

Varicella-related hospitalizations in the vaccine era

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Background and aim. Varicella is normally a self-limited disease of childhood that does not require hospitalization. In the prevaccine era varicella caused >9000 hospitalizations per year. To determine whether the varicella vaccine, licensed in 1995, has decreased hospitalizations because of varicella, we examined national rates of varicella-related hospital discharges (VRHD) covering a 12-year period that included pre- and postvaccine data.

Methods. Data from the 1988 to 1999 National Hospital Discharge Survey and population estimates from the National Center for Health Statistics were used to calculate biennial rates of VRHD. To control for coding consistency, rates of invasive disease caused by *Haemophilus influenzae* were calculated for the same time period.

Results. The rate of VRHD for 1998 to 1999 (4.42 hospitalizations per 100 000 person-years) was the lowest of any of the periods measured, but this difference was not statistically significant. The same was true of VRHD limited to cases with varicella coded as the primary diagnosis. A trend toward a decrease in VRHD was observed in all age groups examined, although none was statistically significant. Calculated rates from this national data set were in agreement with prior studies using active surveillance, and the previously documented fall in hospitalizations caused by invasive *H. influenzae* disease was demonstrated using these methods.

Conclusions. Although it is uncommon for children with varicella to require hospitalization, these cases are an important contributor to cost and morbidity of varicella. In contrast to predictions of prelicensure mathematical models, there has not been a significant decrease in total or first diagnosis VRHD since the vaccine became

available. Current coverage levels are below those used in prelicensure models. Increased acceptance of the varicella vaccine by parents and practitioners may aid in the further decrease of varicella-related hospitalizations.

INTRODUCTION

Before the live attenuated vaccine for varicella was approved in 1995 and incorporated into the recommended immunization schedule the following year, mathematical models¹ and cost-benefit analyses² predicted a prompt decrease in hospitalizations caused by varicella as a result of its use. Varicella is typically a self-limited disease that does not require hospital admission. Yet before 1995 varicella was estimated to account for >9000 hospitalizations annually in the United States.³ A study performed before vaccine licensure reported a rate of 35.1 hospitalizations per 100 000 patient years in the 0- to 4-year age group.⁴

Because hospitalization is a rare consequence of varicella disease, most studies of vaccine efficacy have evaluated protection from disease after exposures within homes or school settings rather than prevention of hospital admission. Few data are available on the ability of varicella vaccine (VV) to prevent varicella-related hospitalizations (VRHD) in any age group. A single retrospective study from a tertiary care pediatric hospital failed to show a reduction in emergency department visits or hospitalizations caused by varicella in the 2 years after vaccine introduction.⁵ However, no assessment of vaccination coverage was available for that study population.

Since its licensure use of VV has risen yearly, according to data from the National Immunization Survey,⁶ and >22 million doses have been distributed.⁷ Numerous studies have demonstrated the safety and efficacy of VV for routine prevention in susceptible populations.^{7,8} Additionally herd immunity within settings such as day-care centers has been documented.⁹ Recently Seward et al.¹⁰ reported the results of an extensive postvaccine active surveillance effort in three counties in the United States, which demonstrated a marked decrease in total number of cases of varicella between 1995 and 2000. In that study there was a trend toward a decrease in the number of varicella-related hospitalizations, but this was not statistically significant.

