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Effect of nationwide vaccination of 3-month-old infants in The Netherlands with conjugate *Haemophilus influenzae* type b vaccine: High efficacy and lack of herd immunity

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Objective: The effect of nationwide vaccination in The Netherlands with conjugate *Haemophilus influenzae* type b vaccine on the incidence of *H. influenzae* meningitis was assessed in the first 3 years after the introduction of vaccination to the birth cohort at 3 months of age.

Study design: Children in The Netherlands born after April 1, 1993, were vaccinated at the age of 3, 4, 5, and 11 months. Children older than 3 months at the inception of the *H. influenzae* type b vaccination program were not immunized. The number of cases among the vaccine cohort was compared with the number in a historical control group of children born in the period April 1, 1990, and April 1, 1993.

Results: The total number of patients with meningitis caused by *H. influenzae* type b reached a low, but constant level, that was expected for absence of herd immunity. Among children in the vaccine era group 22 cases occurred, whereas among the historical control group (prevaccine era) 342 cases were found. In the vaccine era cohort, 2 patients with *H. influenzae* type b meningitis had been vaccinated three times, 13 received one or no vaccine dose because of their age, and 7 were not vaccinated for religious or logistic reasons. The number of cases among nonvaccinated children older than 3 years and the number of *H. influenzae* meningitis cases caused by strains other than type b did not change.

Conclusions: Conjugate *H. influenzae* type b vaccine prevents *H. influenzae* type b meningitis very effectively (99.4%) in children vaccinated twice or more. To reach rapid prevention of all *H. influenzae* type b disease simultaneous introduction of *H. influenzae* type b vaccination of children at various ages is recommended. (J Pediatr 1997;131:869-73)

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Infant vaccination with conjugate *Haemophilus influenzae* type b vaccines prevents Hib disease by inducing protective immunity^{1,2} and has now been introduced in many countries.¹⁻⁸ In the Finnish trial children too old for the infant vaccinations in the first year of life were vaccinated once at later age. Vaccination in Finland and the United States resulted in protection against Hib disease and in eradication of nasopharyngeal carriage of Hib among vaccinated

children, which may play a role in protection (i.e., diminished exposure) of nonvaccinated children. Carriage of Hib among nonvaccinated children has been observed.⁹⁻¹¹

Nationwide efficacy studies have only been reported for Finland.¹⁻³ In The Netherlands, Hib vaccination with conjugate vaccine was embodied in the National Vaccination Program for children born on

CI	Confidence interval
CSF	Cerebrospinal fluid
DKTP	Diphtheria, whole cell pertussis, tetanus, and inactivated poliomyelitis
Hib	<i>Haemophilus influenzae</i> type b
RBM	Netherlands Reference Laboratory for Bacterial Meningitis of the University of Amsterdam and the National Institute for Public Health and the Environment (RIVM), Bilthoven

or after April 1, 1993, at the age of 3, 4, 5, and 11 months. In contrast to other countries, children born before the introduction were not vaccinated. The Netherlands Reference Laboratory for Bacterial Meningitis of the University of Amsterdam and the National Institute for Public Health and the Environment (RIVM), Bilthoven, have performed active nationwide surveillance of bacterial meningitis by collecting and analyzing laboratory records, bacterial isolates, and cerebrospinal fluid samples since 1975, recording more than 80% of all meningitis cases.¹² Participation of the clinical microbiologic laboratories in The Netherlands did not change over the years as deduced from the constant number of cases of pneumococcal meningitis recorded.¹³ Before the nationwide introduction of Hib vacci-

Fig. 1. Number of cases of meningitis in The Netherlands caused by type b (x-x) and non-type b *H. influenzae* (●-●) in 1990-1996, shown by 3-month periods. **Insert.** Actual and expected decline in the number of Hib cases per annual quarter after introduction of Hib vaccination is depicted and analyzed by univariate regression analysis.

nation in The Netherlands, the age-specific incidence of *H. influenzae* meningitis was 22/100,000 per year for children less than 5 years old, with a maximal incidence of 250/100,000 per year for 11-month-old infants.¹⁴ From 95% of the meningitis cases caused by *H. influenzae*, Hib was recovered from CSF, blood, or both.¹³

Here we report the incidence of Hib meningitis in the 3 years after the universal immunization starting at the age of 3 months with conjugate Hib vaccine in The Netherlands. The occurrence of Hib meningitis in the population in the 3 years after and in the 3 years before the introduction of Hib vaccination in The Netherlands National Vaccination Program was compared to determine the contribution of herd immunity to the decline of Hib meningitis.

