rabbits. During the 1970s, researchers demonstrated that serum antibodies to the type b capsular polysaccharide were bactericidal and protected against invasive infection.[3] Accumulating evidence therefore led researchers to focus on this polysaccharide as a potential immunizing agent.

The Vaccines

In 1985, *Haemophilus* b polysaccharide vaccine was licensed in the United States. The vaccine was designed to induce antibodies against polyribosylribitol phosphate (PRP), the capsular polysaccharide and major virulence factor for Hib.[4] Despite proven efficacy in a large Finnish trial, use of the vaccine in the United States was associated with a large number of failures and a postlicensure efficacy ranging from 41% to 88%.[5] More importantly, the vaccine was clearly ineffective in infants and was only approved for use in children 24 months or older, thus not benefiting the group at highest risk for Hib infection.



It had been known since at least the 1920s that conjugation of poorly immunogenic haptens (such as PRP) to protein "carriers" could greatly enhance the immunogenicity of the hapten. Indeed, conjugation of PRP to certain proteins appeared to alter the immune response such that the conjugated PRP acted as a T-cell-dependent antigen.[6] Therefore, to improve immunogenicity and to obtain infant protection, conjugate vaccines were developed in which the PRP capsule was linked to a protein carrier.

Three conjugate vaccines have been licensed for use in children 15 months of age or older: ProHIBiT (Connaught Laboratories), HibTITER (Praxis Biologics), and PedvaxHIB (Merck). Two of these vaccines, HibTITER and PedvaxHIB, were approved in 1990 for use in infants as young as two months of age.[7] Each of the conjugate vaccines differs in protein carrier, polysaccharide size, the number and scheduling of doses necessary to achieve protective concentrations of antibody (serum anti-PRP concentrations ranging from 0.15 to 1.0 µg/mL are considered protective), and the duration of protective antibody induced.[8] A study conducted in Alaskan infants suggested that PedvaxHIB was the most immunogenic after two doses, but the anti-PRP concentrations achieved with two doses of PedvaxHIB were lower than those achieved after three doses of HibTITER. Antibody concentrations at 12 to 15 months (pre-booster age) were markedly lower for PedvaxHIB than for HibTITER. Although this finding suggests a shorter duration of protection with PedvaxHIB, the clinical significance of this difference is unknown. ProHIBiT was the least immunogenic vaccine after three doses and at prebooster age.[9] These results initially led the U.S. Food and Drug Administration to refuse to license ProHIBiT for use in infants younger than 15 months. Nevertheless, after considering the findings from several subsequent studies, the FDA very recently approved ProHIBiT for use as a booster at **12 months of age.**

Both the Centers for Disease Control's Immunization Practices Advisory Committee (ACIP) and the American Academy of Pediatrics (AAP) recommend that all infants be immunized with either HibTITER or PedvaxHIB beginning routinely at two months of age or as soon as possible thereafter.

A large clinical trial involving approximately 60,000 infants in northern California studied the efficacy (not the immunogenicity) of HibTITER. Of the nearly 30,000 infants who received three doses of the vaccine, none contracted Hib disease, indicating a protective efficacy of 100%. However, only a 26% efficacy was noted in those infants receiving one dose, and the possibility that one dose of vaccine had no efficacy could not be excluded. PedvaxHIB has been demonstrated to be 93% efficacious in over 2,500 Navajo infants who received two doses of the vaccine at two and four months of age. There was one case of Hib disease in a patient receiving only the first series of doses. Thus for both vaccines, completion of the entire regimen is essential to ensure maximum immunity.[10]

Concerning adverse effects, each of the vaccines seems to be extremely safe when given to infants and children. Minor adverse effects that have been reported include elevated temperatures greater than 38.3° C and local reactions such as erythema, swelling, and tenderness. The incidence of these reactions is low, ranging from less than 1% to 4.6%.[11]

These newer conjugate vaccines appear to be a major factor in the noticeable decline in the number of *H. influenzae* meningitis cases in infants and children. A surveillance study by the Centers for Disease Control (CDC) covering the San Francisco and Atlanta metropolitan areas, the entire state of Oklahoma, and four counties in Tennessee (approximately 10.4 million people) identified 50 cases of invasive *H. influenzae* type b disease among children younger than 5 years during a period in 1991. By comparison, over the same period in 1989, there were 176 cases in this study area. The CDC also reported that in 1991 over 10 million doses of vaccine

