

Estimation of the indirect effect of *Haemophilus influenzae* type b conjugate vaccine in an American Indian population

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Background Oropharyngeal carriage studies of *Haemophilus influenzae* type b (Hib) and the rapid drop in Hib invasive disease in countries with widespread Hib conjugate vaccine immunization programmes for infants have indicated there may be significant indirect effects (herd immunity) associated with these vaccines. Our goal was to quantify the magnitude of these effects in an American Indian population during its early years of Hib immunization.

Methods In a synthetic case-cohort study, we combined data from an efficacy trial, an immunization uptake records survey, and ongoing surveillance for Hib disease on the Navajo Nation from 1988 to 1992. Decline in the incidence of invasive Hib disease among children <2 years old was estimated via proportional hazards survival models as a function of individual immunization status and the proportion of immunized children in a community.

Results The predominant vaccine during the study period was Hib-OMPC (92% of immunizations). The effectiveness of receipt of at least one dose was 97.2%. Compared to communities with 0–20% coverage with at least one dose, residence in communities with 20–40% and 40–60% coverage was associated with risk reductions of 56.5% and 73.2%, respectively.

Conclusions The results indicate substantial indirect effects of Hib-OMPC immunization may occur even at relatively low levels of immunization coverage. Countries that implement Hib immunization programmes may receive greater benefits at the community level than those due to the direct protection conferred to the individual through vaccination.

Keywords *Haemophilus influenzae*, indirect effect, epidemiology, vaccine, biometry

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Haemophilus influenzae type b (Hib) conjugate vaccines have been licensed in the US for use in children >15 months old since 1988 and in infants <15 months since 1990. Since then, there has been a rapid uptake of these vaccines in the US, reaching 93% coverage for three doses by 24 months old in 1997 in the general population. Concomitant with the widespread

use of Hib conjugate vaccines has been a rapid decrease in Hib invasive disease, with incidence dropping 99% in children <5 years of age between 1989 and 1997.¹ The degree to which the decrease in incidence may be attributed to the indirect effects of the vaccines as compared to their direct effects, particularly at lower levels of immunization coverage, is not known. Here, we employ the definitions of direct and indirect effects given by Halloran *et al.*² in which direct effects are those that reduce host susceptibility, and indirect effects are those that reduce transmission and secondary attacks among household and community contacts (the latter is also referred to as the effect of herd protection).

Many researchers have documented that Hib conjugate vaccines reduce oropharyngeal (OP) carriage of the Hib organism in immunized infants^{3–5} and young children, as well as their unimmunized siblings.³ Such reductions are presumed to translate into decreased transmission of Hib among children.

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Prior Hib Vaccine Studies on the Navajo Nation

The efficacy of Hib-OMPC vaccine (Merck Hib-OMPC: PedvaxHIB®), a conjugate vaccine that links the *Haemophilus influenzae* type b capsular polysaccharide to the outer membrane protein complex of *Neisseria meningitidis* B, was first established in a Phase III trial in Navajo infants residing on the Navajo Nation.⁶ That study concluded that administration of the vaccine at 2 and 4 months of age conferred 95% protection (95% CI : 72, 99) through 18 months of age for infants who received at least one dose of the vaccine. Soon after the study ended on 2 August 1990, the vaccine was licensed and was made available to all Navajo children. The effectiveness of Hib-OMPC when delivered in the post-study, standard delivery-of-care setting has been shown to be just as high in two further studies.^{7,8}

An important mechanism through which an indirect effect could result would be reduced oropharyngeal (OP) carriage of Hib. Takala *et al.*⁹ investigated Hib OP carriage in the Navajo and Apache populations. Of 1423 OP swabs obtained during well-child visits for children aged 4 months to 4 years, 40 were positive for Hib, with an adjusted odds ratio for carriage of 2.7 associated with not being age-appropriately immunized. This biological evidence of the potential for significant indirect effects was a strong factor in prompting us to use disease incidence rates to quantitatively assess the degree of protection indirectly conferred to non-immunized individuals relative to vaccine coverage on a population level.

Subjects and Methods

Study population

Infants in this study are American Indians who resided on or adjacent to the Navajo Nation, an area administratively divided into eight Service Units (SU) of the Navajo Area Indian Health Service (NAIHS), in the states of Arizona, New Mexico, and Utah. There are 28 health care facilities: six hospitals, seven health centres open at least 40 hours per week, and 15 health stations open on a part-time basis. All health services are rendered free-of-charge. About half of the infants live in rural areas and more than 20 miles from a hospital.

Denominators were constructed for each SU by using US Census 1990 results and projecting for each year using IHS estimates of residents and catchment area user populations.

Written informed consent was obtained from parents or guardians of all infants enrolled in the Johns Hopkins University efficacy trial. The study protocols were approved by Institutional Review Boards of the Navajo Nation, the Johns Hopkins University, and the Indian Health Service.