METHODS

Demographic Data

On April 1, 1996, the population of The Netherlands consisted of 15.5 mil-

lion inhabitants, including the vaccination cohort of 800,000 children of 3 years old or younger. The control cohort was the same size.¹⁵

The Netherlands National Vaccination Program

Children in The Netherlands are vaccinated at the age of 3, 4, 5, and 11 months with a combined vaccine for diphtheria, whole cell pertussis, tetanus, and inactivated poliomyelitis. Boostering with the DKTP vaccine is repeated at the age of 4 and 9 years. A vaccine to prevent mumps, rubella, and measles is administered at the age of 14 months and 9 years.¹⁶

Hib Vaccination

Hib vaccination was introduced for the first time and nationwide. Children born on or after April 1, 1993, were offered the PRP-T vaccine (Pasteur Mérieux Sérums et Vaccins; Lyon, France) to prevent Hib disease. This vaccine has been registered by the National Institute of Public Health and the Environment (Bilthoven, The

Netherlands) for administration to infants at the age of 3, 4, 5, and 11 months. Hib-T and DKTP vaccines were administered simultaneously but at separate injection sites. The protocol for vaccination was in agreement with international standards.¹⁷ The acceptance rate of Hib and DKTP vaccination in The Netherlands is 97%.¹⁸

Registration of Cases

National surveillance of bacterial meningitis is performed by active laboratory surveillance. Bacterial isolates from CSF and/or blood cultures and culture-negative CSF specimens from meningitis patients were sent by the clinical microbiologic laboratories in The Netherlands to the RBM. *H. influenzae* isolates were identified and typed by capsular polysaccharide serotyping using coagglutination.¹⁹ Nontypable *H. influenzae* isolates showed no reaction with antiserum specific for *H. influenzae* type a-f. Outer membrane protein analysis of these strains showed that the nontypable isolates were different from the common Hib isolates in The

Netherlands,²⁰ excluding that they were nonencapsulated variants of Hib.

Study Design

The number of Hib meningitis cases occurring in the cohort of children born between April 1, 1993, and April 1, 1996 ($n = 800,000$, vaccination cohort), and in the cohort similar in size of nonvaccinated children born between April 1, 1990, and April 1, 1993 (control cohort), was compared to assess the efficacy of vaccination. The decline in the total number of meningitis cases after the introduction of Hib vaccination was compared with the decline calculated by subtracting the number of cases expected to be prevented during each annual quarter from the average number of cases in the 3 years preceding the introduction of Hib vaccination in the similar period of the year (to correct for seasonal variation). The number of cases expected to be prevented was determined from the age distribution of Hib meningitis cases in The Netherlands in the period 1990 to 1993.¹³ The expected number per annual quarter, starting April 1993, was calculated by subtracting the "prevented" cases from the average number in the quarters of 1990 to 1993, starting with April 1990. Furthermore, a comparison was made of the number of Hib meningitis cases among unvaccinated children more than 3 years old in both periods to assess the effect of the nationwide Hib vaccination on the frequency of Hib meningitis among unvaccinated children. The number of meningitis cases caused by non-type b *H. influenzae* more than the 3 years before and after introduction of Hib vaccination in different age groups was also analyzed.

Vaccine Failures

The Hib vaccination records of all patients with Hib meningitis born after April 1, 1993, were analyzed. Cases were defined as vaccine failures when children had received at least the first three vaccinations.

Statistical Analysis

Differences between the number of Hib and non-Hib meningitis cases and between cases younger and older than 3 years were determined with the McNemar

Fig. 2. Comparison of the number of cases of Hib meningitis among children ≤ 3 years old (●) and > 3 years old (■) from 1993 to 1996.

test. Differences between the number of patients in vaccinated and unvaccinated children were analyzed with the chi-squared test and by determination of 95% confidence intervals. Probability (p) values less than 0.05 were regarded as significant. The actual and expected decline in the number of cases in the period from 1993 to 1996 was compared by univariate regression analysis.

