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## Impact of the Maturing Varicella Vaccination Program on Varicella and Related Outcomes in the United States: 1994–2012

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### Abstract

**Background**—Although the 1-dose varicella vaccination program, introduced in 1996, has led to significant declines in varicella disease, outbreaks continued to occur which led to the adoption of a 2-dose vaccination program in 2007. We previously reported an 88% decline in varicella-related hospitalizations and 59% decline in outpatient visits during 1994–2002. We now update data on varicella health care utilization with 10 years of additional data, during a period of stabilizing first-dose coverage and rapidly-increasing second dose coverage.

**Methods**—We performed a retrospective cohort study using claims data from 1994–2012 Truven Health MarketScan® databases. We examined trends in rates of varicella-related outpatient visits and hospitalizations for MarketScan enrollees aged 0–49 years, including outpatient laboratory testing, outpatient antiviral use and pediatric strokes, with 1994–1995 as the pre-vaccination period and 2006–2012 as the 2-dose varicella vaccination period.

**Results**—Varicella outpatient visits declined 84% in 2012 versus the pre-vaccination period, with a 60% decline during the 2-dose period. Varicella hospitalizations declined 93% in 2012 versus the pre-vaccination period, with a 38% decline during the 2-dose period. The proportion of those with a varicella outpatient visit having varicella laboratory testing increased from 6% in 2003 to 17% in 2012. There were 21,445 (17%) with a claim for antivirals, which was relatively stable over time. There was no reduction in pediatric strokes during 1994–2012.

**Conclusion**—We document from our large study population that the varicella vaccination program has led to significant declines in outpatient visits and hospitalizations from the pre-vaccination period through 2012, with additional declines during the 2-dose varicella vaccination period.

### Keywords

Varicella; Vaccination; MarketScan; Hospitalizations; Outpatient Visits

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**Disclaimer:** The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, US Department of Health and Human Services.

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## Introduction

Historically, varicella was a common pediatric condition. While generally self-limited, it was responsible for significant morbidity and mortality due to serious secondary bacterial infections, pneumonia, cerebellar ataxia, transverse myelitis, encephalitis, Reye Syndrome, myocarditis, hepatitis, and hemorrhagic complications[1]. Strokes have also been putatively linked to acute varicella[1–5].

The one-dose varicella vaccination program in the U.S., which began in 1996[6], led to significant declines in disease burden from varicella: deaths declined by 88%, including a 97% decline among children and adolescents 20 years of age during 2005–2007 compared to 1990–1994[7], and hospitalizations declined 65% in 2000–2006 compared to 1988–1995[8]. Nevertheless, despite 89% vaccine coverage among preschool-children ten years into the program[9], varicella outbreaks continued to be reported even among school populations with high 1-dose coverage[10]. In 2007, a routine 2-dose schedule for varicella vaccination was recommended in order to improve protection, and further decrease varicella cases and outbreaks[10].

Since these new recommendations were adopted, first-dose coverage has remained stable at 90% among pre-school aged children[9] and increased from 65% in 2006 to almost 95% for adolescents in 2012[11]. Second-dose vaccination coverage has also been quickly increasing. Second-dose coverage among kindergarten students in 36 states and Washington DC reached a median of 93.8% by 2012[12] and reached 80–92% among children aged 7 years in six sentinel sites[13].

Previous data from the MarketScan<sup>®</sup> health care claims databases showed an 88% decline in varicella-related hospitalizations and 59% decline in outpatient visits between 1994, prior to varicella vaccine licensure, to 2002, when 1-dose vaccine coverage among preschool children reached 81%[14]. We now update these analyses with an additional 10 years of data to describe the impact of high, stable levels of first-dose coverage among pre-school children and rapidly-increasing levels of second-dose coverage on the epidemiology of varicella and related outcomes. We also investigated whether rates of pediatric strokes have been affected by order-of-magnitude declines in varicella rates in order to explore hypothesized associations between varicella infection and increased risk of pediatric stroke[1–5].

