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The Epidemiology Of Primary Varicella And Herpes Zoster Hospitalizations In The Post-Varicella Vaccine Era: Connecticut, 1996-2012

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Abstract

Background: A vaccine for primary varicella (VZV) was licensed and recommended for use in children as a single dose in 1996, and as two doses in 2006. A vaccine for herpes zoster (HZ) was licensed and recommended for use in adults ≥60 years in 2006. Both vaccines have the potential to modify the epidemiology of VZV and HZ. Rates of hospitalization due to VZV and HZ were examined in the post-vaccine era to characterize the epidemiology of severe disease and to assess the possible impact of vaccination on the incidence of hospitalization.

Methods: Statewide hospital discharge data in Connecticut were used to identify cases of VZV and HZ from 1994-2012. Trends in hospitalization rates were assessed using Poisson regression models or Mantel-Haenszel chi-square tests.

Results: Primary varicella hospitalization rates declined 82.9% from the pre-vaccine (1994-1995) to the 1-dose (2001-2005) era ($p<0.001$). Rates further decreased significantly in the 2-dose era (2010-2012) only among 5 to 9 year olds. HZ hospitalization rates decreased in individuals 0-29 years and 30-39 years by 4.8%/year and 6.1%/year, respectively, from 2001-2012. Individuals <15 years experienced the largest decline, at 19.4%/year from 2001-2012. Among individuals ≥60 years, hospitalization rates increased by 5.1%/year from 2001-2006 but then decreased by 4.2%/year from 2007-2012.

Conclusions: Introduction of the varicella vaccine appears to have had an impact on both varicella and HZ hospitalizations. Varicella hospitalization rates decreased across all age groups following vaccine introduction, though the main impact occurred during the 1-dose era. HZ hospitalization rates decreased among individuals <15 years from 2001-2012, providing early evidence of varicella vaccine impact. The increase in HZ hospitalization rates among individuals ≥60 years 2001-2006 may be due to decreased varicella virus circulation and lack of immune boosting. However, the reduction in HZ morbidity from 2007-2012 suggests HZ vaccine, despite low usage rates, is offsetting the increase. Increased use of the HZ vaccine in individuals ≥60 years is needed to reduce hospitalization rates first to the levels seen prior to varicella vaccine introduction and then lower. Ongoing surveillance for HZ is needed to monitor anticipated long-term changes in disease epidemiology; hospital discharge data is a feasible method to do so.

Introduction

Over the past two decades, the Advisory Committee on Immunization Practices (ACIP) issued several important recommendations for vaccination against primary varicella and herpes zoster (HZ). In the year after the licensure of the varicella vaccine in 1995, it was recommended that children aged 12-18 months receive 1 dose of the vaccine, and that susceptible children aged 19 months-12 years receive a catch-up dose [1]. Following reports of leveling of varicella incidence after an initial decline, continued outbreaks in schools and waning immunity, the ACIP revised its recommendation in 2006 to include (1) two-dose vaccination in children, with the first dose administered at 12—15 months and the second at 4—6 years, (2) catch-up vaccination with a second dose for individuals who previously received one dose, and (3) two-dose vaccination of susceptible persons aged ≥13 years [2]. After the licensure of the herpes zoster vaccine (Zostavax®) in 2006, the ACIP recommended that individuals ≥60 years be vaccinated with a single dose of the vaccine [3].

Prior to 1995, it was estimated that 98.1% of the US population was infected by age 49 years [4]and that 10-30% of varicella-infected individuals would eventually develop herpes zoster [5]. However, the introduction and widespread use of the varicella and HZ vaccines have the potential to modify the epidemiology of both diseases.

For varicella, it has been shown that the incidence of varicella decreased sharply after the 1-dose recommendation and decreased again after the 2-dose recommendation [6-8]. At the same time, it is expected that the average age at infection will increase due to lack of early exposure, and this may result in higher severe morbidity since complications are more common with older age [9].

For HZ, a long-term reduction in the incidence of disease is predicted to occur due to fewer people becoming infected with varicella. It is also expected that there will be a reduction in incidence among adults aged 60 or older who receive the HZ vaccine. At the same time, it has been hypothesized that there may be a short-term increase in the incidence of HZ due to a decrease in immune "boosting" that circulating varicella virus used to provide to adults previously infected with varicella [10].

Although public health surveillance is being conducted to monitor the impact of varicella vaccine on varicella incidence, few if any state health departments conduct ongoing surveillance

for HZ [6, 8]. Hospital discharge datasets provide an opportunity to monitor trends and possible vaccine impact at the population level and severe end of the disease spectrum.

The epidemiology of primary varicella and herpes zoster requiring hospitalization in the 10 years prior to the vaccine has been characterized in Connecticut [11]. However, to our knowledge, there are no reports of the epidemiology of HZ hospitalizations in the varicella and HZ vaccine eras and no reports of the additional impact of the 2-dose schedule on varicella hospitalizations.

