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Estimating lifetime risk of varicella infection and future herpes zoster for select age and birth cohorts – United States, 1950-2060.

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Global Epidemiology

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By

Michael Daugherty

B.A., Wheaton College, 2015

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An abstract of
A thesis submitted to the Faculty of the
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2018

Abstract

Estimating lifetime risk of varicella infection and future herpes zoster for select age and birth cohorts – United States, 1950-2060.

By Michael Daugherty

Background: Varicella vaccine was introduced in the United States in 1995 and herpes zoster vaccines were recommended to older adults in 2008 and 2017. The proportion of the U.S. population that is infected with wild-type varicella-zoster virus (VZV) and vaccine-strain VZV has changed dramatically over the past few decades. It is unknown how the changing VZV status of the population will impact zoster epidemiology.

Methods: We used age-specific incidence and coverage data from the Centers for Disease Control and Prevention (CDC) to estimate population susceptibility to VZV. A time-series analysis was performed to estimate lifetime risk of varicella infection and forecast the lifetime risk of herpes zoster in different herpes zoster vaccine uptake scenarios for select birth cohorts.

Results: Herpes zoster increased with age and across decades, with increases appearing before varicella vaccine introduction and stabilizing after high coverage levels were reached by the year 2000. If herpes zoster vaccine uptake increases 1.5% each year from 2016 onward, risk of herpes zoster infection between 60 and 80 years of age is projected to decrease by 14% among persons born in 1950, 25% among persons born in 1960, 36% among persons born in 1970, and 48% among persons born in 1980.

Conclusions: This study estimates the impact of herpes zoster vaccination on risk of herpes zoster among older adults in the United States. Varicella incidence continues to decline, and our analysis suggests that herpes zoster vaccines could cause major reductions in zoster incidence as long as vaccination coverage levels are maintained or increase in the future.

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Chapter I: Literature Review

Varicella and herpes zoster background

Varicella-zoster virus (VZV) is a herpes virus that causes varicella (chickenpox) and herpes zoster (HZ, shingles). The virus was isolated in 1952 from vesicular fluid from patients exhibiting a rash (1). The virus was named VZV after studies isolated identical viruses from subjects with varicella and herpes zoster (2). There is one serotype and five major genotypes (clades 1 to 5) of wild-type VZV, with four additional genotypes that are either rare or remain to be confirmed by whole-genome sequencing (3,4). All five major clades have been observed in the United States, although the majority of isolates are clade 1 and clade 3.

VZV infection is limited to humans and some higher primates. VZV is transmitted person-to-person by direct contact, inhalation of aerosols from vesicular fluid of skin lesions due to acute varicella or herpes zoster, or infected respiratory tract secretions that become airborne (5,6). The virus is highly contagious, with secondary attack rates in susceptible household contacts of varicella patients ranging from 61% to 100% (7,8). Viral transmission from patients with herpes zoster to susceptible contacts can cause varicella, although the attack rate is lower (16-74%) (9). History of varicella or of at least one dose of varicella vaccine is indicative of immunity to varicella. Further diagnosis of varicella and herpes zoster can be done by PCR of viral DNA in vesicles or by enzyme-linked immunosorbent assay (ELISA) for measurement of antibodies.

Symptoms of varicella are typically self-resolving and include a fever and a generalized vesicular rash. The rash is first concentrated on the trunk, scalp, and face before spreading to extremities, and appears in crops; each crop progresses from macules

to pustules and crusts within 24 hours. New lesions occur in crops for 5-7 days after initial infection and fever usually parallels the extent of the rash. Typically, the number of skin vesicles ranges from 250 to 500 in otherwise healthy children (10). The incubation period is 14-16 days after exposure to rash, and individuals are contagious 1-2 days before rash onset and until all lesions are crusted (typically 4-7 days after rash onset) (11). VZV-specific IgG antibodies are detected in most patients within the first 4 days after rash onset (12).

Although varicella is a mild disease for most previously healthy persons, it has a wide range of complications that can cause morbidity and some mortality with primary infection. The most common complication in children is a secondary bacterial infection, which may lead to subsequent complications such as pneumonia, encephalitis, arthritis, hepatitis, glomerulonephritis, pericarditis, cerebellar ataxia, and orchitis (13). Varicella severity increases with age. Adults with varicella have higher morbidity and mortality with varicella and related complications than children, including longer duration of fever and greater number of lesions and duration for clearing (14,15). Compared to adolescents and children, respectively, adults have a 10- to 20-fold higher rate of varicella pneumonia and a 3- to 17-fold higher rate of hospitalization (16,17).

VZV becomes latent in the dorsal root ganglia after primary infection and can reactivate (generally) after a long period to cause herpes zoster (18). Although VZV generally infers lifelong immunity, waning immunity can occur later in life (beginning around age 50) or during immunosuppression (19). Reactivation of VZV to cause herpes zoster—usually a unilateral, painful vesicular rash—occurs in 15 to 25% of individuals, and is associated with severe morbidity (4% of cases are hospitalized) and high case

fatality (0.1% of cases) (20,21). Itching and severe pain are associated with these skin lesions one to five days before lesions appear. Most patients report headache, photophobia, and malaise with rash and aches, but rarely fever. Varicella and herpes zoster can become especially serious in immunocompromised patients (22,23).

Risk of herpes zoster increases with age, as virus-specific cell-mediated immune responses decline. A study in Olmsted County, Minnesota, found herpes zoster incidence per 1,000 person-years to be 1.6 among 22-29-year-olds, 1.9 among 30-39-year-olds, 2.3 among 40-49-year-olds, 4.7 among 50-59-year-olds, 7.1 among 60-69-year-olds, 10.0 among 70-79-year-olds, and 12.0 among those greater than 80 years of age (24). Those aged 50-59 years have the greatest number of reported herpes zoster cases each year. Further, men have slightly higher rates of herpes zoster than women in the U.S, from 3.9 per 1,000 person-years to 3.2 per 1,000 person-years, respectively. Post-herpetic neuralgia, classified as persistent pain for greater than 90 days following the resolution of herpes zoster rash, occurs in 10-13% of herpes zoster cases in persons aged greater than 50 years (25). There are nearly one million new cases of herpes zoster each year (24).

Prevaccine epidemiology

Before the varicella vaccination program was launched in the United States in 1995, varicella was a widespread childhood disease with an annual average incidence of 15-16 cases per 1,000 population (4 million cases per year) (26). National seroprevalence data from 1988 to 1994 indicate that the U.S. population had high immunity to VZV by the fourth decade of life: 86% for children aged 6 to 11 years, 93% for adolescents aged

12 to 19 years, 96% for adults aged 20 to 29 years, 99% for adults aged 30 to 39 years, and >99.6% for adults aged ≥40 years (27).