## Methods

### Data Source

We used claims data from 2003–2012 Truven Health MarketScan<sup>®</sup> Commercial and Medicare Databases, which include data from public and private employers, health insurance plans, and Medicare as previously described[14]. Data on varicella outpatient visits and inpatient admissions were taken from the previous publication on 1994–2002 data by Zhou et al [14]. Annual enrollment ranged from an average of 4 million during 1994–2002 to > 50 million in 2012. The enrolled population increased as Truven Health recruited new large employers and health insurance plans into its system. This study constituted analysis of

secondary data without identifiers, and therefore did not require IRB approval or informed consent.

### Study Definitions

The study population consisted of persons aged 0–49 years who were enrolled in MarketScan during 1994–2012. The pre-vaccination period was defined as the years 1994–1995; the 2-dose varicella vaccination period was defined as the years 2006–2012. A varicella outpatient visit or inpatient admission was defined as a medical claim with a varicella International Classification of Diseases (ICD)-9 code (0.52xx). We excluded persons with a coexistent ICD-9 herpes zoster diagnostic code (053.xx). Our main analysis focused on varicella coded as the primary diagnostic code, but we also looked at outpatient and inpatient claims with varicella coded in any of the diagnostic positions.

Laboratory testing was defined as a medical claim with one of 38 relevant Current Procedure Terminology (CPT) codes (Supplementary Appendix 1) 1 day before to 10 days after the claim with a varicella diagnostic code; actual test results were not available. Antiviral prescription was defined as one of 134 antiviral National Drug Codes (NDC) (Supplementary Appendix 2) 1 day before to 10 days after the claim with a varicella diagnostic code.

Pediatric stroke was defined as a claim among children 0–17 years of age for an ischemic cerebrovascular with no recognized secondary etiology (primary diagnostic ICD-9 codes: 433.x; 434.xx, 436; and 437.xx, excluding 434.1, 434.10, 434.11, 437.2, 437.3, 437.5, 437.6, and 437.7).

### Data Analysis

For 2003–2012, we calculated rates of varicella-related outpatient visits and hospitalizations per 100,000 enrolled population, using relevant enrollment denominators for our sub-group analyses; rates for 1994–2002 were taken from our previous publication[14]. We conducted Poisson regression analysis to assess changes in varicella rates and pediatric stroke rates over time.  $P < 0.05$  was considered statistically significant. To investigate whether changes in varicella hospitalization rates during 2003–2012 could be due to changes in healthcare utilization or changes in the database occurring over time, we also examined varicella hospitalization as a proportion of all hospitalizations[14]. To assess changes in disease severity, we calculated the ratio of varicella hospitalizations to outpatient visits during 2003–2012 with varicella as the primary diagnostic code[14]. s

Historically, varicella was a seasonal illness[15]. We examined whether varicella continued to demonstrate seasonality during 2003–2012 by calculating the proportion of varicella cases that occurred each year during December through May. We assessed the proportion of varicella cases with laboratory testing, and the proportion with antiviral claims during 2003–2012. We compared rates of hospitalizations for stroke among children aged 0–17 years (primary diagnostic code) in 1993–1996 versus 2010–2012. Analyses were performed using Excel and SAS (version 9.2; SAS Institute Inc, Cary, NC).

## Results

### Rates of Varicella-Related Outpatient Visits

Outpatient and hospitalization trends for varicella did not differ qualitatively whether we assessed varicella coded in the primary versus any diagnostic position. We therefore only present outpatient and hospitalization data based upon primary diagnostic positions since these are more specific. We excluded 0.6% of varicella claims that had a co-incident herpes zoster code.

Overall, varicella outpatient visits declined 84% in 2012 versus the pre-vaccination period (1994–1995) from an average rate of 215 per 100,000 population to 33 per 100,000 population ( $p<0.001$ ) (Figure 1). Seventy-eight percent of this decline in outpatient visits occurred during the 1-dose period and 22% of this decline occurred during the 2-dose period. During the latter part of the 1-dose program (2002–2006), outpatient visits were fairly stable ranging, from 73 to 89/100,000 population. During the 2-dose varicella vaccination period (2006–2012), outpatient visits declined 60% ( $p<0.001$ ). Among the 44 states that had at least 100,000 MarketScan beneficiaries, the rate of varicella outpatient visits in 2012 ranged from 12.2/100,000 in Wisconsin to 42.5/100,000 in Kansas. By region, outpatient visits per 100,000 population ranged from 24.4 in the Northeast to 27.2 in the West.