Data on hospitalizations in Connecticut were reviewed for the time period 1994-2012 to (1) establish the epidemiology of severe varicella and HZ disease in the post-vaccine eras and (2) assess the impact of vaccination recommendations on the incidence of varicella and HZ hospitalizations.

Methods

Data sources: The Connecticut Department of Public Health Office of Health Care Access Acute Care Hospital Inpatient Discharge Database was used to identify hospitalizations due to primary varicella or herpes zoster. The database contains discharge information on all persons hospitalized at any one of the 30 acute care hospitals in CT.

Study definitions: The discharge database was examined for the period January 1, 1994 through December 31, 2012. Cases were defined as any individual admitted during this period who had a discharge code of 052.xx for primary varicella (in any one of the ten diagnostic positions) or a discharge code of 053.xx for herpes zoster (in either the first or second diagnostic position). All diagnostic positions were chosen for primary varicella so as to be inclusive of the small number of hospitalizations. HZ was limited to diagnoses in the first two positions to capture incident cases and not persons with HZ incidental to the primary reason for hospitalization. Patient records containing codes for both primary varicella and HZ were excluded from the analysis. For patients admitted multiple times, only the first hospitalization was included.

Trends in the epidemiology of primary varicella were examined from the pre-vaccine period to the 1-dose era to the 2-dose era. The pre-vaccine era was defined as 1994-1995, prior to the licensure of varicella vaccine. The 1-dose era was defined as 2001-2005, the period in Connecticut prior to the 2-dose recommendation when the incidence of varicella was low and stable[12]. The 2-dose era was defined as 2010-2012, which gave sufficient time for the 2-dose recommendation to be largely implemented and some impact to have occurred. For HZ, two time periods were examined for changes in incidence rates: 2001-2006, the period with low and stable varicella circulation prior to the licensure of the HZ vaccine, and 2007-2012, the period following its licensure.

Demographic data: Patient data available through the database included a unique patient ID, admission year, age, the principle diagnostic code and up to nine secondary discharge diagnostic codes, length of stay (LOS), and ZIP code of residence.

Data on the percent of individuals living below the poverty level in a ZIP code tabulation

area (ZCTA) was extracted from the 2000 US Census and 2008-2012 American Community Survey 5-year estimate, and joined to the hospital dataset based on ZIP code. The 2000 data were joined to cases admitted 1994-2004 and the 2010 data were joined to cases admitted 2005-2012. ZCTA-level poverty was categorized as 0-4.9%, 5-9.9%, 10-19.9%, or 20+% of residents of the ZCTA living below the federal poverty level based on recommendations by the Public Health Disparities Geocoding Project [13].

The same methodology using discharge diagnosis codes was used to classify patients with underlying conditions as in an earlier Connecticut study [11], with the exception that one new code for HIV was added to the search (V08) due to a national coding change implemented in 1994 [14].

Statistical analysis: Age-specific hospitalization rates were calculated for each year using intercensal denominator data for Connecticut obtained from the US Census Bureau (years 1994-2011) and the annual Connecticut Department of Public Health population estimates (2012). Hospitalization rates by ZCTA-level poverty group were calculated using denominator data for Connecticut obtained from the 2000 US Census (for years 1994-2004) or the 2010 US Census (for years 2005-2012). Age groups for varicella were <1 year, 1-4, 5-9, 10-14, 15-19, 20-29, 30-39 and ≥40 years. For HZ they were 0-29, 30-39, 40-49, 50-59 and ≥60 years

For primary varicella, changes in hospitalization rates from 1994-1995 to 2001-2005 to 2010-2012 were examined by the Mantel-Haenszel chi-square test for trend. Mantel-Haenszel chi-square was also used to evaluate changes in the proportion of cases by age group and underlying conditions, and to test the significance of increasing hospitalization rates by increasing ZCTA-level poverty group. For herpes zoster, Poisson regression models were used to evaluate annual trends in age-specific hospitalization rates over the years from 2001-2012 (overall and for age groups <60 years), and from 2001-2006 and 2007-2012 (age groups ≥60 years). The Mantel-Haenszel chi-square test for trend was used to evaluate changes in the proportion of HZ cases with underlying conditions in selected age groups within the above time periods.

All statistical analyses were done with SAS 9.3 or Epi Info 7.

This study was approved by the Yale University School of Medicine and Connecticut Department of Public Health human subjects committees.

Results

Primary Varicella

Overall hospitalization rate: Over the 19-year study period, there were 1,181 hospital discharges for primary varicella. After excluding those with concurrent varicella and HZ diagnoses (n=72) and multiple admissions of the same person (n=35), there were 1,074 unique persons with primary varicella-related discharges. There was an annual average of 4.9 hospitalizations/100,000 population in the pre-vaccine era, 0.8 hospitalizations/100,000 population in the 1-dose era, and 0.7 hospitalizations/100,000 population per year in the 2-dose era (Table 1). Hospitalization rates declined 82.9% from the pre-vaccine to the 1-dose era ($p<0.001$). The additional 11.9% decrease from the 1-dose to the 2-dose era was not statistically significant.