Figure 2. *H. influenza* Meningitis Cases Reported in Children ≤5 Years of Age, by Age, Virginia, January 1982-June 1992

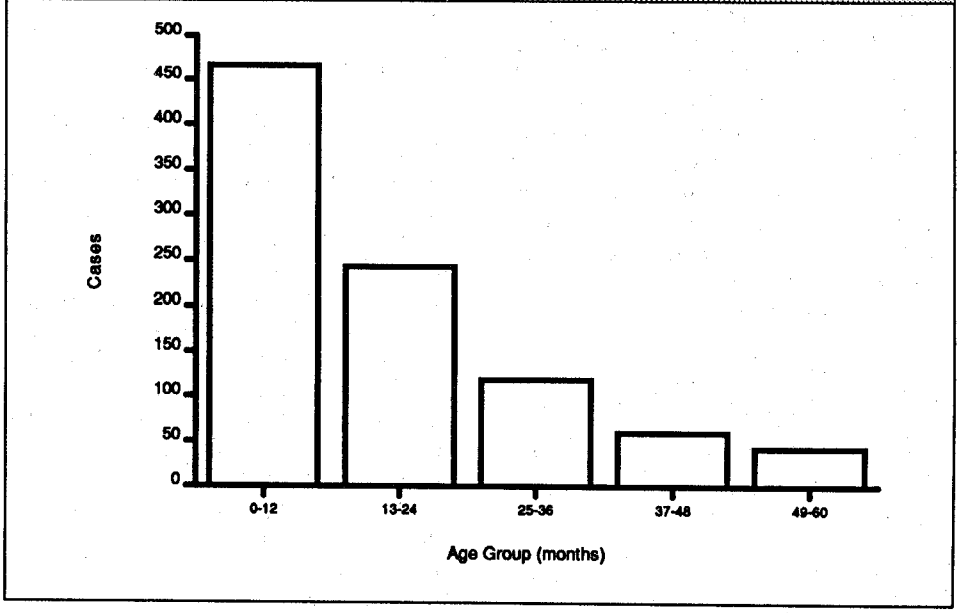
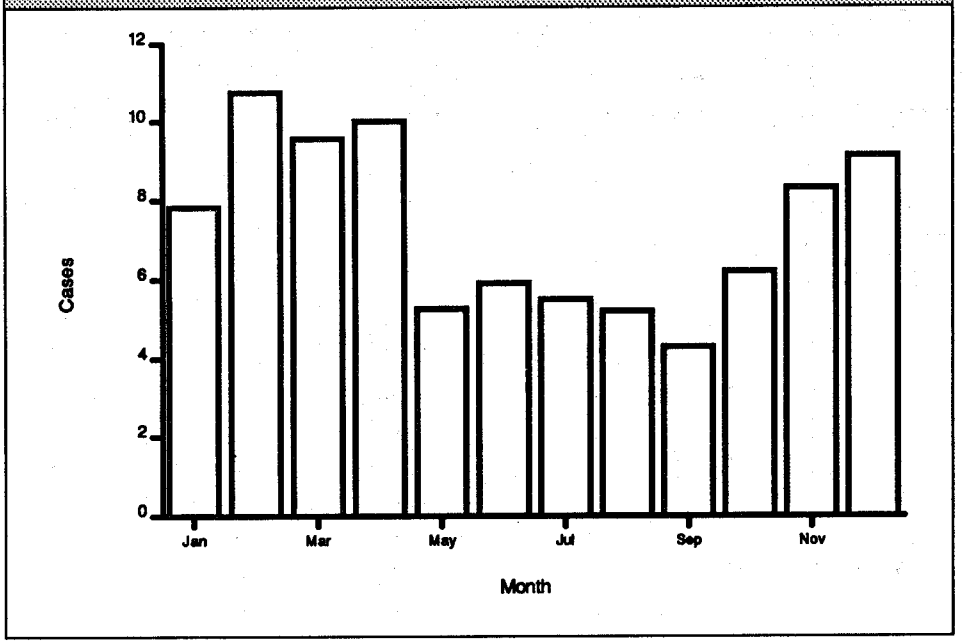