Most cases occurred among children in daycare, preschool, and early elementary school. Between 1980 and 1990, 33% of varicella cases occurred among children aged 1-4 years (age-cohort annual incidence: 83 cases per 1,000 children), 44% of cases occurred among children aged 5-9 years (91 per 1,000 children), 14% of cases occurred among children aged 10-14 years, and cases were rarely seen among persons aged ≥50 years (26). However, data from studies conducted between 1990 and 1995 indicate that the highest incidence of varicella shifted to among very young and preschool-aged children (aged 1-4 years), likely a result of increased social contact within daycares and among school-aged siblings (28,29). Other factors associated with an increased risk of varicella exposure include urban residence, childcare and school attendance, school size, and presence of older siblings in the household (30).

During the immediate prevaccine era, 4.1 to 5.0 varicella-related hospitalizations per 100,000 population were observed each year (31). Survey data from 1988 to 1995 indicate that otherwise healthy persons compromised 89% of all varicella-related hospitalizations each year, with 44% of hospitalizations being among children aged ≤4 years and 32% of hospitalizations being among adults aged ≥20 years (32). For example, adults aged ≥20 years were 13-times more likely to be hospitalized due to varicella than children aged 5-9 years (32). Between 1970 and 1994, the average case-fatality ratio for varicella is estimated to be 2.0 to 3.6 per 100,000 cases, with the highest rates of death among adults aged ≥20 years (31). The case-fatality ratio for varicella declined steadily

during this period overall; yet, the risk of death for varicella cases between 1990 and 1994 was still 25-times higher for adults than for children aged 1-4 years (31).

Risk of herpes zoster in the prevaccine era was estimated to be ~50% by the age of 80 years (33). Among children aged <5 years during 1960-1981, females had an incidence rate of 27 per 100,000 person-years and males had an incidence rate of 13 per 100,000 person-years (34). Herpes zoster rarely occurs in children and is usually not as severe in pain or in complications when it develops. The overall age-adjusted incidence rate of herpes zoster during 1990-1992 was found to be 287 per 100,000 person-years in the Harvard Community Health Plan (HCHP) study (35). Age-specific incidence rates per 100,000 person-years were as follows: 47 among those aged less than 15 years old, 106 among 15-24-year-olds, 192 among 25-34-year-olds, 228 among 35-44-year-olds, 313 among 45-54-year-olds, 568 among 55-64-year-olds, 999 among 65-74-year-olds, and 1,374 among those greater than 74 years old (35).

Vaccines and vaccination programs

The varicella vaccine was licensed in 1995. Merck produces the commonly-used monovalent vaccine, Varivax, although varicella vaccine is also available in combination with MMR vaccine. Seward et al. reviewed vaccine effectiveness studies in the United States and observed that one dose of Varivax vaccine was 84.5% effective (median, range: 44-100%) in preventing varicella and 100% effective in preventing severe disease (36). Studies with long-term follow-up of healthy children vaccinated with one dose indicate 1-3% of vaccinated children will develop breakthrough disease each year (37).

Two-dose vaccine effectiveness in preventing varicella was most recently found to be 94% (38).

In 1995, the Advisory Committee on Immunization Practices (ACIP) recommended one dose of varicella vaccine to be administered routinely to all healthy children aged 12-18 months in the United States, with a catch-up dose to older susceptible children aged 19 months to 12 years and to designated high-risk groups (e.g., healthcare workers, family contacts of immunocompromised persons) (39). In 1999, the ACIP updated the recommendations to include use of vaccine for certain HIV-infected children, outbreak control, and child care and school entry requirements (40). Between 1997 and 2005, national coverage of one dose of varicella vaccine among children aged 19-35 months increased from 27% to 88% (41). Due to school outbreaks of varicella despite high rates of vaccination, contagiousness of breakthrough varicella, and the projected higher vaccine efficacy with two doses, the ACIP recommended a routine second dose of vaccine in 2006. The routine second dose is for children 4-6 years of age or before a child enters school. At that time, a catch-up program was recommended for persons aged ≥13 years who previously had only one dose of vaccine (42).

Herpes zoster vaccine (Zostavax) was licensed in 2006 and recommended for preventing herpes zoster and its complications among adults aged ≥60 years by the ACIP in 2008 (43). In a placebo-controlled study, this vaccine was shown to reduce the incidence of herpes zoster by 51% and reduce the incidence of post-herpetic neuralgia by 67% among recipients (44). Further, Zostavax was approved by the Food and Drug Administration (FDA) for adults aged 50-59 years in 2011 but the ACIP recommendation was not extended to this age group. Shingrix was licensed by the FDA and recommended

for adults aged ≥50 years by the ACIP in October 2017 (45). Since licensure of herpes zoster vaccines, vaccination coverage has steadily increased and 33% of adults aged ≥60 years had received vaccine in 2016 (CDC, unpublished data).

Post-vaccine epidemiology

Varicella incidence in the United States has declined dramatically since varicella vaccine introduction in 1995. For example, CDC's Varicella Active Surveillance Project (VASP) in Antelope Valley (AV), California, and West Philadelphia (WP), Pennsylvania, found that varicella incidence declined by 89.8% in AV from 1995 to 2005, from 10.3 cases per 1,000 population to 1.1 cases per 1,000 population (46). Similarly, varicella incidence in WP declined by 90.4%, from 4.1 cases per 1,000 population to 0.4 cases per 1,000 population from 1995 to 2005. The greatest declines in incidence were observed among children aged 1-9 years in both sites and among adolescents aged 10-14 years in WP (90-95%). Findings support the benefits of indirect protection from vaccination for infants (ineligible for vaccination) and adults (relatively low rates of vaccination during this time period).

The VASP was continued in the same sites from January 2006 to December 2010. Varicella incidence declined by a further 67.1% in AV and 76.3% in WP, showing age-specific incidence rates to decline up to 98.8% (among children aged 5-14 years in WP) from 1995 to 2010 (47). As of 2010, 43.4% of vaccinated case patients aged 4-14 years had received two doses of varicella vaccine. This surveillance project offers support for the prevaccine assumption that the second dose of varicella vaccine would improve protection for children with vaccine failure from one dose (15-20%), since the greatest

declines were noted among children for whom the second dose was recommended (5- to 9-year-olds in both sites).