RESULTS

Since 1993 the number of cases of Hib meningitis in The Netherlands decreased steadily and sharply (Fig. 1). The well-established seasonal variation observed in the absence of vaccination had largely disappeared. The number of Hib cases in the 6-month period from October 1995 to April 1996 after universal introduction of vaccination at 3 months of age was only 16 compared with the average of 130 cases in the corresponding 6-month period of the years 1990 to 1993, representing an 88% decline within 2.5 years after the introduction of vaccination. Then, the number of Hib meningitis cases did not decrease further. Among the 16 cases occurring in the last half year of the study period (last annual quarter of 1995 and first quarter of 1996), eight were in the cohort to which the vaccine had been offered, whereas eight were older than 3 years—the cohort not included in the vac-

cination program. During the 3-year period, a shift to higher ages was observed in the age-specific incidence of Hib meningitis because of the gradual disappearance of the youngest patients.

Although the relative proportion of non-type b *H. influenzae* increased since 1993, no significant absolute increase of non-type b Hib cases was observed compared with the years preceding Hib vaccination (Fig. 1). Among vaccinated patients, one had non-type b *H. influenzae* meningitis develop (type f). This case was not counted as a vaccine failure.

Several analyses were performed to determine whether Hib vaccination had an effect on disease among unvaccinated individuals. As shown in the insert of Fig. 1, statistical comparison of the actual and expected decline curves using regression analysis showed an almost perfect match. Secondly, the number of cases among children older than 3 years remained at the same level as in the years before vaccination (Fig. 2).

The efficacy of vaccination was assessed by comparing the number of Hib meningitis cases among children born between April 1993 and 1996 (vaccination cohort) with children born in the prior 3 years (control cohort). In total, 342 Hib meningitis cases occurred in the 3 years before the vaccination program was started, and 22 cases occurred in the 3 years after the start of the program, indicating 93.6% efficacy (95% CI = 90.4% to 95.9%).

Table. *H. influenzae* type b meningitis cases ($n = 22$) among children to whom one or more PRP-T Hib vaccine doses were given in the period April 1993 through April 1996

Age (mo)	No. patients	No. vaccine doses	
		Expected according to vaccination program	Actually administered
0-2	7	0	0
3	3	1	1
4	3	1	1
7	2	3	0
8	2	3	0
9	1	3	0
10	1	3*	3
11	1	4	0
13	1	3*	3
16	1	4	0

* Vaccine failures.

Only two cases of the expected number of 342 (0.6%; 95% CI = 0.1% to 2.1%) were vaccine failures, being vaccinated three times. Of the remaining 20, 13 were younger than 4 months and had not been vaccinated or had been vaccinated only once because of their age at the start of the vaccination program, and 7 were not vaccinated (Table). Either their parents refused the vaccination because of religious reasons or the patients were not covered by the health care system in The Netherlands at that time. These seven patients are the expected number accounting for the 97% acceptance rate of vaccination in The Netherlands. In the age group 0 to 2 months the number of cases in the vaccination period ($n = 7$) and in the period before the start of the vaccination ($n = 11$) was not significantly different.

DISCUSSION

Since April 1993, Hib vaccination using the PRP-T vaccine is embodied in The Netherlands National Vaccination Program. Infants are vaccinated at the ages of 3, 4, 5, and 11 months. In the 3 years after the introduction of Hib vaccination, the number of cases of Hib meningitis fell sharply (Fig. 1). Because the RBM receives more than 80% of the isolates of all

meningitis cases in The Netherlands¹² and the number of isolates of *Streptococcus pneumoniae* from patients with meningitis remained stable over the period 1990 to 1996,¹³ the reduction of *H. influenzae* isolates is most likely not due to a deficient submission of meningitis isolates.