Age-specific hospitalization rate: Age-specific hospitalization rates declined significantly within each age group from the pre-vaccine to the 1-dose era, with the largest declines (~90% each) seen among the three youngest age groups (Table 1). Only the 5 to 9 year old age group experienced a significant (100%, $p=0.01$) decline from the 1-dose to the 2-dose era.

Proportion of cases by age: In the pre-varicella vaccine era, individuals aged 9 or younger made up 50% of the hospitalizations. By 2001-2005, they made up ~20% and by 2010-2012 they made up ~10% (Fig. 1). The majority of hospitalizations in the 2010-2012 period included individuals aged $\geq$40; there were no hospitalizations among children aged 5-9 (Fig. 1).

ZCTA poverty level: Prior to the introduction of the varicella vaccine, the hospitalization rate increased as ZCTA-level poverty increased. Persons living in high poverty ZCTAs had a 3.8-fold higher rate than those in the lowest poverty ZCTAs (Table 2). The hospitalization rate and relative risk decreased from the 1-dose to the 2-dose era within all ZCTA poverty groups, although a significant disparity in the hospitalization rate still persisted as of 2010-2012 (Table 2).

Underlying Conditions: The overall prevalence of having at least one underlying condition was

25.1% and did not change during the three time periods (Table S1).

HZ

Overall hospitalization rates: Over the 19-year study period, there were 14,089 hospital discharges for HZ. After excluding those with concurrent varicella and HZ diagnoses (n=72), multiple admissions of the same person (n=2,348), and those with tertiary or higher DX codes (n=6,976), there were 4,693 unique persons with HZ-related discharges. From 1994-2000, hospitalization rates did not change significantly over time (Figure 2, Table S2). For the time period 2001-2012, there was a significant relationship between year and the hospitalization rate, with an average 2.2% increase per year in the hospitalization rate (Fig. 2). However, while 2001-2006 rates increased significantly at 3.8% per year, 2007-2012 rates decreased significantly by 1.8% per year.

Age-specific hospitalization rates: During 1994-2000, rates did not change significantly within any age group, except for a marginally significant decrease in the 40-49 age group ($p=0.046$) (Table S2).

During 2001-2012, only the two youngest age groups experienced a significant decrease in the hospitalization rate, with rates decreasing by 4.8% each year among 0-29 year olds and by 6.1% among 30-39 year olds (Figure 3, Table S3). When the 0-29 age group was divided into two groups aged 0-14 and 15-29, only the 0-14 age group experienced a significant decrease in the hospitalization rate from 2001-2012 (19.4% per year, $p<0.001$) (Fig. 3, Table S3a). This decrease was of the same magnitude for both those with an underlying condition and those with no underlying conditions (Table S3b).

When cases with an HIV diagnosis were excluded, the measured drop in HZ incidence in 30-39 year olds disappeared, and there was no change in the proportion of those remaining with underlying conditions (25.0% overall) (Tables S4, S5). In the 0-29 age group, however, a decrease in the hospitalization rate was still observed, and there remained a decrease in the proportion of cases with an underlying condition (Tables S4, S5).

For individuals ≥60, there was a 5.1% increase in the hospitalization rate each year from 2001-2006 (p=0.031) switching to a 4.2% annual decrease from 2007-2012 (p<0.001) (Figure 3, Tables S6, S7). When an age-stratified analysis was performed using 5-year age groups to examine whether a specific age group was driving each trend, there was no difference between the rates at which each age group increased (Table S6). However, for the 2007-2012 decrease, those 60-79 years had a more pronounced decrease (5.8% per year, p=0.013) than those ≥80 (1.8% per year, p=0.415) (Table S7).

None of these trends were changed when the excluded 6,000+ persons with discharge HZ diagnoses in the 3rd or later positions were included.

We looked at median LOS as a possible indicator of changed diagnostic criterion to explain the progressive changes in incidence over time. There were no changes in median LOS (4 days) during 2001-2012 in those 0-14 years, or during 2001-2006 or 2007-2012 in those ≥60 years.

Underlying conditions: Overall, the proportion of cases with an underlying condition decreased from 28.4% in the pre-vaccine era to 20.3% in 2001-2006 to 16.0% in 2007-2012 (p<0.001) (Table 3). When an age-stratified analysis was performed, only the three youngest age groups had a significant decrease in the proportion of cases with an underlying condition (Table 3).

When the time periods 2001-2006 and 2007-2012 were examined for changes in the annual proportion of cases with an underlying condition among cases ≥60 years, no significant trends were observed (Tables S8, S9).

ZCTA poverty level: No significant association was found between ZCTA poverty level and incidence of HZ hospitalization for the time periods 1994-1995 and 2007-2012. However, during 2001-2006, persons living in the highest poverty ZCTAs had a 1.25-fold higher rate of disease than those living in the lowest poverty ZCTAs (p=0.006) (Table 2).