Outpatient rates declined for all age groups in 2012 compared to the pre-vaccination period. From the pre-vaccination period to 2012, there was a 95% decline in varicella outpatient visits for infants aged <1 year and 75–89% declines for enrollees aged 1–49 years (Table 1). During the 2-dose period (2006–2012), varicella outpatient visits declined 35% for <1 year-olds, 66% for 1–9 year-olds, 65% for 10–19 year-olds, and 37% for 20–49 year-olds. However, outpatient visits for infants <1 year did increase slightly in 2011–2012 from 81 per 100,000 in 2010 to 83 per 100,000 and 89 per 100,000 in 2011 and 2012 respectively.

### Rates of Varicella-Related Hospitalizations

Overall, varicella hospitalizations declined 93% in 2012 versus the pre-vaccination period from an average rate of 2.35 per 100,000 population to 0.16 per 100,000 population ( $p<0.001$ ) (Figure 2). Eighty-nine percent of this decline in hospitalizations occurred during the 1-dose period and 11% of this decline occurred during the 2-dose period. During the 2-dose varicella vaccination period (2006–2012), hospitalizations declined 38% ( $p=0.0230$ ).

Hospitalization rates declined for all age groups in 2012 compared to the pre-vaccination period. From the pre-vaccination period to 2012, there was a 99% decline in varicella hospitalizations for infants aged <1 year and 86–96% declines for enrollees aged 1–49 years (Table 1). During the 2-dose varicella vaccination period, varicella hospitalizations declined 46% for <1 year-olds, 47% for 1–9 year-olds, 56% for 10–19 year-olds and 10% for 20–49 year-olds.

We found that varicella hospitalizations as a proportion of all hospitalizations declined 32% from 0.0055% in 2003 to 0.0037% in 2012. When compared to the pre-vaccination period, that proportion declined 85% from an average of 0.025%.

We examined the severity of varicella cases by calculating the ratio of varicella hospitalizations to outpatient visits. Compared to the pre-vaccination period, these ratios declined by 65%, 64%, and 30% for enrollees aged <10 years, 10–19 years, and 20–49 years, respectively. During 2003–2012, these ratios declined 2% for infants aged <1 years (0.004 in 2003 to 0.004 in 2012), 25% for adolescents aged 10–19 years (0.005 in 2003 to 0.004 in 2012), and 44% for adults aged 20–49 years (0.015 in 2003 to 0.008 in 2012).

### **Seasonality, Laboratory Testing, and Antiviral Use**

We examined varicella-related visits by month of onset to determine whether varicella seasonality had changed over time. In 1994, 65% of visits occurred during winter-spring months (December through May), but this proportion declined to 52% by 2012.

Of 128,616 enrollees with outpatient varicella diagnoses during 2003–2012, the proportion having varicella laboratory testing increased from 6% in 2003 to 17% in 2012 (Figure 3); the increase was 133%, 165%, and 125% for <10, 10–19, and 20–49 year-olds. Furthermore, 21,445 (17%) of outpatient cases were prescribed antivirals, including 9%, 18%, and 36% of those aged <10, 10–19, and 20–49 years, respectively. Proportions prescribed antivirals were relatively stable over time, with 17% prescribed antivirals in both 2003 and 2012. Of the 21,445 prescriptions, 75% were for acyclovir, 21% for valacyclovir, and 4% for famciclovir.

### **Rates of Pediatric Stroke**

The rate of stroke hospitalizations for children aged 0–17 years remained stable over time, with an average rate of 1.02 per 100,000 population during 1993–1996 and 0.93 per 100,000 during 2010–2012. There was no statistically significant change in pediatric stroke rates over time ( $p=0.8087$ ).

