Partial Uptake of Varicella Vaccine and the Epidemiological Effect on Varicella Disease in 11 Day-Care Centers in North Carolina

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Background: The increasing use of varicella vaccine in children attending day care has rapidly decreased the incidence of wild-type varicella disease. The herd immunity noted is significant and will have an effect on the epidemiology of natural varicella.

Objective: To monitor the change in varicella incidence in day-care attendees after the licensure of varicella vaccine.

Design: A prospective observational cohort study design.

Setting: Eleven private day-care centers and preschools in North Carolina participated in the study from January 1, 1995, through December 31, 1999.

Participants: All children in the 11 centers were eligible for participation. Some participated more actively, supplying information on a regular basis. Others participated passively. Day-care personnel provided information about all cases of varicella.

Interventions: None.

Main Outcome Variables: The change in the incidence of varicella disease was documented as the use of varicella vaccine increased.

Results: Varicella vaccine coverage increased substantially from 4.4% in 1995 to 63.1% in December 1999. The vaccination rate accelerated dramatically in 1996 and 1997, leveled off in 1998, and rose again in 1999. Cumulative varicella incidence decreased from 16.74 cases per 1000 person-months in July 1996 to 1.53 cases per 1000 person-months in December 1999 in unvaccinated children.

Conclusions: The varicella vaccination rate continued to increase slowly in the day-care population after an initial rapid uptake. The decrease in varicella disease is greater than the increase in varicella vaccination. This herd effect is welcome and even apparent in the unvaccinated children younger than 1 year.


Varicella is often viewed as a common and benign illness of childhood. Serologic evidence has shown that by 20 years of age, 90% of the US population is exposed to the varicella-zoster virus. Most disease occurs in children younger than 10 years, with the highest incidence rates from 3 to 6 years of age. It has also been suggested that increased use of day-care services has lowered the average age of varicella illness.

Despite the perception of varicella as a mostly benign disease, potential complications exist, including secondary bacterial infection, pneumonia, cerebellar ataxia, encephalitis, Reye syndrome, glomerulonephritis, arthritis, and, in the immunocompromised host, disseminated disease. The rate of hospitalization due to varicella has been shown to be 5 to 10 times higher among adults older than 20 years. However, because of the high prevalence of disease in younger groups, children still account for the largest percentage of total complicated cases. Before 1995, approximately 100 deaths per year were attributed to varicella, with more than half occurring in adults. After the licensing of Haemophilus influenzae type b vaccine and until the licensing of conjugate pneumococcal vaccine, varicella was the leading cause of death in US children preventable by childhood vaccination.

The live attenuated varicella vaccine (VARIVAX; Merck & Co, Inc, West Point, Pa) was licensed by the US Food and Drug Administration in March 1995 for use in...
MATERIALS AND METHODS

STUDY DESIGN

This study used a prospective, dynamic observational cohort design. We studied subjects in 11 North Carolina day-care centers or preschools between January 1, 1995, and December 31, 1999. These 11 centers serve a total of 1100 to 1500 children younger than 5 years, and are located in Durham, Raleigh, Cary, Asheville, and Youngsville. All children attending these 11 centers were eligible for inclusion in the study. Enrollment in the study began in 1995 and is ongoing. Subjects were followed up from the time of enrollment in the center until completion of the study or withdrawal from the center.

DATA COLLECTION

Data were collected strictly through observational techniques. Information regarding varicella vaccination status and disease status was collected through brief questionnaires sent to the parents of all children enrolled in one of the participating centers. These questionnaires were distributed 2 to 4 times per year throughout the study.

To monitor varicella outbreaks within the day-care centers and preschools, close varicella surveillance was maintained at each of the 11 sites. Passive surveillance was performed by asking the parents and day-care center or preschool staff to report all suspected cases of varicella to the study coordinator (C.L.B.). In addition, active surveillance was performed by the study coordinator, who visited or called each participating center on a weekly basis to ascertain cases. If a case of varicella was identified, a thorough investigation was initiated to determine the varicella vaccination status and case status of all children within that center. Then, the study coordinator made a visit to that center to ascertain additional cases. In addition, a letter was sent to parents to inform them of the case of varicella in the center and instruct them to call the study coordinator if they suspected that their child had varicella. The study coordinator maintained daily contact with that center to ascertain other possible cases of varicella and recorded information in a surveillance log.