The Behavioral Risk Factor Surveillance System (BRFSS) in Massachusetts observed similar declines in varicella incidence after varicella vaccine introduction. From 1998 to 2003, varicella incidence declined for all age groups, with greatest declines among infants, children aged 1-4 years, children aged 5-9 years, and adolescents aged 15-19 years (100%, 89%, 80%, and 92%, respectively) (48). Further, data from the National Notifiable Disease Surveillance System (NNDSS) show that average annual varicella incidence declined 84.6% from 2005 to 2014 (3.9 cases per 100,000 population in 2014) (49). All age groups reported declines during this period, with the largest declines among children aged 5-9 years (89.3%) and 10-14 years (84.8%). Overall, data from earlier-reporting states (IL, MI, WV, TX) show an average decline in incidence of 97.4% from the 1993-1995 period to the 2013-2014 period.

Varicella mortality and healthcare utilization for varicella-related illness has declined in the post-vaccine era as well. In a study by Nguyen et al., age-adjusted U.S. mortality rates were shown to decrease by 67%, from an average 0.41 deaths per 1 million population from 1990-1994 to 0.14 from 1999-2001 (50). The decrease was primarily among persons aged <50 years (>73%), specifically for the 1-4 age group (92%). A study utilizing claim records from MarketScan databases found that varicella hospitalization rates declined 88% (overall) from 1994-2002, with a 100% decline among infants, 91% decline among aged children <10 years, 92% decline among those aged 10-19 years, and 78% decline among adults aged 20-49 years (51). Further, the estimated annual medical expenditures for varicella hospitalizations and ambulatory visits declined

from an average $84.9 million in 1994 to $22.1 million in 2002 (74%). These findings confirm that varicella vaccine is effective against severe disease (52).

Trends in herpes zoster incidence pre- and post-vaccine era are a bit more complex. MarketScan data show that overall herpes zoster incidence increased from 1.7 per 1,000 enrollees in 1993 to 4.4 per 1,000 enrollees in 2006 (53). Overall, age-standardized herpes zoster incidence increased 90% from 1995 to 2005 (2.5 more cases per 1,000 population) and are supported by multiple studies (29,48,54). Reported increases in herpes zoster incidence fall in line with modeling estimates that predicted herpes zoster increase due to increased exposure to corticosteroids (known to suppress immune function) and reduced boosting by natural infection (55,56). As of 2006, age-specific incidence rates per 1,000 males and females, respectively, were: 1.0 and 1.2 (0-17 years), 2.0 and 2.5 (18-34 years), 2.8 and 3.6 (35-44 year), 3.4 and 5.5 (45-54 years), 5.6 and 8.3 (55-64 years), and 8.9 and 11.0 (≥65 years) (53).

A population-based study of Kaiser Permanente Northwest Plan (KPNW) members living in Oregon and Washington found that the overall zoster incidence during 1997-2002 (369 per 100,000 person-years) was higher than the 1990-1992 rate after adjusting for age differences, further indicating the increase in herpes zoster cases as predicted in previous modeling studies (35,57). Herpes zoster incidence is also shown to steadily increase by age and adults aged greater than 80 years have the highest incidence rate of herpes zoster (1336 probable cases per 100,000 person-years); children aged less than 18 years make up only 10.3% of probable cases.

However, increases in herpes zoster predated varicella vaccine licensure (1995); early years of the vaccination program (1995-1998; before vaccination coverage reached

high levels) showed the most rapid increases. Civen et al. report herpes zoster incidence data from the active VASP-surveillance site in AV, California, since last publication (58,59). From 2000 to 2010, herpes zoster incidence declined 84% among children aged <10 years. This is consistent with previous reports of a lower risk of herpes zoster among varicella-vaccinated children (60,61).

Further, although zoster incidence among children and adolescents aged 10-19 years increased 63% from 2000 to 2006, incidence seems to plateau from 2007 to 2010 (58). This plateau could be due to an increased interval between varicella infection and herpes zoster onset—another interesting study finding—or due to an increase in herpes zoster incidence among adolescents and adults that started before vaccination was introduced (both instances would result in an increased number of cases among 10-19-year-olds during 2000-2006) (24).

Conclusion

In summary, we have reviewed the pathophysiology and epidemiology of varicella-zoster virus (VZV) in the United States. Nearly all U.S. adults are seropositive to VZV (98%) (62,63). While the highest burden of varicella infection is among young children, risk and burden of herpes zoster increases with age. The varicella vaccine was introduced in the United States in 1995, with a second dose included in routine immunization in 2006. Varicella incidence has declined dramatically since vaccine introduction. Herpes zoster incidence increased among all ages after varicella vaccine introduction, but increases were also observed prior to vaccine introduction and have recently stabilized as high vaccination coverage was reached. Live zoster vaccine was

recommended to those ≥60 years of age in 2008 and a subunit zoster vaccine was recommended to those ≥50 years of age in the fall of 2017. Future research is needed to address: (i) the age-specific population susceptibility to varicella infection and VZV status in the pre- and post-vaccine eras, (ii) the risk of herpes zoster among birth cohorts in the pre- and post-vaccine eras, and (iii) the future impact of herpes zoster vaccine recommendations.

Chapter II: Manuscript

Introduction

Varicella-zoster virus (VZV) is a herpes virus that causes varicella (chickenpox) and herpes zoster (shingles). Before the varicella vaccination program was launched in the United States in 1995, varicella was a widespread childhood disease with an annual average incidence of 15-16 cases per 1,000 population (4 million cases per year). Varicella vaccine was first recommended to all healthy children aged 12-18 months and, by 2005, coverage of one dose of varicella vaccine among young children reached 88% and incidence across all ages had been reduced by 90% (41,46). Still, due to continued outbreaks and the projected higher vaccine efficacy with two doses, a routine second dose of vaccine was recommended for children aged 4-6 years (with a catch-up program for adolescents) in 2006.

VZV becomes latent in the dorsal root ganglia after primary infection and can reactivate (generally) after a long period to cause herpes zoster. Reactivation of VZV to cause herpes zoster—usually a unilateral, painful vesicular rash—occurs in 15-25% of individuals (an estimated one million cases each year), and is associated with severe morbidity (4% of cases are hospitalized) and mortality (0.1% of cases) (20,21,24). Herpes zoster can have detrimental effects on quality of life, with 12-24% of older adults reporting persistent pain for 90 days or more after onset of rash (64). Nearly all adults in the United States have latent VZV infection by the fourth decade of life (>99%) (27,62). The risk of herpes zoster increases with age, most commonly in adults aged >50 years, but can occur in healthy children and young adults with generally mild symptoms.