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This study examines national trends in varicella-related hospitalizations using data from the National Hospital Discharge Survey (NHDS) covering a 12-year period from 1988 through 1999. Cases were extracted using International Classification of Diseases, 9th ed., Clinical Modification (ICD-9-CM) codes specific for varicella disease, and rates were calculated by census-derived population estimates. Comparison was made to rates of disease due to invasive *Haemophilus influenzae* disease, which, as previously shown in active surveillance studies, decreased dramatically during an overlapping time period after introduction of conjugate vaccines against *H. influenzae* type b.^{11, 12}

METHODS

The NHDS is a nationally representative annual sampling of discharges from nonfederal short stay hospitals that is conducted by the National Center for Health Statistics (NCHS). The design of the NHDS has been described in detail.¹³ Briefly a three stage survey design includes all US hospitals with 1000 or more beds and a representative sample of others based on geographic location, size and specialty. Each year ~500 hospitals participate in the survey. A random selection of discharges from each of these facilities provides a total sample of ~250 000 entries per year. Discharge records are weighted according to size of hospital and region to allow calculation of national estimates. Each discharge record contains demographic information about both the patient and the hospital as well as up to 7 diagnosis codes, consistent with the ICD-9-CM.

We examined data from the NHDS for 1988 through 1999. Extraction of records was based on ICD-9-CM codes for varicella (052) and for invasive disease caused by *H. influenzae* including bacteremia (038.41, 041.5) and meningitis (320.0). A VRHD was defined as a record containing a code for varicella in any of the seven discharge diagnosis fields. Appropriate ICD-9-CM codes for varicella-associated underlying conditions and complications were previously defined by Meyer et al.¹⁴ These included conditions such as malignancy and immunodeficiency (including HIV/AIDS) and sequelae such as pneumonia, cellulitis, encephalitis and death. Records were subdivided into four age categories (0 to 4, 5 to 14, 15 to 44 and ≥ 45 years). Because racial data are missing for ~20% of records in the NHDS, records were not subdivided by race. Record extraction was done using MATLAB software (The MathWorks, Natick, MA) and Epi-Info 2000 (Version 1.1.2; CDC, Atlanta, GA). Population estimates used in the calculation of rates were supplied by the NCHS and were consistent with census estimates.

Standard errors and 95% confidence intervals were calculated according to published NCHS guidelines. According to these procedures estimates derived from the NHDS that are based on fewer than 30 actual

discharges should not be reported, because these often have unacceptably large relative standard errors (i.e. $>30\%$). Projected values based on 30 to 60 discharges should not be assumed to be reliable, and the same is true of any estimate with a calculated relative SE of $>30\%$, regardless of sample size. Potentially unreliable data points are noted where appropriate in this report. Because of sample size limitations, data were aggregated into 2-year periods to assist in the analysis of broad trends. This allowed for a comparison between the two 2-year periods after VV licensure (1996 through 1997 and 1998 through 1999) and preceding periods of equal length. Statistical testing among these groups was done using one-way ANOVA (Instat Version 3.00; Graphpad Software, San Diego, CA). Pooled pre- and postvaccine data were compared with unpaired two tailed *t* tests. Similar comparisons were made for estimates of hospitalization caused by invasive *H. influenzae* disease before (1988 through 1989) and after (1990 through 1999) the introduction of conjugate vaccine. According to NCHS guidelines census-derived denominators were assumed to be free of error.

RESULTS

From a total of 3 263 036 records in the NHDS from 1988 through 1999, 1584 (0.05%) contained a code for varicella. These corresponded to an estimated 179 868 VRHD during the 12-year study period. Varicella was the primary diagnosis in 875 (55%) of these records. The rate of VRHD was lowest in the two postvaccine time periods (Table 1), but this change was not statistically significant ($P = 0.31$ by ANOVA). The same was true of the change in rate of varicella as a first listed diagnosis ($P = 0.29$). Aggregation of data into pre- and postvaccine time periods produced similar results (Table 2).

As described in prior studies, the rate of VRHD was much greater in the 0- to 4-year age group than in older groups (Fig. 1). During the 12-year study period, the rate of VRHD did not significantly change either in this group or in two consecutively older groups (ages 5 to 14 and 15 to 44 years). Small numbers of hospitalizations in the ≥ 45 -year age group led to relative standard errors that were too great to allow similar statistical testing.