In addition, the study coordinator contacted the parents or guardians of all children suspected of having varicella. If informed consent had already been obtained, the study coordinator directly contacted the parents by telephone. If consent had not been obtained, a letter was sent to parents requesting consent to contact them by telephone. During the telephone interview, the study coordinator obtained a detailed clinical history to determine exposure history, date of onset of illness, number and type of lesions, location of lesions, history of fever or respiratory symptoms, history of physician visit, and medications given. If a telephone interview was not adequate for assessment, the study coordinator or one of the principal investigators made an attempt to examine the child at the Duke Children’s Primary Care Clinic, Durham, or in the day-care centers. A follow-up telephone call was made 10 to 14 days after the initial assessment, to determine possible complications and the number of days of day care or preschool missed by that child. If a child was suspected of having varicella disease but had declined to participate in the study, his/her parents were asked to complete a brief questionnaire regarding symptoms and varicella vaccination status. In addition, the center staff provided anonymous information regarding the vaccination status of non-participating children for whom we had no information.

STUDY DEFINITIONS

Varicella Case

A case described an eligible child presenting with a typical varicella rash or modified varicella-like syndrome as determined by the study coordinator.

Vaccination Status

Vaccination history was determined by a parental yes response to the question, “Has your child ever received the chickenpox vaccine?”

Susceptibility

A child was regarded as susceptible if there was no history of vaccination and a parent responded no to the question, “Has your child ever had the chickenpox?” If the study coordinator subsequently confirmed a case of varicella, the child was no longer considered susceptible. Vaccinated children were considered nonsusceptible after the recorded date of vaccination.

Varicella Vaccine Coverage

Vaccine coverage was defined as the number of children vaccinated divided by the number of children ever eligible for vaccine. Eligibility was defined as at least 12 months of age and no history of varicella or vaccination before 12 months of age.

Varicella Vaccine Uptake

Uptake percentage was calculated by dividing the number of children who received the varicella vaccine between survey healthy individuals aged at least 12 months without history of varicella. Research has demonstrated this vaccine (and a similar product by Oka/Biken in Osaka, Japan) to be highly effective in the clinical setting, preventing 100% of severe clinical disease and more than 80% of all disease. One Oka/Biken long-term study demonstrated no waning of immunity during 20 years of follow-up. When varicella occurs in vaccinated individuals after exposure to individuals with wild-type disease, it has been shown to be a milder, modified varicella-like syndrome occurring at a rate of 1% to 3% annually. Since the vaccine was licensed more than 4 years ago, uptake has increased steadily. The National Immunization Survey has reported national coverage among children aged 19 to 35 months of 26.0%, 43.2%, and 59.4% in the years 1997, 1998, and 1999, respectively. This study considers the effect of varicella vaccination on a North Carolina day-care population when vaccine is administered to only a portion of the day-care par-
The cumulative incidence of previous varicella disease was determined by dividing the number of children with a history of disease by the total number of children at a particular observation point.

**PERSON-TIME CALCULATIONS**

Day-care enrollment records collected at the time of questionnaire distribution were used to assess person-time contributed between survey periods, stratified by age. Observations and calculations were performed as follows. If a child was verified as enrolled at one of the study day-care centers at two consecutive survey periods (at times $t_1$ and $t_2$), then he/she was assumed to have been present for the entire survey period, contributing the entire length of person-time ($t_2 - t_1$).

If a child was verified as enrolled at one survey point ($t_1$) but not at the next survey point ($t_2$), it was assumed that the child had withdrawn at some point between the surveys. Total observed person-time was estimated to be one half of the interceding interval, i.e., $(t_2 - t_1)/2$.

If a child had not been verified at one survey point ($t_1$) but was present at the next survey point ($t_2$), it was assumed that he/she had enrolled at some point between the surveys. Total observed person-time was estimated to be one half of the interceding interval.

Total person-time contributed since the beginning of observation in January 1995 was then stratified into the following 4 mutually exclusive categories:

**Unvaccinated Nondiseased**

If a child had no history of vaccination or varicella disease according to our definitions, the total person-time of observation was classified as unvaccinated and nondiseased. This is equivalent to susceptible or at-risk person-time. If a child subsequently experienced varicella illness or vaccination, he/she was considered immune, and all person-time was entered into a different, appropriate category.

**Vaccinated Nondiseased**

If a child had previously received varicella vaccine or was given vaccine at some time during study enrollment but had not yet experienced varicella illness, the person-time contributed after the date of vaccination was classified as vaccinated but nondiseased.