Discussion

We found evidence that the introduction and widespread use of varicella vaccine may have had an impact not just on varicella hospitalizations, but on herpes zoster hospitalizations as well. In addition, we found that the switch from the 1-dose to the 2-dose varicella vaccine recommendation in 2006 has had only a very modest impact on varicella hospitalizations thus far, and that the introduction of HZ vaccine may be having an impact on HZ trends. These findings have implications for surveillance for HZ and for more aggressive use of the HZ vaccine.

We detected a significant decrease in the HZ hospitalization rate in the two youngest age groups (0-29 and 30-39) from 2001-2012. There are at least two possible explanations for our findings: 1) reduction in the prevalence of underlying conditions that are associated with a higher risk of HZ, and 2) a vaccine induced reduction in the number of persons with latent wild varicella infection. Both the 0-29 and 30-39 age groups had significant decreases in the proportion of cases with an underlying condition that was partially explained by a decrease in the proportion of cases with HIV. It is possible that the decline in HIV perinatal transmission since the 1990s and increasing use of highly active anti-retroviral therapy (HAART) may explain some of the decrease in the HZ hospitalization rate among these age groups [15]. Additionally, the reduction in varicella incidence since the introduction of the vaccine could contribute to the lowered HZ hospitalization rates. This is supported by our finding that the 0-14 age group, including both those with and without underlying conditions, experienced a significant decline in the hospitalization rate from 2001-2012 and suggests that varicella vaccination has had an impact on herpes zoster rates among the age groups targeted for varicella vaccination.

In contrast to the trends observed in the two youngest age groups, we detected a significant increase in the hospitalization rate in the ≥60 age group from 2001-2006 and a decrease from 2007-2012. This increase could not be explained by an increase in the proportion of cases with underlying conditions or reduction in the threshold for admitting persons with HZ to the hospital as measured by LOS. The main remaining hypothesis is that hospitalization rates increased because of decreased boosting from natural varicella. Studies in the literature have been mixed regarding the effect of boosting on herpes zoster epidemiology. Data from the Antelope Valley Varicella Surveillance Project on HZ incidence suggest that HZ incidence increased during the 1-dose varicella vaccine era, though baseline data were not available prior

to the introduction of the varicella vaccine [16]. Other studies have used medical claims data to examine changes in HZ over time. One study conducted during a comparable time period (1993-2004) detected a significant increase in population-adjusted HZ hospitalization rates in 2003-2004 compared to 1993-2001 [17]. Another study that examined health insurance claims data from 1993-2006 found that HZ rates trended upwards across all age groups since 1993, prior to the introduction of the varicella vaccine [18]. By contrast, we did not detect changes in the HZ hospitalization rate from 1994-2000.

The decrease in HZ hospitalization rates from 2007-2012 could not be explained by a reduction in the proportion of cases with an underlying condition, and is suggestive of vaccine impact. National herpes zoster vaccine coverage data indicate that vaccine uptake among the 60+ age group has increased from 6.7% in 2008 to 20.1% in 2012 [19, 20].

We found a significant decrease in primary varicella hospitalization rates in the 1-dose vaccine era compared to the pre-vaccine era across all age groups, and a significant change only among those 5-9 from the 1-dose era to the 2-dose era. Only one other study has examined the impact of 2-dose vaccination on hospitalization rates, and this study reported a >40% overall decrease in varicella-related hospitalizations from the 1-dose era (2002-2005) to the 2-dose era (2006-2010) [6]. However, this study did not note whether this decline was significant or age-group specific. Our study did not include data on vaccination status of hospitalized patients, so it is not possible to ascribe the changes in the hospitalization rate to the 2-dose vaccine recommendation itself. However, our finding of a reduction in varicella morbidity among 5 to 9 year olds in the 2-dose vaccine era is consistent with this age group being targeted for the 2nd varicella vaccine dose.

The association between higher ZCTA-level poverty and higher primary varicella hospitalization rates has persisted from the pre-vaccine era through to the 2-dose era, though the gap in incidence between the lowest poverty group and the highest poverty group has decreased over the years. To our knowledge, no other study has reported on the association between varicella hospitalizations and poverty. However, we would expect that vaccination would eliminate disparities due to the Vaccines for Children Program and the fact that CT has mandatory school-age vaccine requirements. It has been suggested that adolescents eligible for the Vaccines for Children Program may not be receiving both doses of the vaccine [21].

Combined with the fact that CT's school-age entry requirement was not put in effect until 2011 for 7th graders, it is possible that children and adolescents from higher poverty ZCTAs may have been relatively under-vaccinated during the 2010-2012 time period that was examined. Studies are needed to examine this link elsewhere.