During the study time period 6.5% of projected VRHD also included an ICD-9-CM code for any malignancy, and 3.4% included an immunologic deficit (including HIV/AIDS). Of the common varicella-associated complications that we examined, secondary infections such as cellulitis were the most common, occurring in 18.6% of cases. Other sequelae such as hemorrhagic complications, central nervous system disease, pneumonia and death were rare, each occurring in fewer than 5% of hospitalizations.

Consistent with findings of studies utilizing active surveillance, the incidence of invasive *H. influenzae*

TABLE 1. Total cases and US population rates projected from the National Hospital Discharge Survey for total (all diagnosis) and primary (first diagnosis) varicella-related hospital discharges (VRHD) by time period, 1988 to 1999. Rates are reported as cases per 100 000 person-years.

Years	All Diagnosis VRHD	Rate	First Diagnosis VRHD	Rate
1988–1989	32 758	6.71 (6.08–7.95)*	13 452	2.76 (2.40–3.11)
1990–1991	27 373	5.41 (4.59–7.00)	16 443	3.25 (2.65–3.85)
1992–1993	29 786	5.75 (4.63–7.94)	16 453	3.18 (2.35–4.00)
1994–1995	37 442	7.09 (6.05–9.11)	23 464	4.44 (3.60–5.28)
1996–1997	28 270	5.25 (4.55–6.63)	13 796	2.56 (2.14–2.98)
1998–1999	24 239	4.42 (3.49–6.23)	14 543	2.65 (2.22–3.08)
Total	179 868		98 151	

* Numbers in parentheses, 95% confidence interval.

TABLE 2. Biennial rates of hospital discharge caused by varicella and invasive *Haemophilus influenzae*, 1988 through 1999, by vaccine status and age group

The prevaccine period represents 1988 through 1995 for varicella and 1988 through 1989 for *H. influenzae*. Rates are reported as cases per 100 000 person-years. Statistical comparison was performed using unpaired two tailed *t* tests.

Disease	Category	Prevaccine	Postvaccine	<i>P</i>
Varicella	Total	6.24 (5.61–7.47)*	4.83 (4.12–6.22)	0.14
	First diagnosis	3.42 (2.98–3.86)	2.61 (2.30–2.92)	0.13
	0–4 yr	35.53 (27.11–44.07)	27.17 (20.78–33.57)	0.42
	5–14 yr	9.48 (7.19–11.76)	7.62 (5.48–9.75)	0.55
	15–44 yr	3.55 (3.14–3.97)	2.78 (1.99–3.56)	0.38
<i>H. influenzae</i>	Total	4.40 (3.66–5.86)	1.20 (0.92–1.73)	<0.0001
	0–4 yr	39.74 (32.97–46.51)	4.93 (3.44–6.42)	<0.0001

* Number in parentheses, 95% confidence intervals.

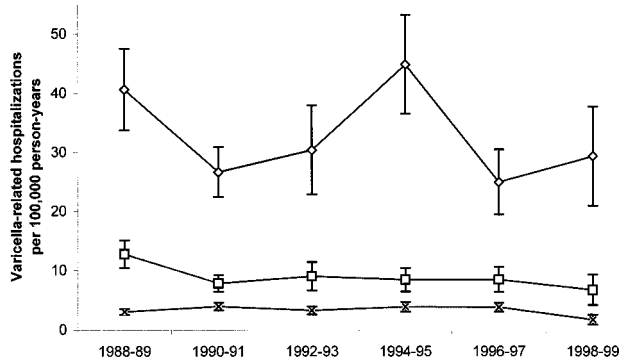


FIG. 1. Rates (per 100 000 person-years) of varicella-related hospital discharge by age group, 1988 to 1999. Bars, standard errors of estimates. Statistical analysis by one way ANOVA showed no difference in any of the displayed age groups. The final point (1998 to 1999) in both the 5- to 14- and 15- to 44-year age groups is based on fewer than 60 actual discharges in the NHDS data set and must be considered a potentially unreliable estimate. ◇, 0 to 4 years; □, 5 to 14 years; ×, 15 to 44 years.

disease decreased markedly during the study period (Table 2). This was observed in both in the total population (a decrease of >70%) and the youngest cohort (0 to 4 years), the group most likely to acquire invasive disease from this organism, in which the decrease was >85%. Estimates of biennial rates after 1991 are based on very small sample sizes and have large relative standard errors. Thus pooled data are presented to demonstrate the overall trend rather than to attempt to accurately quantify the incidence of invasive *H. influenzae* disease during those periods.