Like wild-type VZV, vaccine-strain VZV can result in latent infection and reactivation to cause herpes zoster. Immunity to and risk of herpes zoster correspond to VZV status, with vaccine-strain VZV having a substantially lower likelihood of reactivation than wild-type VZV infection, although the exact estimate is unknown (65,66). Over the past few decades, the proportion of the U.S. population that is infected with wild-type VZV and vaccine-strain VZV has changed dramatically. Today, persons born before 1970 (as of 2018, 48 years old) are nearly all infected with wild-type VZV, while persons born in 2010 (as of 2018, 8 year olds) will be mostly infected from vaccine-strain VZV only or VZV naïve by the time they reach adulthood. Progressive birth cohorts between 1970 and 2010 will be infected with varying mixes of VZV status.

Estimates of the lifetime risk of varicella infection and herpes zoster in the pre- and post-vaccine era are incomplete or unknown, and more research is needed to determine the ongoing and potential impact of vaccination programs on varicella and zoster epidemiology. We used age-specific incidence and coverage data from the Centers for Disease Control and Prevention (CDC) to estimate the distribution of VZV status among persons by age and birth cohort from 1970 to 2015. We then used this data to estimate the population susceptibility to varicella infection and to project the lifetime risk of herpes zoster in different herpes zoster vaccine uptake scenarios. These analyses have important programmatic implications for both varicella and herpes zoster vaccination policy, surveillance, control measures, and treatment.

Methods

Varicella and herpes zoster incidence

Varicella incidence data was received from three different reporting systems of the U.S. Centers for Disease Control and Prevention (CDC) (**Table 1**).

First, age-specific varicella incidence rates were compiled in summary form during the 1970-1994 period from the National Health Interview Surveys (NHIS) conducted by the National Center for Health Statistics (NCHS) and provided by the National Center for Immunization and Respiratory Diseases (NCIRD). The NHIS is a cross-sectional household interview survey of U.S. civilian, noninstitutionalized population conducted continuously throughout the year. These data yielded an average estimated total of 3,440,736 varicella cases each year based on an annual sample size (completed interviews) of approximately 87,500 individuals from 35,000 households (67,68). The annual response rate of NHIS is 60-80% of the eligible households in the sample. Average estimates were generated for five-year periods for all 50 states and the District of Columbia, and all estimates meet NCHS standard of reliability (i.e., an estimate must have a relative standard error of <30.0%). Case counts were noted to reflect about 10% underreporting from 1979-1982 but no adjustments were made to any of the data due to variability of estimated underreporting over the 25-year period (17).

Second, age-specific varicella incidence rates during the 1995-2010 period were obtained through CDC's Varicella Active Surveillance Project (VASP) for Antelope Valley (AV) surveillance area in California and provided by three published studies (46,47,69). AV had a population of approximately 284,000 in 1995, 350,000 in 2004, and 373,000 in 2010. Reporting sites were asked to submit biweekly case reports and were contacted if no reports were received (i.e. to confirm no cases occurred). There were 306

reporting sites in 2005 and 263 sites in 2010. Surveillance staff conducted case investigations for all reported varicella cases through a structured telephone interview or home visit for households where telephone contact was unsuccessful, and only verified cases were included in analysis. In 2005, completeness of reporting was estimated to be at 74% (46). To account for this, rates for this period were divided by a correction factor of 0.74 (underreporting assumed to be consistent during 1995-2010).

Third, age-specific varicella incidence rates during the 2011-2015 period were obtained from the National Electronic Disease Surveillance System (NEDSS) and provided by the National Center for Immunization and Respiratory Diseases (NCIRD). The NEDSS allows health jurisdictions within states to transmit weekly data regarding nationally notifiable diseases to the CDC. CDC reviews all varicella cases in states with consistent reporting. In our analysis, 21 states[α] were considered to have consistent reporting, with an average 6,758,806 cases reported by each state in 2011 and 6,720,270 average cases per state in 2015.

Annual state and age-group population estimates were obtained from the U.S. Census Bureau (https://seer.cancer.gov/popdata/download.html). Average annual incidence was calculated by using all cases reported in the selected states divided by the selected states' total population. Annual age-specific incidence was calculated by multiplying annual average incidence by annual age-group proportions for each year; cases of unknown age group were not included in annual average incidence and were accounted for by subtracting the respective proportion of unknown cases from the selected states' total population. NEDSS data is likely underreported since there is variation in surveillance practices between healthcare providers and local and state health

departments. To account for this, NEDSS rates were compared to adjusted VASP rates from 2005-2010 and the differences in yearly rates were averaged to calculate an adjustment factor of 0.49.

Age-specific herpes zoster incidence data was taken directly from four sources: (i) a population-based study in Minnesota that provided estimates for children and adolescents aged <15 years during the 1960-1981 (prevaccine) period; (ii) a population-based study conducted among members of the Harvard Community Health Plan in Massachusetts for adults aged ≥15 years during the 1990-1992 (prevaccine) period; (iii) a retrospective cohort study conducted by the CDC using medical claims from MarketScan databases for all ages during the 1993-2006 period; a retrospective cohort study conducted by CDC using medical claims from Medicare databases for all ages during the 1992-2010 period (34,35,53,70). Estimates from Medicare data were applied to the 2007-2016 period.

Varicella and herpes zoster vaccination coverage

National Immunization Survey (NIS) results from all 50 states and the District of Columbia were used to estimate 1-dose varicella vaccination coverage among children 19-35 months of age during 1996-2015. NIS results were also used to estimate varicella vaccination coverage of one dose or greater among adolescents 13-17 years of age during 2006-2015 and herpes zoster vaccination coverage of one dose or greater among adults aged ≥60 years during 2008-2016. In brief, NIS is a group of telephone surveys conducted by the CDC using a dual-frame survey design for household interviews with parents or guardians. Methods for the NIS have been previously described (71).