**Vaccinated Diseased**

If a child had previously received varicella vaccine but had already experienced varicella illness, the person-time contributed was categorized as unvaccinated but diseased from the date of disease forward.

**Unvaccinated Diseased**

If a child had not received varicella vaccine but had already experienced varicella illness, the person-time contributed was classified as vaccinated and diseased continuing from the date of the later of the 2 events (normally varicella disease).

For children who enrolled between survey points, the person-time of observation contributed before the first verified enrollment was classified according to the child's person-time category status (eg, unvaccinated diseased) at that initial survey point. Similarly, for children who left a day-care center between survey points, all person-time contributed after the last verified enrollment was classified according to the child's person-time category at that last survey point. Assuming that enrollment or withdrawal from each day-care center was not related to individual vaccination or varicella status, any misclassification resulting from these assumptions would be nondifferential.

**INCIDENCE RATES**

The incidence rates for varicella were defined as the number of new varicella cases divided by the total person-time at risk for development of disease. Incidence rates were further stratified by vaccination status and age group. The incidence rate in those unvaccinated was defined as the number of new cases of varicella in unvaccinated children, divided by the total unvaccinated and nondiseased person-time. Incidence rate in those vaccinated was the number of new cases among vaccinated children, divided by total vaccinated and nondiseased person-time. Age group for the duration of an entire interval between observations was determined by the age of the child at the beginning of the interval.

**STATISTICS AND ANALYSIS**

Vaccination rates and incidence rates with 95% confidence intervals (CIs) were calculated using Stata for Windows Version 6.0 (Stata Corporation, College Station, Tex), and $\chi^2$ statistics were used for comparison of proportions or analysis of trends.

If a date of birth for a child was unknown or not available, a value was imputed by assigning the mean age of all other children in the same classroom during the first survey point at which the child was verified as enrolled.

A total of 4064 children were observed during the 1995-1999 study. The mean number of children present at each survey point was 1422, contributing an average total of 8713.2 person-months per observation period. An average of 4.8%, 10.6%, 13.0%, 16.6%, and 55.0% of observed person-time in each interval was contributed by children aged 0 to 11, 12 to 23, 24 to 35, and 36 to 47 months and 48 months or older, respectively. The population consisted of 50.5% boys for the entire study period. Information regarding vaccination status and history of varicella disease was obtained on 74.3% and 76.7% of subjects, respectively.
Vaccine coverage increased substantially in all eligible age groups during the study period ($P<.001$) (Figure 1). Overall vaccine coverage increased from 4.4% (95% CI, 3.3%-5.9%) during January through March 1995 to 63.1% (95% CI, 59.8%-66.4%) in December 1999.

The average monthly vaccine uptake increased from 0.17% per month to 1.57% per month since the beginning of observation ($P=.02$). The highest monthly uptake in any group was recorded during 1997 (Figure 1).

Cumulative varicella incidence decreased significantly ($\chi^2$ test for trend, $P<.001$) in all age groups (Figure 2). Within the last year of observation, cumulative incidence continued to decrease significantly among children at least 36 months of age. Age-related differences in varicella remained apparent.

Overall varicella incidence rate per 1000 person-months decreased in the vaccinated children from 5.35 (95% CI, 1.74-12.50) before July 1996 to 1.01 (95% CI, 0.12-3.65) in December 1999. The overall incidence rate

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**Figure 1.** Varicella vaccine coverage by age in months and date interval.

**Figure 2.** Varicella cumulative incidence by age in months and date interval.
also decreased among the unvaccinated children, from 16.74 (95% CI, 12.77-21.54) before July 1996 to 1.53 (95% CI, 0.50-3.58) in December 1999 (Figure 3), suggesting strong indirect effects of vaccination at the current level of partial uptake. Disease in children younger than 1 year (not eligible for vaccination) has recently disappeared.

Among the oldest children observed (aged ≥48 months), the distribution of observed person-time is displayed in Figure 4. The proportion of vaccinated person-time has increased significantly (P < .001), with a reciprocal decrease in unvaccinated person-time. As a proportion of the unvaccinated (including diseased and non-diseased children) person-time, the unvaccinated and diseased person-time has also decreased significantly (P < .001). This trend has permitted the susceptible person-time (without a history of disease or vaccination) to approach about 39.0% of observed person-time in the last observation period.

Figure 3. Varicella incidence rate in unvaccinated children by age in months and date interval.