## **Discussion**

The U.S. varicella vaccination program has matured with substantial increases in population immunity since 1996 due to evolving immunization recommendations, school entry requirements, and other factors affecting age-appropriate coverage and catch-up vaccination (Supplementary Appendix 3). We document from our large study population that in the 16 years since the varicella vaccination program was implemented, there has been an 84% decline in outpatient visits and 93% decline in hospitalizations from the pre-vaccination period through 2012. Previously, Zhou et al reported a 59% decline in outpatient visits and an 88% decline in hospitalizations from pre-vaccination to 2002[14]. These declines in healthcare utilization provide an indication of the declines in the national incidence of varicella and its complications. Varicella seasonality appears to have waned over time with the proportion of varicella visits occurring during December to May declining to 52% from 65% in the pre-vaccination period[14]. The second dose of varicella vaccination was introduced in 2007 to further decrease varicella disease and primarily to decrease the number of varicella outbreaks. These declines in varicella are likely due to the combined effect of improving implementation of both 1-dose and 2-dose varicella vaccination. Our data suggest that the 2-dose program has prevented additional disease, with subsequent declines of 60% in outpatient visits and 38% in hospitalizations during the 2-dose varicella

vaccination period. Severity of varicella declined during the study interval as well, presumably because varicella vaccine has shown a vaccine-effectiveness of 100% against severe disease, as defined by number of skin lesions, complications, or hospitalization[16]. Data suggesting substantial second-dose impact have also been documented in a small number of states, communities, and health systems[17–20].

The largest declines in outpatient visits and hospitalizations from the pre-vaccination period to 2006 were seen in children and adolescents aged 1–19 years who are targeted for varicella vaccination[10]. During 2006–2012, this same age-cohort experienced the largest subsequent declines as well with declines higher in younger children aged 1–9 years (66% in outpatient visits and 47% in hospitalizations). Dramatic declines also occurred among age groups not targeted for vaccination, likely due to reduction in varicella circulation in the population (i.e., herd protection) attributable to the vaccination program. Substantial declines were seen among adults, who are not often vaccinated. The reduction in outpatient visits and hospitalizations (95% and 99%, respectively) during our study interval among infants, for whom the vaccine is not indicated, provide even stronger evidence of herd protection. We observed increased rates of outpatient visits for varicella among these infants during 2011–2012, despite the implausibility that they had increased opportunities for exposure. It is premature to attribute this increase to a decline in passive maternal protection that might occur for mothers who themselves had received varicella vaccine and not experienced varicella (i.e., in analogy to measles[21]). With just 2 data points, it is quite premature to draw conclusions based on this possibly-chance observation. Nonetheless, this pattern will bear monitoring in coming years.

National patterns of laboratory testing of varicella cases have not been previously reported. We found considerable increases in the portion of outpatient patients that underwent testing during 2003–2012. Half of testing was among cases aged 20–49 years, perhaps because clinicians are more prone to seek confirmation of adult cases. But the largest increases in laboratory testing during 2003–2012 occurred among children and adolescents aged 0–19 years. These increases may be due to the declining familiarity with, and the increasing proportion of varicella cases that is clinically modified due to prior vaccination, and more widespread availability of laboratory tests. As varicella cases continue to decline and providers become less familiar with the clinical presentation of varicella, even for classic varicella cases, laboratory testing will become increasingly important for diagnosing varicella to guide providers in clinical management and health departments in outbreak control and surveillance.

National patterns of treating outpatient varicella have also not been previously reported. We found that antiviral treatment increased with age from 9% in those aged < 10 years to 36% in those aged 20–49 years. These findings are consistent with current recommendations which restrict antivirals to people at increased risk of moderate/severe varicella, including unvaccinated persons > 13 years of age[10]. In contrast to increases in antiviral use noted in two communities under active varicella surveillance[18], we did not find that national patterns of antiviral use changed with time.

We found that rates of hospitalization for pediatric stroke were stable over time among children 0–17 years of age at a rate of approximately 1 per 100,000 population. Several studies and case series suggest that varicella triggers strokes in children[1, 5]. However, we found no evidence in this ecologic analysis that rates of pediatric strokes have changed among children 0–17 years of age during our study interval to parallel the large declines in rates of varicella that we observed. These results, however, do not inform regarding reactivation of latent varicella zoster virus as a trigger for strokes in older populations.