Constructing life histories of exposure to varicella infection and vaccination

Life histories (of exposure) were calculated using the proportion of the U.S. population ever infected with wildtype VZV (Equation 1), the proportion ever infected from vaccine-strain VZV (Equation 2), and, subsequently, the proportion still susceptible to VZV by age and calendar year (Equation 3), as shown below:

$$CI_{ij} = \sum_{0}^{80} I_{i,j+i} \quad (1)$$

$$CV_{ij} = \sum_{0}^{5} V_{i,j+i} \quad (2)$$

$$S_{ij} = 100 - CI_{ij} - \left(\left(100 - CI_{ij}\right) * CV_{ij}\right) \quad (3)$$

where *i* indicates age (years), *j* indicates calendar year, CI_{ij} is cumulative incidence for a given age and year (%), CV_{ij} is cumulative vaccination level for a given age and year (%), and S_{ij} is susceptibility for a given age and year (%). In each life history, time (in years) was represented on the horizontal axis and age (ranging from 0-80 years) was represented on the vertical axis. Incidence rates for age groups (<1 years, 1-4 years, 5-9 years, 10-14 years, 15-19 years, ≥20 years) were dispersed according to age and calendar year, from 1970-2015. Rates per 1,000 person-years (over a one year period) were converted to percentages. Age-specific proportions were compiled into 5- and 10-year age groups. It was assumed that persons born before 1970 had the same exposure history as those in 1970, and that persons acquire lifelong immunity after natural varicella infection.

In a second life history calculation, vaccination coverage (%) was allocated by birth year for those aged 0-80 years from 1996 (first year of NIS coverage data) to 2016. It was assumed that no U.S. child gets vaccinated before 12 months of age, children get vaccinated with one dose of varicella vaccine on the day of their first birthday, children

get vaccinated with a second dose of vaccine on the day of their fifth birthday, persons aged >5 years in the same birth cohort have the same level of vaccination coverage, and coverage levels from the most recent years have plateaued and represent coverage levels for the next 15 years. Since most recent vaccination coverage data for 5-year-olds begins in 2008—tracing NIS data backwards from 2016 for 13-year-olds—a moving 5-year average was calculated to predict coverage levels through 2030. To account for vaccine failure, coverage levels were multiplied by pooled 1-dose and 2-dose vaccine effectiveness (VE) estimates against all varicella disease to approximate the age-specific proportion of persons infected with vaccine-strain VZV (1-dose VE=0.81 for those aged 1-4 years, 2-dose VE=0.92 for those aged ≥5 years) (72).

Time series analysis and projection

We used Box and Jenkins autoregressive integrated moving-average (ARIMA) time series model in order to predict the proportion of persons ever infected with wildtype VZV from 2016-2060 (73). This model-building process takes advantage of associations in the sequentially-lagged relationships that usually exist in data collected periodically (74). This univariate forecasting method was reasonable because sufficient data was available and a linear trend was observed on a year-to-year basis. The model assumes high uncertainty for forecast estimates after estimating five units into the future. Stationarity was induced by taking non-seasonal differences of the series and correcting the mean. Sample autocorrelation function (ACF) and partial autocorrelation function (PACF) graphs were used to identify the appropriate order of autoregressive (AR) and

moving average (MA) terms included in the ARIMA model. For all birth cohort series tested, we selected an ARIMA (1,1,0) model.

Ascertainment of herpes zoster risk in different scenarios of vaccine uptake

Herpes zoster vaccine coverage data and VE estimates for one dose of live zoster vaccine among adults aged ≥60 years (0.779 for 51-60-year-olds, 0.659 for 61-70-year-olds, and 0.385 for 71-80-year-olds) were multiplied together to find the proportion of adults who had acquired immunity to herpes zoster (75). Then, forecasted values of lifetime risk of varicella served as reference for calculating the proportion of the population that would have experienced herpes zoster infection if no zoster vaccination program was implemented. In a separate step, we calculated the true attack rate for herpes zoster specifically among those with VZV-titers (either wildtype or vaccine-strain) by subtracting the proportion of these 'herpes zoster susceptibles' from the entire population. Effects of vaccine uptake (+0.25% through +2.00% annual increase) could then be calculated using these reference values and attack rates. Our starting point for increasing coverage was 33% in 2016 (most recent NIS data).

For lifetime risk of herpes zoster in the setting of static vaccine uptake, we assume that incidence rates reported in 2010 will be the same rates in 2030 for older age groups. Although herpes zoster subunit vaccine was recommended in 2017 for adults aged ≥50 years (with higher VE than live zoster vaccine), our predictions assume that coverage levels include live zoster vaccine only. Since live zoster vaccine has lower VE estimates than subunit HZ vaccine (1-dose subunit VE=0.90 for 50-69-year-olds, VE=0.69 for 70-80 year olds), we purposefully underestimate—rather than

overestimate—the potential impact of vaccination on zoster incidence (75). We assume that waning immunity from zoster vaccination does not occur within 20 years of vaccination (an over-simplification). Calculations were only done for cohorts born during 1950-1980, since the observed series for these cohorts included over 40 observations.

Statistical analysis

We used R version 3.4.1 (R Studio, Boston, MA) for compiling varicella and herpes zoster incidence data. Excel version 15.0 (Microsoft Excel, Redmond, WA) was used in the development of life histories and to calculate appropriate proportions for herpes zoster risk. Finally, we used SAS 9.4 (SAS Institute, Cary, NC) in order to obtain forecasted values, plot forecasted values according to different settings of zoster vaccine uptake, and conduct a sensitivity analysis.

Results

Lifetime risk of varicella infection

The average annual varicella incidence declined from 12 per 1,000 population in 1994 to 0.2 per 1,000 population in 2015 (a 99% decline). The most marked reduction in incidence occurred among 1-4-year-olds (99.9%), the age group targeted for the first dose of varicella vaccine. Further, comparing 1994 to 2015 data, the risk of ever reporting varicella infection declined by >98% among children aged <10 years, 96% among 10-14-year-olds, 88% among 15-19-year-olds, and 32% among 20-29-year-olds, with minimal declines in older age groups. In 2015, 0.1% of <1-year-olds, 0.3% of 1-4-year-olds, 1%

of 5-9-year-olds, 3% of 10-14-year-olds, 11% of 15-19-year-olds, and 64% of 20-29-year-olds ever reported varicella infection.

Declines in lifetime risk of varicella infection are observed for younger ages (<30 years) from 1995-2015 following introduction of the varicella vaccination program; declines are delayed until persons eligible for vaccination move into each age cohort, with immediate declines observed for 1-4-year-olds starting in 1995 (**Figure 1**). Still, we see declines earlier than expected for persons aged 10-14 years, 15-19 years, and 20-29 years, suggesting community protection of vaccine-ineligible individuals due to decreased circulation of wildtype VZV in younger age groups (76). For example, persons directly eligible for routine vaccination would not be included in the 15-19-year age cohort until 2009 (some may have been eligible for a catch-up campaign for 1-12-year-olds in 1995, but with minimal coverage levels at best), yet we observed a 6% reduction in the proportion ever infected with varicella for this age cohort by 2000 and a 26% reduction by 2008 (**Figure 1**).