Figure 3. Mean Number of *H. influenza* Meningitis Cases Reported in Children ≤5 Years of Age, by Month of Report, Virginia, January 1982-June 1992



against *H. influenzae* type b were sold, compared with 3 million doses in 1989.[12]

Conclusion

In little more than half a century science has come a long way toward the eventual elimination of invasive Hib disease. Based on Virginia data as well as other studies examining the incidence of *H. influenzae* meningitis, it appears that the new conjugate vaccines are having a significant effect on the decline of this disease in Virginia as well as the rest of the United States. Future studies should continue to assess the protective efficacy of the Hib conjugates in differing populations and for differing vaccine schedules.

Submitted by Christopher J. Donahue, 4th year medical student, Medical College of Virginia, on elective with the Office of Epidemiology, and Carl W. Armstrong, MD, Office of Epidemiology.

References

1. Wilfert CM. Epidemiology of *Haemophilus influenzae* type b infections. Pediatr 1990;85(4 Part 2):676-81.

2. Anonymous. *H. influenzae* vaccine for infants. Med Let Drugs and Therap. 1991;33:5-7.

3. Cochi SL, Broome CV. Vaccine prevention of *H. influenzae* type b disease: past, present, and future. Pediatr Infect Dis 1985;5:12-9.

4. American Academy of Pediatrics, Committee on Infectious Diseases: *H. influenzae* type b vaccine. Pediatr 1985;76:322.

5. Shapiro ED, Murphy TV, Wald ER, Brady CA. The Protective efficacy of *Haemophilus* b polysaccharide vaccine. JAMA 1988;260:1419-22.

6. Shapiro ED. New vaccines against *H. influenzae* type b. Pediatric Clinics of North America 1990;37:567-78.

7. Anonymous. *H. influenzae* vaccines gain favor. JAMA 1990;264:1375.

8. Committee on Infectious Diseases. *H. influenzae* type b conjugate vaccines: recommendations for immunization of infants and children two months of age and older: update. AAP News. 1991;(3):37-9.

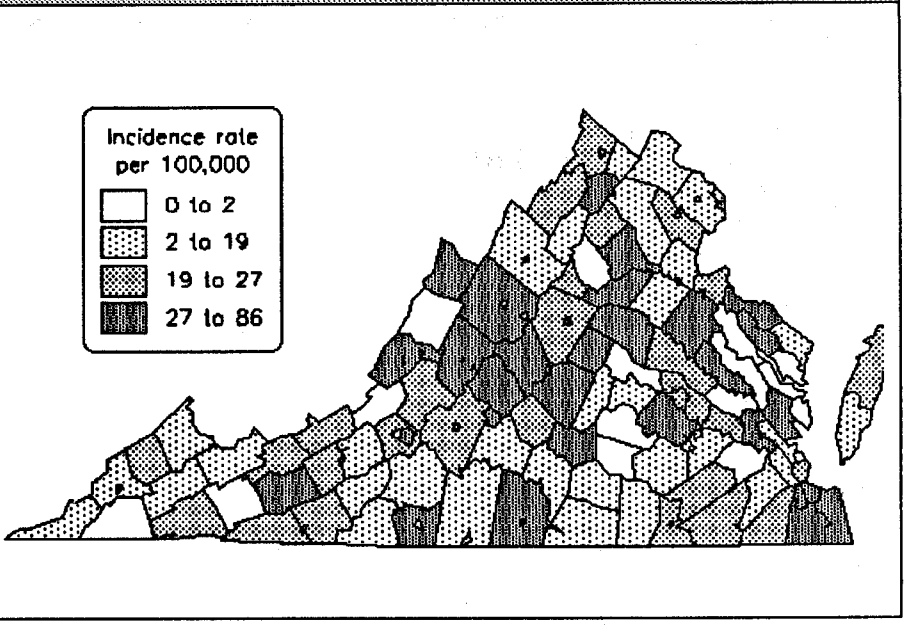
9. Wenger JD, Deaver KA, Brown CV. Efficacy of *H. flu* type b polysaccharide-diptheria toxoid conjugate vaccine in U.S. children aged 18-59 months. Lancet 1991;338:395-8.