There are limitations to this study. Administrative data are subject to coding errors, and the diagnoses themselves were subject to errors. It is possible that there may have been some misclassification or miscoding of herpes zoster cases miscoded as varicella cases. To address this, we excluded persons with a varicella code who were aged  $\geq 50$  years and those with a coexistent herpes zoster diagnostic code (053.xx) because these persons are more likely to represent herpes zoster cases. In terms of healthcare utilization as an index of varicella incidence, we only ascertained cases that sought medical attention; vaccinated patients with milder varicella may have been less likely to seek medical care. It is possible that the decreases seen in outpatient visits and hospitalizations were related to changes in secular patterns of healthcare utilization. We attempted to control for secular changes in utilization by examining the proportion of varicella hospitalizations over all hospitalizations and continued to see a decline in varicella hospitalizations. We were unable to control for changes in some demographic variables across time (i.e., region, race). However, given the substantial rates of declines in varicella rates, any changes in these factors across time are unlikely to alter the conclusions of this study. Some of the antiviral and laboratory testing codes used were not specific to varicella, nor have they been validated in other studies. However, the antiviral testing and drug claims occurred within several days of a claim for varicella. Finally, our data are derived from persons with private health insurance who may not be nationally representative.

In our study, we were unable to directly link varicella health care utilization rates to vaccination coverage rates. The National Immunization Survey (NIS) serves as the backbone for monitoring immunization coverage among preschool children and adolescents in the United States[9]. During the initial decade of the varicella vaccination program, most of the vaccine was administered to preschool children, so we were able to rely on data from the NIS to link state-level one-dose varicella vaccination coverage to state-level declines in varicella outpatient visits[9, 14]. However, over time, one-dose coverage among preschool children has converged across states, so that any differences between states in vaccine-mediated population protection would be due to 2-dose coverage. Since there is currently no ongoing national surveillance of vaccination uptake among school-aged children, and since states have enacted a varied patchwork of school-entry requirements with different catch-up vaccination requirements, we were unable to assess 2-dose coverage across states and link state-level population coverage with disease outcomes, as we had in our prior analysis. We do, however, have evidence from selected age groups and states to suggest that national 2-dose coverage increased dramatically between 2007 and 2012[12, 13]. Additionally, available data has shown that the number of states requiring 2-doses of varicella vaccine for school entry increased from 4 to 36 states between 2007 and 2012[13].

In conclusion, after 16 years, the varicella vaccination program continues to mature and to provide increasing beneficial national impact. We provide evidence from our large study population that outpatient visit and hospitalization rates continue to decline, as does case-severity. The portion of the population that received varicella vaccine at least 10 years ago is increasing as the vaccination program approaches its 20th year, raising the question of whether these cohorts might be at risk for waning of vaccine-induced protection. However, we cannot use the decreasing population incidence of varicella as proof that waning is not occurring among vaccinated individuals since the continually-increasing levels of 1- and 2-dose vaccination are still causing the force of varicella infection to decline. Nonetheless, the ongoing decrease in varicella rates in all older age groups is reassuring. It will be important to continue to monitor rates of varicella disease to evaluate the performance of the varicella vaccination program.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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**Key Points**

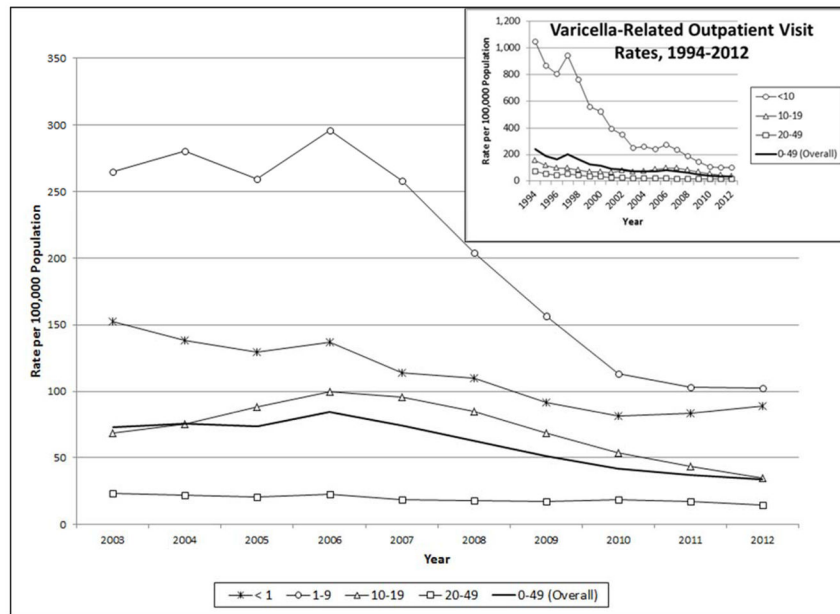
While varicella vaccination led to substantial declines in varicella morbidity during the first decade of the program, additional significant declines in morbidity have occurred since the implementation of the 2-dose varicella vaccination program.