Disease surveillance

Beginning with the efficacy trial in 1988, a Navajo Nation-wide practice was instituted to obtain a blood culture from any child under 2 years of age presenting to an IHS facility with a temperature of at least 103°F. This relatively high cut-off was chosen to help ensure uniformity of culture rates, and may have slightly lowered overall incidence rates, although not necessarily differentials in incidence rates. The blood cultures were taken to the in-house laboratories, and processed using standard bacteriology techniques. All laboratories with the NAIHS are Joint Commission on Accreditation of Healthcare Organization

(JCAHO) accredited. Specimens that were positive for Hib were collected by Johns Hopkins University (JHU) staff and sent to the JHU laboratory in Whiteriver, AZ. The specimens were identified again using *Haemophilus-Neisseria* identification panels, and further serotyped using standard antisera methods (Microscan; Baxter Laboratories, West Sacramento, CA). During the efficacy trial, no suspected case (infant thought to have sepsis or meningitis) with a negative culture had a positive latex agglutination assay for *H. influenzae* capsular polysaccharide antigen.

Immunization status

Information on vaccine utilization among approximately 18 000 Navajo infants born from April 1988 through June 1992 was obtained from an immunization coverage study conducted by Johns Hopkins personnel. This period was divided into calendar quarters, within each of which one in every 17 live births was sampled from sequential entries in logbooks kept in each Indian Health Service geographical area (SU). Chart reviews of the 894 sampled children were performed to yield basic immunization information up to 24 months of age.

Greater accuracy was gained by combining these coverage study data with data on the 5190 infants enrolled in the efficacy trial from 1988 to 1990, forming a synthetic cohort through use of sampling fractions. From 1988 to August 1990, only efficacy trial participants were receiving Hib vaccine, and thus they perfectly reflect Hib vaccine uptake during that time. After that, the participants continue to represent themselves, while the sampled chart data were used to estimate vaccine coverage among non-participants. Duplicates were eliminated through the use of chart information on participation in the efficacy trial, and by matching on the IHS Medical Registration Number. For each date of a positive Hib culture, a pass was made through the synthetic cohort data to calculate the proportion of children who were <24 months of age as of that date who had received at least one dose with a Hib conjugate vaccine.

Statistical methods

The analytical approach was that of a case-cohort study. All Navajo infants born between 1 May 1988 and 30 June 1992 constituted the full cohort. All infants who were either enrolled in the efficacy study or were sampled in the immunization coverage study were considered to be in the subcohort for which complete immunization status was known.

Cox proportional hazards regression models were fit to examine the relationship of the proportions of children in a SU immunized with Hib conjugate vaccine to risk of invasive Hib disease. A calendar time line with staggered entry was employed to adjust for seasonality.¹⁰ Infants in the subcohort entered the risk set on their dates of birth and then were censored on the date of positive Hib culture, the date they reached 24 months of age, or 30 June 1992, whichever came first. Those who became invasive Hib disease cases in the designated calendar and age frame but were not in the subcohort entered the risk set on the dates of their positive Hib cultures.

We closely controlled for age through use of a spline function. A dichotomous, time-varying covariate indicated receipt of first Hib conjugate vaccine: 0 until vaccination, then 1. The focus of the investigation was a set of four time-varying dummy terms for the percentage of children <24 months of age in the index (case) child's SU of residence who had received at least one Hib

immunization, representing: 0–19% (reference category), 20–39%, 40–59%, 60–79%, and 80–99%.

Results

During 1988 and 1989, the only Hib conjugate vaccine in use on the Navajo Nation was the Hib-OMPC product. During 1990–1992, Hb-OC vaccine (HibTITER®, Lederle-Praxis Biologicals), consisting of oligosaccharides of capsular material (PRP) conjugated to CRM₁₉₇, was introduced on a low level, with a yearly average of 13% of Hib immunizations. Of Hib conjugate immunization given from 1988 to 1992, 92% were Hib-OMPC. The low use of Hb-OC precluded use of vaccine type in analyses. By the end of 1988, 10% of Navajo children <24 months old had received one of the Hib vaccines; this rose to 82% by mid-1992 (Figure 1), by which time well over 90% of the birth cohort was being immunized. Over the same period, rates of invasive Hib disease fell from 1173 per 100 000 child-years in the second half of 1988 to 23 in the first half of 1992 (Figure 1). There were a total of 109 cases, 91 (83%) of which occurred before 1991. In a case-cohort study, there is a theoretical positive correlation between cases not in the subcohort and any cases occurring before then; we assessed this correlation by implementing the bootstrapping algorithm of Wacholder *et al.*¹¹ Because of

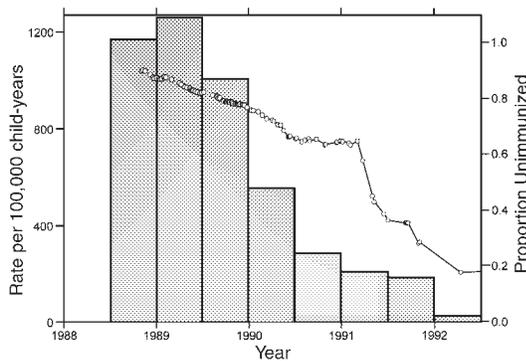


Figure 1 Half-yearly incidence rates of invasive Hib disease in children <2 years old on the Navajo Nation, beginning July 1988

The bars represent half-yearly incidence rates of invasive Hib disease in children <2 years old on the Navajo Nation, beginning July 1988 (left-hand scale). At each point in time a case occurred, the proportion of unimmunized children in the population <2 years old was calculated. Each dot indicates the date of culture of a case (relative to the bottom, calendar axis) and the proportion of children not immunized against Hib at that time (right-hand scale). The difference between the line and the bars approximates the population level indirect effect of the vaccine

negligible correlation, we report standard Cox model-based estimates of standard errors.