10. Black SB, Shinefield HR, Fireman B, Hiatt R. Safety, immunogenicity, and efficacy in infancy of oligosaccharide conjugate *H. influenzae* type b vaccine in a United States population: possible implications for optimal use. J Infect Dis 1992;165(suppl 1):S139-43.

11. Pinson JB, Weart CW. New considerations for *H. influenzae* type b vaccination. Clin Pharm 1992;11:332-36.

12. Marwick C. *H. influenzae* declining among young? JAMA 1991;266:3398-9.

Figure 4. Average Annual Incidence Rates of *H. influenza* Meningitis Reported in Children ≤5 Years of Age, by Locality, Virginia, January 1982-June 1992



Cases of Selected Notifiable Diseases, Virginia, September 1 through September 30, 1992.

Disease	Total Cases Reported This Month						Total Cases Reported to Date in Virginia		
		Regions							
	State	NW	N	SW	C	E	This Yr	Last Yr	5 Yr Avg
AIDS	53	4	25	8	6	10	477	531	350
Campylobacter	63	15	15	11	13	9	492	492	482
Gonorrhea*	1658	-	-	-	-	-	12787	13602	12102
Hepatitis A	11	1	6	2	1	1	86	130	213
Hepatitis B	11	1	0	3	2	5	146	167	234
Hepatitis NANB	2	0	0	2	0	0	28	24	42
Influenza	0	0	0	0	0	0	122	689	1406
Kawasaki Syndrome	4	0	1	0	0	3	20	22	18
Legionellosis	3	2	0	0	0	1	14	11	9
Lyme Disease	15	1	2	3	3	6	95	113	59
Measles	1	0	0	0	0	1	15	30	61
Meningitis, Aseptic	39	7	19	7	1	5	196	299	214
Meningitis, Bacterial~	4	1	0	2	0	1	88	97	118
Meningococcal Infections	1	0	0	1	0	0	48	31	45
Mumps	3	0	2	0	0	1	49	53	88
Pertussis	0	0	0	0	0	0	10	18	27
Rabies in Animals	44	16	16	4	2	6	266	195	223
Reye Syndrome	0	0	0	0	0	0	0	2	1
Rocky Mountain Spotted Fever	5	3	0	1	1	0	17	14	16
Rubella	0	0	0	0	0	0	0	0	3
Salmonellosis	107	11	40	15	11	30	720	1029	1142
Shigellosis	23	7	12	0	3	1	177	322	257
Syphilis (1° & 2°)*	42	0	3	6	9	24	564	709	485
Tuberculosis	25	1	2	1	9	12	273	258	286

Localities Reporting Animal Rabies: Alexandria 3 raccoons; Augusta 3 skunks; Bath 1 fox; Botetourt 1 bat; Chesterfield 1 raccoon; Clarke 2 raccoons; Fairfax 1 bat, 1 mink, 5 raccoons; Fauquier 1 skunk; Fluvanna 1 fox; Frederick 1 raccoon, 1 skunk; James City 1 fox; King William 1 skunk; Loudoun 1 fox, 1 raccoon, 2 skunks; Madison 1 cat; Middlesex 1 raccoon; Montgomery 1 skunk; Prince George 1 raccoon; Prince William 1 raccoon, 1 skunk; Pulaski 2 raccoons; Shenandoah 4 raccoons; Spotsylvania 1 skunk; Suffolk 1 raccoon; Virginia Beach 2 raccoons.

Occupational Illnesses: Asbestosis 10; Carpal Tunnel Syndrome 63; Coal Workers' Pneumoconiosis 19; Lead Poisoning 1; Loss of Hearing 15; Repetitive Motion Disorder 4.

*Total now includes military cases to make the data consistent with reports of the other diseases.

~Other than meningococcal

Published monthly by the
VIRGINIA HEALTH DEPARTMENT
Office of Epidemiology
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Richmond, Virginia 23218

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