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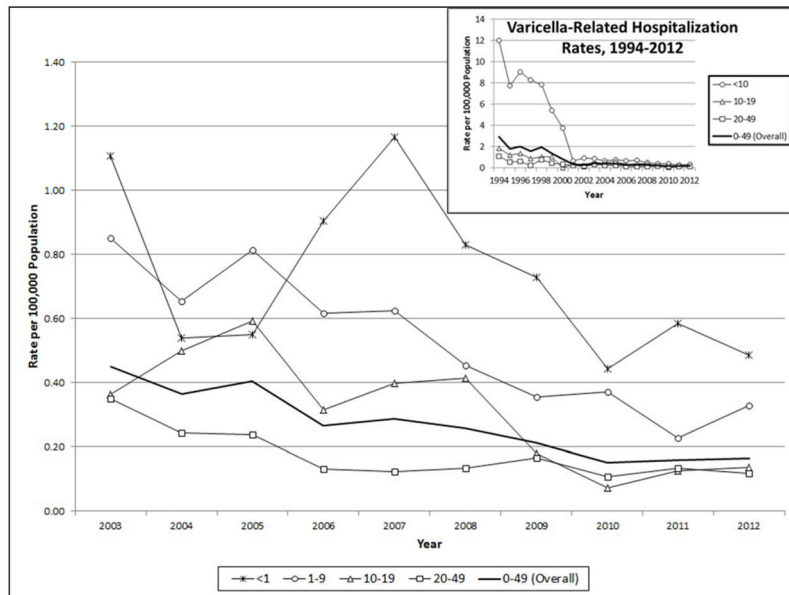
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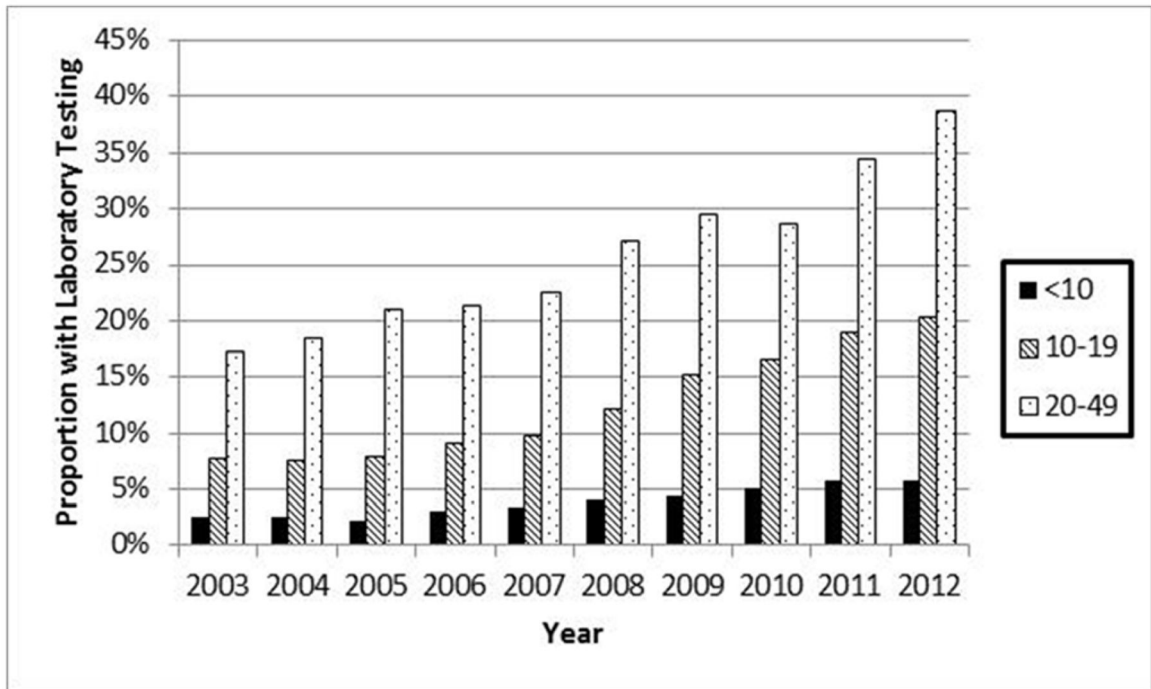
**Figure 1.** Varicella-Related Outpatient Visit Rates by Age Group, MarketScan 2003–2012<sup>ab</sup> (Insert Graph-Varicella-Related Outpatient Visit Rates by Age Group, MarketScan 1994–2012)