Figure 4. Distribution of categorized person-time among children 48 months or older by date interval. UV indicates varicella unvaccinated; V, varicella vaccinated; D, past varicella disease; and ND, no past varicella disease.
These results demonstrate a significant increase in vaccine coverage for all eligible age groups in the study period. There is a correlated decrease in varicella disease in both vaccinated and unvaccinated children. At a partial uptake of 60%, vaccine has been administered to a high enough proportion of the children in the population that incidence of varicella disease has decreased within the unvaccinated population. In the geographically concentrated environment of the day-care centers, a strong herd immunity effect is clearly evident. The indirect effects of vaccine use are important to consider in evaluating the success of vaccination programs, and they have undergone extensive mathematical modeling. This study shows the varicella vaccine to be extremely effective, given partial uptake by a limited population.

It is also apparent that vaccine uptake has slowed for our population after the initial early rise. We believe that as varicella disease becomes increasingly infrequent, there may be a decreased motivation to obtain an elective vaccine for eligible children. This trend has already been demonstrated to occur with respect to the pertussis vaccination program. Research has shown in general that as caregivers perceive decreased risk for disease, the motivation for and likelihood of vaccination also decrease. The recent high levels of pertussis (and other) vaccination is a tribute to the effectiveness of school entry and day-care immunization requirements.

As vaccine coverage rises and stabilizes, disease becomes increasingly rare. By 48 months and older, children are immune to varicella due to vaccine or due to the increasingly rare wild-type disease. Thus, although the unvaccinated children constitute a continually smaller proportion of the entire population as assessed by person-time, there remains a large proportion of susceptible person-time among school-age children. Based on observed trends, it is possible that the unvaccinated proportion of person-time eventually will be constituted entirely of susceptible (nondiseased) person-time. If vaccine coverage does not increase, a large population of children will remain susceptible to varicella.

The unvaccinated children may remain free of disease through indirect effects of the vaccine only as long as they remain in populations with coverage levels that are high enough. Day-care centers typically demonstrate higher levels of vaccine use compared with the national rates for similar-aged children not enrolled in day care. Without school entry and day-care admission requirements for varicella vaccination, areas with low vaccine use will always exist. Varicella vaccine coverage rates vary tremendously, last reported by the Centers for Disease Control and Prevention to range from 3% to 33% among states from July 1996 to June 1997 and 13% to 40% among various urban areas for all of 1997. National Immunization Survey data reported for 1999 suggest that 59.4% of children in the United States are now immunized against varicella. Even if children remain free of disease in areas with high vaccine uptake, continued existence of areas with low vaccine uptake creates the potential for circulating wild-type virus. A child who remains susceptible and who is placed in a region with low vaccine coverage and higher levels of circulating wild-type disease will be at significantly increased risk of contracting disease, with potential complications. Partial vaccination uptake, with disparate levels of coverage in different areas, will place an unacceptable number of older children at risk for complications of varicella.

Physicians previously have demonstrated poor adherence to the recommendations for varicella immunization by the American Academy of Pediatrics and the Advisory Committee on Immunization Practices. Several years ago, a Washington State survey of 574 pediatricians demonstrated that less than 50% of the 434 respondents recommended immunization in their practices. The main reasons for low adherence were continued perceptions of varicella as a benign disease and questions regarding the persistence of immunity from the varicella vaccine. A campaign for adding varicella to our already effective vaccination requirements for school entry is needed to increase physician adherence and to educate families regarding the advantages of vaccination.

A distinct shift in the epidemiological susceptibility to varicella with the use of vaccine is already perceptible because of the compact and accelerated nature of disease transmission in the day-care setting. There has been a marked decrease in varicella disease in children attending day care due to vaccination and significant herd immunity. Rates of vaccination appear to be continuing to climb, but the elevation may not be sustainable unless varicella vaccination is incorporated into the school admission requirements.

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REFERENCES


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**Correction**

Error in Reported Figures and in Reference Name. In the nutrition article titled “Beverage Choices Affect Adequacy of Children's Nutrient Intakes,” published in the November issue of the ARCHIVES (2000;154:1148-1152), on page 1151, the fifth line in column 2 should have read “by 1% to 4% per ounce (OR, 0.99-0.96)” and the sentence starting on the eighth line should have read: “For 2- to 5-year-old girls, the median serving of 8 oz of carbonated soda would decrease the likelihood of achieving recommended calcium intake by 28%. Substituting 8 oz of milk for the soda would increase the likelihood by 1141%, that is, more than 10 times.” On page 1152, in paragraphs 2 and 3 and reference 4, the first author should have been Harnack.