The analysis of this study has several limitations. First, the ICD-9 coding that was used for case ascertainment is prone to coding errors and discharge diagnosis assignment. Since no attempt was made to validate the discharge diagnosis codes, it was not possible to distinguish between hospitalizations due to primary varicella or HZ infection incidental to the primary reason for hospitalization versus hospitalizations where primary varicella or HZ infection was the primary reason for hospitalization. This could lead to an over-estimate of the hospitalization rates for each disease. For HZ, we attempted to minimize this bias by using only the first or second diagnostic position to identify cases. For primary varicella, however, it is possible we overestimated hospitalization rates, since a primary varicella code in any DX position was classified as primary varicella. Another limitation is that no information on patient vaccination history was obtained, so it is not possible to directly attribute changes in hospitalization rates to each of the vaccines. Third, for primary varicella, the 2010-2012 time period that was examined for changes in the hospitalization rate may have been too close to initiation of the 2-dose recommendation to fully evaluate its impact. Similarly, the evaluation of possible decreases in HZ hospitalizations in younger age groups as a result of decreased circulation of varicella and in older age groups as a result of HZ vaccine may have been too soon to see their effects. National HZ vaccination coverage ranged from 6.7% in 2008 to 20.1% in 2012 [19, 20] and the first varicella cohorts to have fully benefited from varicella vaccine are children born in the 1990s, i.e., <20 years ago.

In summary, this study reports on changes in the epidemiology of severe primary varicella and herpes zoster disease requiring hospitalization, and highlights characteristics of individuals who continue to bear the burden of disease. Findings from this study add to the body of evidence that is consistent with vaccine impact on primary varicella and with a short-term increase in herpes zoster morbidity among the oldest age groups. This study also provides early evidence of varicella vaccine impact on herpes zoster among individuals under the age of 15 years, as well as early evidence of herpes zoster vaccine impact on individuals aged ≥60. These

findings suggest that more aggressive use of the herpes zoster vaccine is needed among adults ≥60 years to offset the possible effect of lack of boosting from circulating varicella. Additionally, long-term monitoring is needed to assess whether these early reductions in HZ hospitalizations continue over time. Since there is no formal surveillance system for HZ in the US, hospital discharge data are a practical method for monitoring long-term changes in the epidemiology of HZ. Caution should be taken with the interpretation of this study due to its ecological design, and more research is needed to understand the associations between age, poverty, and underlying conditions with the hospitalization rates for each disease over time.

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Table 1. Reported nos. of primary varicella hospitalizations and rates, 1994-1995, 2001-2005, and 2010-2012

	1994-1995		2001-2005		2010-2012		Rate difference	
	No. (%)	Hospitalization rate per 100,000 population	No. (%)	Hospitalization rate per 100,000 population	No. (%)	Hospitalization rate per 100,000 population	2001-2005 vs 1994-1995	2010-2012 vs 2001-2005
Overall	324	4.9	145	0.8	79	0.7	-4.0***	-0.1
Age group								
<1	30 (9.3)	33.7	9 (6.2)	4.3	4 (5.1)	3.6	-29.4***	-0.7
1--4	78 (24.1)	20.5	12 (8.3)	1.4	4 (5.1)	0.8	-19.1***	-0.5
5--9	55 (17.0)	11.6	11 (7.6)	0.9	0 (0.0)	0.0	-10.7***	-0.9*
10--14	7 (2.2)	1.6	4 (2.8)	0.3	2 (2.5)	0.3	-1.3**	0.0
15--19	12 (3.7)	3.0	12 (8.3)	1.0	5 (6.3)	0.7	-2.0**	-0.4
20--29	60 (18.5)	6.7	13 (9.0)	0.7	8 (10.1)	0.6	-6.1***	-0.1
30--39	49 (15.1)	4.2	24 (16.6)	1.0	13 (16.5)	1.0	-3.3***	0.1
>=40	33 (10.2)	1.2	60 (41.4)	0.7	43 (54.4)	0.8	-0.4*	0.1

*<0.05

**<0.01

***<0.001

Table 2. Primary varicella and herpes zoster hospitalization rates by ZCTA-level poverty and time period

	Primary Varicella				Herpes Zoster		
Poverty level	**Rate per 100,000 population**	**Relative Risk**	**p-value***	**Poverty level**	**Rate per 100,000 population**	**Relative Risk**	**p-value***
1994-1995				**1994-1995**			
0-4.9%	3.2	1.00	<0.001	0-4.9%	4.9	1.00	0.044
5.0-9.9%	3.7	1.16		5.0-9.9%	7.5	1.55	
10.0-19.9%	7.1	2.23		10.0-19.9%	7.2	1.48	
>=20%	12.1	3.83		>=20%	6.6	1.36	
2001-2005				**2001-2006**			
0-4.9%	0.6	1.00	<0.001	0-4.9%	6.3	1.00	0.006
5.0-9.9%	0.7	1.22		5.0-9.9%	7.4	1.17	
10.0-19.9%	1.0	1.62		10.0-19.9%	7.5	1.20	
>=20%	1.8	3.03		>=20%	7.9	1.25	
2010-2012				**2007-2012**			
0-4.9%	0.6	1.00	0.012	0-4.9%	7.5	1.00	0.679
5.0-9.9%	0.7	1.28		5.0-9.9%	8.3	1.10	
10.0-19.9%	0.7	1.24		10.0-19.9%	8.9	1.19	
>=20%	1.3	2.23		>=20%	7.7	1.03	