Population susceptibility

Population susceptibility to varicella infection has changed dramatically since one dose of varicella vaccine was recommended to children aged 12-15 months in 1995 and a second dose recommended to children aged 4-6 years in 2006. In the pre-vaccine era, children aged 1-4 years and 5-9 years had the highest proportion of susceptibles (not including infants <1 year old, who are susceptible regardless of the vaccination program) (**Figure 2**). As of 2015, 1-4-year-olds are still at highest risk of infection (26% susceptible) and susceptibility is likely due to children delaying vaccination and one-dose

vaccine failure (81% VE). Burden of disease remains highest for children aged <10 years; incidence rates in 2015 were found to be 1.0 per 1,000 population for infants, 0.8 per 1,000 population for children aged 1-4 years, and 0.8 per 1,000 population for children aged 5-9 years. The second most at risk age cohort is 20-29-year-olds (25% susceptible to infection; a 12% increase compared to 1994) since the majority of these young adults are unvaccinated. Children aged 5-9 years experienced a quick decline once the second dose of varicella vaccine was recommended in 2006 (**Figure 2**). Varicella incidence coupled with estimates of population susceptibility to natural varicella infection by age cohort are shown in **Figure 3**.

Predicting lifetime history of varicella infection

After the data were handled by exponential smoothing, model identification, and diagnosis, the ARIMA (1,1,0) models were established for birth cohorts born between 1950 and 1980 and, in general, had similar statistical outputs. For example, the forecasted series for persons born in 1950 had a Box-Ljung Q test value to be 15.66 (p=.0013), the residual sequence to be white noise, and the Akaike's information criterion (AIC=161) to be lowest for this model compared to others. These diagnostics suggest that the ARIMA (1,1,0) models fit the trends for cumulative risk well and that the predicting results were reliable. This method is preferable to simple assumptions like extending flat-line incidence for future years because it takes into account earlier trends and outlier values (allowing for a small increase in risk, as we know to be the case for varicella) while also providing precision estimates.

The proportion of persons to ever report being infected with wildtype VZV plateau for all persons born in the pre-vaccine era after adolescence (**Figure 4**). By 2020, the risk of reporting varicella infection is estimated to be 87% (95% Confidence Interval [CI]: 72%, max 100%) for persons born in 1950, 86% (95% CI: 70%, 100%) for persons born in 1960, 93% (95% CI: 77%, 100%) for persons born in 1970, and 90% (95% CI: 69%, 100%) for persons born in 1980. 15-year forecast estimates for more recent birth cohorts were also obtained but not shown in **Figure 4** for sake of simplicity.

The recent declines in lifetime history of varicella are expected, since persons born in 1990 were eligible for one-dose varicella vaccine catch-up campaigns, persons born in 1995 were eligible for one dose of vaccine, and persons born in 2000 were the first birth cohort eligible for a second dose of vaccine (**Figure 4**). For example, by the age of 10, 40% of persons born in 1950 had been infected with wildtype VZV whereas only 3% of persons born in 2005 had been infected by this age. Further, the risk of having ever been naturally infected by 35 years of age was 92% for those born in 1970 and 2% for those born in 2005, a 98% reduction in risk. The ARIMA models for predicting lifetime history of varicella also provide a data series for predicting adult-aged herpes zoster risk in older birth cohorts.

Predicting lifetime history of herpes zoster

We found that risk of herpes zoster infection increases with age and across decades, with increases appearing before varicella vaccine introduction and stabilizing after high coverage levels were reached by the year 2000 (**Figure 5**). By the age of 35, 8% of persons born in 1995 had experienced herpes zoster whereas only 4% of persons

born in 1950 had experienced herpes zoster at this age. However, the median age of herpes zoster cases has not changed over time (median age=66 years olds for birth cohorts 1950-1980).

Our analyses suggest that herpes zoster vaccines could cause substantial reductions in herpes zoster incidence as long as zoster vaccination coverage levels increase in the future (**Figure 6**). As coverage by 2025 is relatively low in either vaccine uptake scenario (42% and 47%, respectively), impact of zoster vaccination is not fully appreciated until more recent birth cohorts reach 60 years of age (**Figure 6**). More modest reductions in lifetime risk of zoster are observed as vaccine effectiveness (VE) estimates decline with age (45,85,87). Currently, VE for live zoster vaccine among adults aged ≥70 years is estimated to be as low as 0.385; further reductions may be observed in the future as use of non-live subunit vaccine (Shingrix) increases, which has higher VE estimates (0.69 for one dose among adults aged 70-80 years) (86). A sensitivity analysis was performed for less-likely herpes zoster vaccine uptakes scenarios in order to show the effect of zoster coverage on lifetime risk of herpes zoster and risk of zoster between the ages of 60 and 80 years (**Table 2**).

If vaccine uptake remains at current levels (33% as of 2016), the risk of experiencing herpes zoster between 60 and 80 years of age for those who do not get vaccinated is approximately 28% for each birth cohort. In the setting of slightly-increasing uptake of herpes zoster vaccines (+1% annual increase among adults aged 60 years and older), risk of herpes zoster infection between 60 and 80 years of age is projected to decrease by 9% among persons born in 1950, 16% among persons born in 1960, 24% among persons born in 1970, and 32% among persons born in 1980 (**Table 3**).

In the setting of quickly-increasing uptake of herpes zoster vaccines (+1.5% annual increase among adults aged 60 years and older), risk of herpes zoster infection between 60 and 80 years of age is projected to decrease by 14% among persons born in 1950, 25% among persons born in 1960, 36% among persons born in 1970, and 48% among persons born in 1980 (**Table 3**).

Discussion

First, and perhaps of most consequence, our time-series analysis provides estimates of the lifetime risk of herpes zoster infection for select birth cohorts and allowed us to demonstrate how different scenarios of herpes zoster vaccine uptake may impact the risk of herpes zoster for older birth cohorts when they reach 60 years of age (**Figure 2, Table 3**). We found that risk of herpes zoster infection increases with age and across decades, with increases appearing before varicella vaccine introduction and stabilizing after high coverage levels were reached by the year 2000. If vaccine uptake remains at current coverage levels, the risk of experiencing herpes zoster between 60 and 80 years of age for those who do not get vaccinated is approximately 28% for each birth cohort. If herpes zoster vaccination coverage increases 1.5% each year from 2016 onward, risk of herpes zoster infection between 60 and 80 years of age is projected to decrease by 14% among persons born in 1950, 25% among persons born in 1960, 36% among persons born in 1970, and 48% among persons born in 1980.