<sup>a</sup>Varicella was the primary diagnosis code for data shown

<sup>b</sup>Annual varicella outpatient visits with varicella coded as the primary diagnostic code ranged from 454–913 varicella outpatient visits for < 1 year-olds, 5,425–9,094 for 1-9 year-olds, 1,885–4,502 for 10–19 year-olds, and 1,709–4,125 for 20–49 year-olds.



**Figure 2.** Varicella-Related Hospitalization Rates by Age Group, MarketScan 2003–2012<sup>ab</sup> (Insert Graph- Varicella-Related Hospitalization Rates by Age Group, MarketScan 1994–2012)  
<sup>a</sup>Varicella was the primary diagnosis code for data shown  
<sup>b</sup>Annual varicella hospital admissions with varicella coded as the primary diagnostic code ranged from 2–7 varicella admissions for < 1 year-olds, 12–22 for 1–9 year-olds, 5–22 for 10–19 year-olds, and 10–33 for 20–49 year-olds.



**Figure 3.** Proportion of Persons with Outpatient Laboratory Testing among Persons with a Varicella-Related Outpatient Visit<sup>a</sup> by Age Group, MarketScan 2003–2012  
<sup>a</sup>Varicella was the primary diagnosis code for data shown

**Table 1** Rates (per 100,000) and Percent Declines of Varicella-Related Outpatient Visits and Hospitalizations by Age Group, for selected years

Year	Age Group				
	< 1 year	1–9 years	10–19 years	20–49 years	All Ages
	<b>Outpatient Visits (Rate per 100,000)</b>				
1994–1995 <sup>a</sup>	1,681	925	136	65	215
2006	137	296	100	22	84
2012	89	102	35	14	33
% Decline from pre-vaccination to 2012 (p-value)	95% <sup>b</sup>	89% <sup>b</sup>	75%(p=<0.001)	78%(p=<0.001)	84%(p=<0.001)
% Decline during the 2-dose vaccine period (2006–2012) (p-value)	35%(p=<0.001)	66%(p=<0.001)	65%(p=<0.001)	37%(p=<0.001)	60%(p=<0.001)
	<b>Hospitalizations (Rate per 100,000)</b>				
1994–1995 <sup>a</sup>	45.1	8.4	1.52	0.82	2.35
2006	0.90	0.62	0.32	0.13	0.27
2012	0.49	0.33	0.14	0.12	0.16
% Decline from pre-vaccination to 2012 (p-value)	99% <sup>b</sup>	96% <sup>b</sup>	91%(p=<0.001)	86%(p=<0.001)	93%(p=<0.001)
% Decline during the 2-dose vaccine period (2006–2012) (p-value)	46%(0.3977)	47%(0.0849)	56%(p=0.074)	10%(p=0.7838)	38%(p=0.0230)

<sup>a</sup>Rates represent average of 2 years

<sup>b</sup>Unable to calculate the p-value for the incidence rate ratios for the <1 and 1–9 year-old age groups to compare rates from the pre-vaccination period and 2012. Data were only available in aggregate for the <10 year-old age group and not separately for the <1 and 1–9 year-old age groups. The difference in the incidence rate ratios for <10 year-olds in the pre-vaccine period compared to 2012 was statistically significant (p<0.001).