*chi-square test for linear trend within individual time periods

Table 3. Proportion of hospitalized herpes zoster cases with an underlying condition

Age	1994-1995	2001-2006	2007-2012	p-value*
Overall	28.4	20.3	16.0	<0.001
Age group				
0-29	59.3	31.5	29.9	0.024
30-39	69.2	51.6	37.5	0.002
40-49	54.2	47.2	29.5	0.001
50-59	18.8	26.0	22.9	0.932
60+	15.6	11.8	11.8	0.193

*Mantel-Haenszel chi-square test for trend

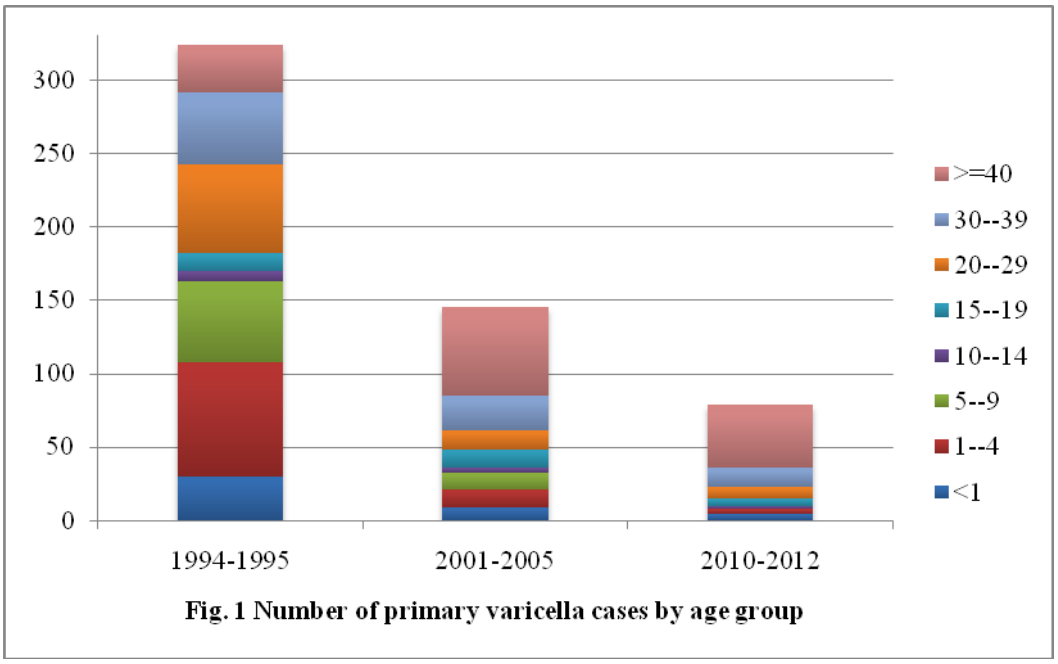

Fig. 1 Number of primary varicella cases by age group

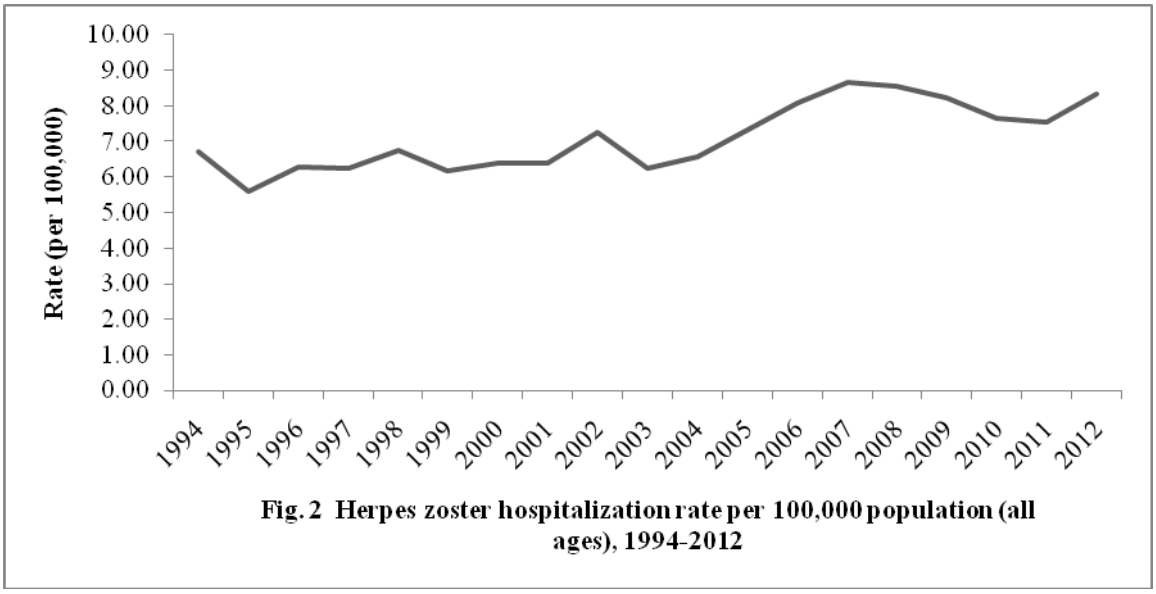

Fig. 2 Herpes zoster hospitalization rate per 100,000 population (all ages), 1994-2012