Other studies confirm that herpes zoster incidence increases with age and that increases in incidence started occurring before introduction of varicella vaccine (24,57-59,77). For example, our incidence data are consistent with data from a retrospective

cohort study in Minnesota and show that herpes zoster is rare in adolescents (<5%), doubles in risk for those aged 50-59 years compared to those aged 40-49 years, and then increases by 1% per year around age 75 (24). Similar to Civen et al., we observed a lower risk of herpes zoster among children aged <10 years born in 2000 and 2005 (during a stabilized period of high coverage rates and low VZV circulation) compared to children aged <10 years born in 1995 (when VZV circulation and subsequent exposure were high) (58). These findings strengthen the evidence that by preventing natural infection, varicella vaccination may reduce the risk of herpes zoster in children (53,58,59,60,77).

To our knowledge, this is the first study to estimate (lifetime) risk of herpes zoster for older birth cohorts according to different scenarios of vaccine uptake in the United States. Horn et al. estimated the effects of different vaccine coverage levels on herpes zoster incidence in Germany long term, but—rather than forecasting—used a dynamic mathematical model that took into account vaccine protection from exogenous boosting (78). Brisson et al. developed a deterministic age-structured model that fits 1- and 2- dose vaccine efficacy, varicella force of infection, and zoster incidence in order to examine the potential impact of alternative varicella vaccination programs on varicella and zoster incidence (79). In epidemiology, univariate forecasting using ARIMA models have been widely applied to infectious diseases, such as for dengue fever and tuberculosis (80,81).

Second, we used ARIMA models to predict risk of varicella infection for the next 15-45 years, in order to 1) demonstrate that the risk of varicella infection has declined in younger birth cohorts (as expected) and 2) provide a sufficient data series for predicting adult-aged herpes zoster risk in more recent birth cohorts. The risk of having ever been infected with wildtype VZV by 35 years of age was 92% for those born in 1970 and 2%

for those born in 2005, a 98% reduction in risk. Risk of infection appears to plateau after adolescence. Again, our estimates of lifetime exposure to varicella are lower for older birth cohorts compared to NHANES data (62). Our ARIMA model provides reliable estimates, but only for a short period. Other studies have used similar forecasting methods to predict disease incidence and risk into the future, but ours is the first to do so for varicella in the United States (82,83).

Lastly, we show that varicella incidence declines dramatically following introduction of varicella vaccine in the United States. We calculated life histories in order to estimate the proportion of the population immune to varicella infection due to previously reported wildtype VZV infection and 1-dose vaccination by age cohort. Comparing 1994 to 2015 data, the risk of varicella infection declined by >98% among children aged <10 years, 96% among 10-14-year-olds, 88% among 15-19-year-olds, and 32% among 20-29-year-olds. Declines among vaccine-ineligible infants and older age cohorts (20-29-year-olds with minimal coverage levels, at best) suggest indirect protection. Burden of disease remains highest for children aged <10 years. Susceptibility to infection is highest for children aged <5 years and adults aged >20 years, as they either wait for vaccine eligibility, wait longer than recommended to get vaccinated, or were vaccine-ineligible.

These results confirm and extend findings from previous studies (48,84). Incidence rates reported from the BRFSS in Massachusetts are slightly higher than our reported rates; however, similar trends are shown, with the greatest declines noted between 1997 and 1999 (once coverage levels were 25-60% among 1-year-olds) and immediately following the addition of a routine second dose of vaccine in 2006 (48).

Increased 1- and 2-dose coverage levels among elementary school-age children in 2006 were noted in two additional studies (47,85). According to national seroprevalence data from NHANES 1988-1994, 95.5% of persons aged 20-29 years had acquired varicella infection, whereas we report an average of 91.2% for this age cohort during this period (data not shown). Our data are likely underestimates of the true burden of varicella infection, since our CDC-sourced data only include reported cases by state health departments and whereby mild cases of varicella may go unreported.

Our study has several advantages. First, we used the most recent varicella and herpes zoster incidence and coverage data available (CDC, unpublished) to show the susceptibility profile of the U.S. population by age, which can be helpful for patients as they decide whether or not to get vaccinated. Second, the results of our study take breakthrough infections and vaccine-associated herpes zoster into account, since our data included vaccine effectiveness estimates and inclusion of vaccinated individuals in our immune population calculations, respectively. Furthermore, the model developed in this study appears to have a high degree of accuracy. This allowed us to explore possible vaccination coverage settings using age-specific vaccine effectiveness estimates for live zoster vaccine, and coupled with sensitivity analysis, to provide suggestions for vaccine policy and coverage targets in the future.

Several limitations should be considered when interpreting our findings. Our data likely underestimate varicella incidence because some with mild varicella may not seek care; thus, the actual number of cases could be many times higher. Subsequently, natural immunity may be much higher than we estimate in our analyses. This is an ecological study, which does not allow us to assess individual exposure level or exclude potential

confounders. Our forecasting model becomes uncertain approximately 5-10 years after each of the observed series because the model does not consider other possible impacting factors such as changing demography, economy, and politics. Data must be continually updated to predict further rates. Further, we assume an equal distribution of herpes zoster incidence across all states and between males and females, although we know this not to be the case (as women have higher rates than men) (53).

Many of the parameters regarding herpes zoster and herpes zoster vaccination are not precisely known. For example, our assessment of herpes zoster risk in different vaccination settings does not take into account waning immunity from vaccine; protection offered by live zoster vaccine is estimated to only last 10 (9-12) years, and even duration of protection beyond five years is still uncertain (86,87). In addition, there is limited evidence available for parameters regarding exogenous boosting and the boosting assumption for herpes zoster and herpes zoster vaccination (58).

Our study provides predictions with consequences for policy and future research. We show that herpes zoster incidence in older birth cohorts will increase in the future if vaccination coverage levels stay the same, but that substantial reductions in incidence will occur among adults aged ≥50 years if coverage gradually increases. Our forecasted values can be used as a baseline for assessing the impact of herpes zoster vaccines on epidemiology. In addition, our estimates can be can be used by healthcare providers to communicate an older patient's risk of herpes zoster and the estimated risk that may be averted from receiving vaccine. Future research should aim at improving (i) herpes zoster surveillance as young, vaccinated cohorts begin to enter adulthood; (ii) understanding of herpes zoster burden attributable to the varicella vaccine strain, underlying mechanisms,

and boosting; (iii) estimates of vaccine effectiveness and long-term duration of protection for herpes zoster vaccines.