The number of Hib vaccine failures was less than 1%, confirming the conclusion from other studies that conjugate Hib vaccines are highly efficacious.¹⁻⁸ Single-vaccine administrations were not fully protective because 6 cases were found among children 3 and 4 months of age who were vaccinated once, although 27 cases were recorded in the same age group of children before the vaccination (Table). In the period April 1993 through April 1996, the cases among the children 5 months of age and older occurred in unvaccinated individuals except for the two cases of vaccine failure.

In the 3 years after the introduction of Hib vaccination in The Netherlands the vaccine was given to approximately 800,000 children, 89% of all children born after April 1, 1993. Although this includes most children at risk for Hib meningitis, Hib meningitis was not completely (88%) eradicated. No significant reduction was observed in the number of cases among infants younger than 3 months and among children older than 3 years who were un-

vaccinated (Fig. 2). In Finland, the number of Hib meningitis cases (and other Hib diseases) decreased more rapidly than in The Netherlands. The introduction of Hib vaccination in Finland and The Netherlands was markedly different because in Finland the conjugate vaccine was also given to 18-month-old children previously not vaccinated.^{1,3} In addition, the age distribution of Hib disease in Finland before Hib vaccination shows that the risk of Hib disease in very young infants in Finland was lower than in The Netherlands.^{1,3,14}

In Finland and the United States herd immunity was reported to contribute to the decrease in the frequency of Hib disease, including meningitis.^{1,9,11} In The Netherlands herd immunity was not obvious during the study period because (1) the number of Hib meningitis cases among unvaccinated children 0 to 3 months of age and among children older than 3 years did not decrease, and (2) the reduction in the total number of Hib meningitis cases over the 3-year period in which the vaccination was embodied was equal to the expected reduction (Fig. 1). The lack of herd immunity in The Netherlands suggests that the method with which the Hib vaccination was introduced is important for the occurrence of herd immunity. Immunization of the birth cohort beginning at 3 months of age leaves older, at-risk children devoid of vaccine-induced immunity. Especially, vaccination of 18-month-old children, which was done both in Finland and the United States where herd immunity was observed, results in anti-Hib protective immunity in children for extended periods. Because nasopharyngeal Hib carriage generally occurs at a higher age than Hib disease,^{9,11} vaccination at 18 months probably reduces nasopharyngeal Hib carriage. Anti-Hib polysaccharide antibodies have been shown to prevent carriage, likely by inhibiting growth of Hib on epithelial cells.^{21,22} Most Hib disease is likely caused by spread of bacteria from healthy carriers and not from the patients themselves because Hib disease is endemic. In addition, if Hib cases were the primary source for spreading the bacteria, a rapid decline in the number of Hib meningitis cases among unvaccinated children

would have been observed after the sharp reduction in the number of cases was achieved at the end of 1995.

The number of meningitis cases caused by non-type b *H. influenzae* in the years preceding and following the start of the Hib vaccination in The Netherlands was similar (Fig. 1). This indicates that non-type b *H. influenzae* has not taken over pathogenic characteristics from Hib in The Netherlands and that non-type b *H. influenzae* has not occupied the niche emptied by eradication of Hib. However, among isolates from Southeast Asia and Africa virulent clones of non-type b *H. influenzae* causing systemic disease have been described.^{23,24} The isolated non-type b *H. influenzae* strains in The Netherlands were shown by outer membrane protein subtyping to be different from the type b strains, thereby excluding that these strains were nonencapsulated variants of type b *H. influenzae* strains selected in the presence of anticapsular antibodies.²⁵ In The Netherlands most meningitis cases caused by nontypable *H. influenzae* occurred in patients older than 10 years. Most had severe predisposing factors, such as skull damage, leakage of CSF, diabetes, alcoholism, and recurrent meningitis for unknown reasons.²⁵

In conclusion, Hib meningitis among vaccinated children has become a rare disease in The Netherlands. After two PRP-T conjugate Hib vaccinations, a 99% reduction of Hib meningitis was noted. Children less than 4 months old who were vaccinated only once or not at all, and unvaccinated children were not protected by herd immunity. Increase in the number of non-type b *H. influenzae* meningitis was not observed. On the basis of the results in The Netherlands and those obtained in Finland and the United States,⁹⁻¹¹ it is recommended that at the introduction of Hib vaccination the vaccine should be given in early infancy but also at higher age to all children.

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