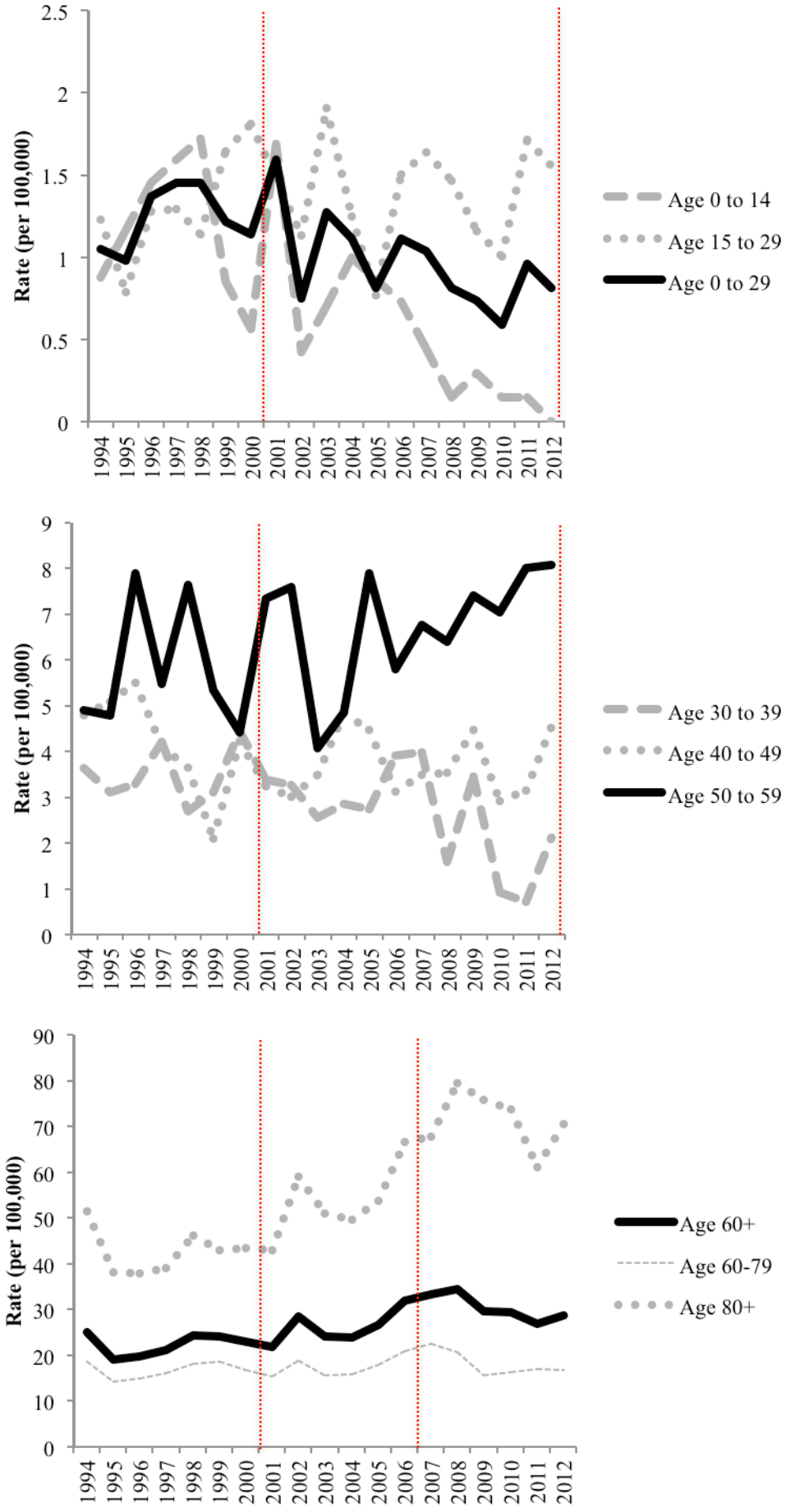

Fig. 3 Herpes zoster hospitalization rate (per 100,000 population), by age group, 1994-2012

Table S1 Proportion of hospitalized primary varicella cases with an underlying condition

Age	1994-1995	2001-2005	2010-2012	p-value*
Overall	24.4	29.7	27.9	0.460
Age group				
<1	0.0	11.1	0.0	0.145
0-4	10.3	8.3	25.0	0.623
5--9	14.6	18.2	N/A**	0.759
10--14	0.0	25.0	0.0	0.602
15-19	41.7	25.0	40.0	0.664
20-29	36.7	15.4	62.5	0.088
30-39	51.0	41.7	30.8	0.390
40+	33.3	38.3	23.3	0.270