The Cox regression analysis resulted in an estimate for the effectiveness of receipt of a Hib immunization of 97.2% (95% CI: 92.3, 99.0) (Table 1). This is similar to estimates made from other studies,^{6–8} but the CI is narrower, being based on many more cases. Of primary interest were the dummy variables for the proportion of the community's <2 year olds who had been immunized. There were significant reductions in risk associated with living in communities with 20–39% immunized and 40–59% immunized as compared to communities with only 0–19% immunized: the estimated reductions were 56.5% and 73.2%, respectively. In an additional model (results not shown), there was no important interaction between the individual and group immunization parameters. Thus, for example, we can interpret the results as: regardless of their own immunization status, children <24 months of age living in communities with about 30% (midpoint of 20–39%) of their peers having received at least one dose of Hib-OMPC have 56.5% less risk of invasive Hib disease as compared to communities with 10% (0–19%) coverage. As for children who have received a dose and live in a more highly immunized community (about 50%), their risk is reduced 99.25% $\{1 - (1 - 0.972) \times (1 - 0.732)\} \times 100\%$ compared to the risk for an unimmunized child in a community with low (0–19%) immunization coverage.

Point estimates of the coefficients for communities that had coverage of 60–79% and 80–99% were positive, indicating increased risk of Hib disease in those communities (i.e. a deleterious indirect effect), but these were not statistically significant. By the time communities had become immunized to that degree, however, there were very few cases of invasive Hib disease occurring. The variances of these estimates therefore were very large, as is evidenced by the wide CI and *P*-values > 0.4.

Discussion

Our analyses furnish direct evidence and estimates of the indirect effect of Hib immunization in a relatively closed population. In a community when about 30% of Navajo children <2 years old had received one or more doses of Hib-OMPC, there was over 50% reduction in Hib invasive disease incidence, and when about 50% were immunized, there was decrease of over 70%. These results correspond to general observations that risk of Hib invasive disease has declined faster than immunization uptake in the US.^{1,12} Other evidence of indirect effects of Hib vaccine in the general US population is the fact that Hib disease declined in infants <12 months old even before conjugate vaccines were licensed for that age group.¹³ Presumably,

Table 1 Estimates of direct and indirect effects of *Haemophilus influenzae* type b (Hib) immunization on the Navajo Nation, mid-1988 to mid-1992. Estimated risk reductions, confidence intervals, and *P*-values from Cox regression model

Model term	Risk reduction (%) (Effectiveness)	95% CI	<i>P</i> -value
Receipt of Hib-OMPC	97.2	92.3, 99.0	<0.001
Live in 20–39% immunized area	56.5	26.3, 74.4	0.002
Live in 40–59% immunized area	73.2	20.4, 90.9	0.018
Live in 60–79% immunized area	-167	-2750, 74.9	0.416
Live in 80–99% immunized area	-521	-51 362, 92.5	0.417

the immunization of children at 15–18 months of age resulted in reduced transmission of Hib disease to younger infants.

Indirect effect of Hib immunization was not seen in a nationwide study in the Netherlands,¹⁴ but the statistical methods used were imprecise, and the immunization uptake of 97% was too high to see effects within age cohorts. In a recent study of Alaskan Native children, high levels of immunization with Hib-OMPC failed to reduce oropharyngeal carriage rates below 6–15% in children <6 years of age,¹⁵ and there was a concomitant rise in incidence of invasive Hib disease among young Hib-OC recipients. Takala *et al.*⁹ showed that in a 1991 sample of children on the Navajo Nation, 1.6% of children <15 months of age who had received at least one Hib-OMPC immunization were positive for Hib OP carriage, compared to 4.7% among those who were unimmunized. Although carriage was not eliminated, our data suggest that this magnitude of reduction in colonization may be sufficient to interrupt transmission to a significant degree in children <2 years of age. One feature of the Hib-OMPC vaccine that may be important in this regard is the high antibody response following a single injection at 2 months old (90% of infants >0.15µg).⁶

By following cohorts and sampled cohorts of children over time, and utilizing information on the varying immunization uptake of their communities of residence, we were able to quantify the degree to which a given level of vaccine coverage corresponds to risk reduction. The opportunity to further quantify the degree of indirect effects still exists in countries where Hib immunization is not routine. Geographically phased-in immunization programmes coupled with surveillance activities could further add to our knowledge of these effects.

The results of our investigation may provide some guidance as to the degree of effect a less industrialized country might realize even with limited coverage levels in a Hib immunization programme. Data on indirect effects provided here could be incorporated into cost-benefit analyses of the introduction of such programmes.

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