DISCUSSION

Analysis of hospital discharges is an inexpensive, relatively simple alternative to active surveillance for monitoring disease trends. Active surveillance allows direct measurement of disease rates but is both time- and resource-intensive. Hospital discharge data has been used to measure patterns of respiratory illnesses,¹⁵ rotavirus disease¹⁶ and pediatric hospitalizations.¹⁷ We investigated changes in VRHD during 12 years using a nationally representative database. This methodology has several limitations, including the assumption that hospital coding for varicella did not change during this period. Varicella is a common, recognizable entity, presumably less subject to miscoding than other diagnoses. Omission of federal and long term facilities certainly resulted in missing cases, more likely in adults than in children. However, we calculated prevaccine rates of VRHD similar to those found in a recent study utilizing active surveillance.⁴ Others have reported lower rates of hospitalization,^{18, 19} but these generally used a stricter case definition (a first or second coded diagnosis) than ours.

Despite increasing use of VV since its licensure,⁶ we observed neither a significant decrease in the incidence of VRHD nor a shift toward an older, unvaccinated cohort. This finding was concordant with data reported by Seward et al.,¹⁰ which demonstrated a similar, nonsignificant trend in three counties with above average vaccination rates. Although data from the National Immunization Survey indicate that the national

rate of VV coverage was 43.2% for children 19 to 35 months old in 1998, there was significant regional variation. South Dakota reported a 12.9% rate of coverage, whereas the District of Columbia had nearly 60%, both below levels used in precicensure models.¹ State hospital discharge data might allow comparison of VRHD among regions with disparate vaccination rates. It is unclear why adoption of VV has not been as rapid as either the conjugate *H. influenzae* type b vaccine that preceded it or the conjugate pneumococcal vaccine that followed. CDC has described barriers to varicella immunization, including the perception of varicella as a mild disease, concerns about efficacy and inadequate insurance coverage.²⁰ NHDS data affords no way of determining whether cases of VRHD had received VV. Determination of the role of vaccine failure *vs.* failure to vaccinate requires separate study.

Another possible explanation for our result is that hospitalized patients might have been excluded from vaccination on the basis of underlying disease. VV is contraindicated in patients with some malignancies or immunodeficiencies.²¹ We examined the prevalence of some predisposing conditions among patients with VRHD. The frequency of each was too low to allow for analysis, but there did not appear to be an increase in any of the categories studied. As described, most hospitalizations caused by varicella appear to occur in previously healthy children.^{14, 19}

To control for changes in coding, we quantified rates of invasive *H. influenzae* disease. Active surveillance has demonstrated a decrease in *H. influenzae* type b cases after vaccine introduction in 1989.^{11, 12} Although there is no separate ICD-9-CM code for the type b serogroup, aggregate rates of *H. influenzae* invasive disease dropped to levels essentially undetectable by NHDS data. The concordance between these data and active surveillance further validates the use of hospital discharge data for monitoring of vaccine efficacy.

The utility of VV has been demonstrated in both pre- and postlicensure studies. It seems likely that the failure, in this analysis, to decrease hospitalization rates in the immediate postlicensure period is the result of reluctance to embrace utilization of this vaccine by both pediatricians and parents. Increasing coverage, especially in underrepresented areas, and expanding use in suitable high risk populations will likely lead to decreases in VRHD.

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