*Mantel-Haenszel chi-square test for trend
**No hospitalizations during time period

Table S2. Herpes zoster hospitalization rate regression model (year as predictor), 1994-2000

Age	β Year	exp β	% change	p-value
Overall	0.0034	1.00	0.34	0.793
Age Group				
0-29	0.0238	1.02	2.41	0.610
30-39	0.0178	1.02	1.80	0.677
40-49	-0.0821	0.92	-7.88	0.046
50-59	-0.0085	0.99	-0.57	0.836
60+	0.0133	1.01	1.34	0.417

Table S3a. Herpes zoster hospitalization rate regression model (year as predictor), 2001-2012

Age	β Year	exp β	% change	p-value
Overall	0.0214	1.02	2.16	<0.001
Age Group				
0-29	-0.049	0.95	-4.78	0.036
0-14	-0.2156	0.81	-19.39	<0.001
15-29	0.0047	1.00	0.47	0.867
30-39	-0.0631	0.94	-6.12	0.009
40-49	0.0066	1.01	0.66	0.722
50-59	0.0230	1.02	2.33	0.118

Table S3b. Herpes zoster hospitalization rate regression model (year as predictor) among 0-14 year olds, 2001-2012

Age	β Year	exp β	% change	p-value
All 0-14	-0.2156	0.81	-19.39	<0.001
No UCs	-0.2142	0.81	-19.28	<0.001
>=1 UC	-0.2194	0.80	-19.70	0.021

Table S4. Herpes zoster hospitalization rate regression model (year as predictor), excluding individuals with HIV, 2001-2012

Age	β Year	exp β	% change	p-value
Overall	0.0253	1.03	2.56	<0.001
Age group				
0-29	-0.0571	0.94	-5.55	0.023
30-39	-0.0278	0.97	-2.74	0.337
40-49	0.0212	1.02	2.14	0.326
50-59	0.0199	1.02	2.01	0.199
60-64	0.0061	1.01	0.61	0.787
65-69	-0.0049	1.00	-0.49	0.802
70-74	0.0262	1.03	2.65	0.126
75-79	0.0186	1.02	1.88	0.193
80-84	0.0323	1.03	3.28	0.016
85+	0.0372	1.04	3.79	<0.001

Table S5. Proportion of hospitalized herpes zoster cases with an underlying condition, excluding HIV

Age	1994-1995	2001-2006	2007-2012	p-value*
Overall	18.4	14.7	12.3	0.002
Age group				
0-29	42.1	24.7	17.5	0.044
30-39	33.3	23.0	18.6	0.242
40-49	21.4	22.0	12.2	0.107
50-59	16.1	18.8	13.8	0.331
60-64	41.4	14.8	23.2	0.306
65-69	23.1	18.4	20.3	0.822
70-74	19.6	16.2	16.3	0.751
75-79	3.6	10.4	11.1	0.140
80-84	15.3	14.4	9.2	0.080
85+	6.4	6.3	6.5	0.918

Table S6. Herpes zoster hospitalization rate regression model (year as predictor), 2001-2006

Age	β Year	exp β	% change	p-value
60+	0.0493	1.05	5.05	0.031
60-64	0.0525	1.05	5.39	0.446
65-69	0.023	1.02	2.33	0.701
70-74	0.0766	1.08	7.96	0.145
75-79	0.0529	1.05	5.43	0.199
80-84	0.0686	1.07	7.10	0.090
85+	0.0394	1.04	4.02	0.271
60-79	0.0422	1.04	4.31	0.109
80+	0.0539	1.06	5.54	0.044

Table S7. Herpes zoster hospitalization rate regression model (year as predictor), 2007-2012

Age	β Year	exp β	% change	p-value
60+	-0.0432	0.96	-4.23	0.009
60-64	-0.0474	0.95	-4.63	0.487
65-69	-0.0914	0.91	-8.73	0.084
70-74	-0.0658	0.94	-6.37	0.164
75-79	-0.0132	0.99	-1.31	0.745
80-84	-0.0119	0.99	-1.18	0.744
85+	-0.0271	0.97	-2.67	0.339
60-79	-0.06	0.94	-5.82	0.013
80+	-0.0182	0.98	-1.80	0.415

Table S8. Proportion of herpes zoster cases with an underlying condition, 2001-2006

Age group	2001	2002	2003	2004	2005	2006	p-value*
60+	12.1	13.8	10.7	11.3	12.4	10.7	0.56

*Mantel-Haenszel chi-square test for trend

Table S9. Proportion of herpes zoster cases with an underlying condition, 2007-2012

Age group	2007	2008	2009	2010	2011	2012	p-value*
60+	12.7	12.8	12.2	12.4	10.8	9.4	0.2307

*Mantel-Haenszel chi-square test for trend