In summary, this study provides the first evidence of the impact of herpes zoster vaccination on risk of herpes zoster among older adults in the United States. We show that varicella incidence continues to decline following introduction of varicella vaccine, and that, perhaps counteractively, much of the population remains susceptible to herpes zoster due to vaccination. Our time-series analysis suggests that increasing herpes zoster vaccine uptake is likely to cause major reductions in incidence for older birth cohorts. Our work extends earlier findings, documenting increases in herpes zoster incidence prior to the introduction of varicella vaccine, but with stabilizing rates for recent birth cohorts. This is reassuring since clinical severity of herpes zoster and risk of post-herpetic neuralgia increase with age (33,88). Still, more research is needed to better understand the relationship between varicella exposure and herpes zoster. Probable benefits of herpes zoster vaccines need to be effectively communicated to healthcare providers and the public in order to achieve high vaccination coverage and subsequently ensure protection from this debilitating disease in those most at risk.

[α] States included were: Arkansas, Colorado, Delaware, Florida, Illinois, Indiana, Louisiana, Michigan, Missouri, Montana, New Hampshire, New Mexico, Ohio, Pennsylvania, South Carolina, South Dakota, Texas, Utah, Vermont, Virginia, and Wyoming.

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Tables

Parameters and related units	Value	Source
Parameter values for the baseline varicella immunization program		
Incidence rate of varicella infection by age	Varying	NHIS [from CDC] VASP [46,47,69] NEDSS [from CDC]
Age at first varicella vaccine dose	1 year	Author's assumption
Age at second varicella vaccine dose	5 years	Author's assumption
First dose estimated coverage (%)	12.0 – 90.6	NIS for Children
Second dose estimated coverage (%)	46.3 – 97.4	NIS for Adolescents
Average duration of vaccine protection	Lifelong	Author's assumption
1-dose vaccine effectiveness	0.81	Marin et al. [72]
2-dose vaccine effectiveness	0.92	Marin et al. [72]
Parameter values for the baseline herpes zoster immunization program		
Incidence rate of herpes zoster by age	Varying	Guess et al. [34] Donahue et al. [35] Civen et al. [58] Hales et al. [70]
Age at first varicella vaccine dose	60 years	Author's assumption
First dose estimated coverage (%)	6.7 – 33.4	NIS for Adults
Average duration of vaccine protection	>20 years	Author's assumption
1-dose live zoster vaccine effectiveness, Among those aged 51-60 years Among those aged 61-70 years Among those aged 71-80 years	 0.779 0.659 0.385	Prosser et al. [85]

Table 1. Baseline parameter values for universal varicella and herpes zoster immunization programs in the United States.

Cumulative risk of herpes zoster at 80 years of age		
HZ vaccine uptake scenario	Average birth cohort risk (%), (range)	Average % decrease from no increase (reference), (range)
If no increase in vaccine uptake (+0.0%) (reference)	**44 (42-45)**	**---**
If +0.25% annual increase in vaccine uptake	43 (41-44)	3 (2-5)
If +0.50% annual increase in vaccine uptake	41 (39-43)	6 (3-10)
If +0.75% annual increase in vaccine uptake	40 (38-42)	10 (5-15)
If +1.00% annual increase in vaccine uptake	**38 (36-41)**	**13 (6-19)**
If +1.25% annual increase in vaccine uptake	37 (34-40)	16 (8-24)
If +1.50% annual increase in vaccine uptake	**36 (32-40)**	**19 (9-29)**
If +1.75% annual increase in vaccine uptake	35 (31-39)	21 (11-29)
If +2.00% annual increase in vaccine uptake	34 (30-38)	23 (12-29)
Cumulative risk of herpes zoster between 60-80 years of age		
HZ vaccine uptake scenario	Average birth cohort risk (%), (range)	Average % decrease from no increase (reference), (range)
If no increase in vaccine uptake (+0.0%) (reference)	**28 (27-29)**	**---**
If +0.25% annual increase in vaccine uptake	26 (25-28)	5 (2-8)
If +0.50% annual increase in vaccine uptake	25 (23-27)	10 (5-16)
If +0.75% annual increase in vaccine uptake	24 (21-26)	15 (7-24)
If +1.00% annual increase in vaccine uptake	**22 (19-26)**	**20 (9-32)**
If +1.25% annual increase in vaccine uptake	21 (16-25)	26 (12-40)
If +1.50% annual increase in vaccine uptake	**19 (14-24)**	**31 (14-48)**
If +1.75% annual increase in vaccine uptake	18 (14-24)	34 (17-48)
If +2.00% annual increase in vaccine uptake	18 (14-23)	37 (19-48)

Table 2. Effects of different herpes zoster vaccine uptake scenarios on lifetime risk of herpes zoster and risk between the ages of 60 and 80 years on U.S. cohorts born between 1950 and 1980. Estimates considered for further evaluation are in bold. In the vaccine uptake scenario of +1.75%, coverage reaches 99% in 2054 and remains at this level from then onward. In the vaccine uptake scenario of +2.00%, coverage reaches 99% in 2049 and remains at this level from then onward.

Cumulative risk of herpes zoster at 80 years of age			
	If no increase in vaccine uptake (%)	If +1% annual increase in vaccine uptake (%, % change)	If +1.5% annual increase in vaccine uptake (%, % change)
For persons born in 1950	44	41 (-6)	40 (-9)
For persons born in 1960	45	40 (-10)	38 (-16)
For persons born in 1970	42	36 (-15)	33 (-22)
For persons born in 1980	45	36 (-19)	32 (-29)
Cumulative risk of herpes zoster between 60-80 years of age			
	If no increase in vaccine uptake (%)	If +1% annual increase in vaccine uptake (%, % change)	If +1.5% annual increase in vaccine uptake (%, % change)
For persons born in 1950	28	26 (-9)	24 (-14)
For persons born in 1960	29	24 (-16)	22 (-25)
For persons born in 1970	27	20 (-24)	17 (-36)
For persons born in 1980	27	19 (-32)	14 (-48)

Table 3. Cumulative risk (%) of herpes zoster (HZ) for select birth cohorts in the United States. “No increase in vaccine uptake” indicates that HZ vaccine coverage levels remain constant at 33% among adults aged ≥60 years from 2016 onward. “% change” indicates the change in risk (%) due to an increase in HZ vaccine uptake compared to the “no increase in vaccine uptake” scenario.

Figures

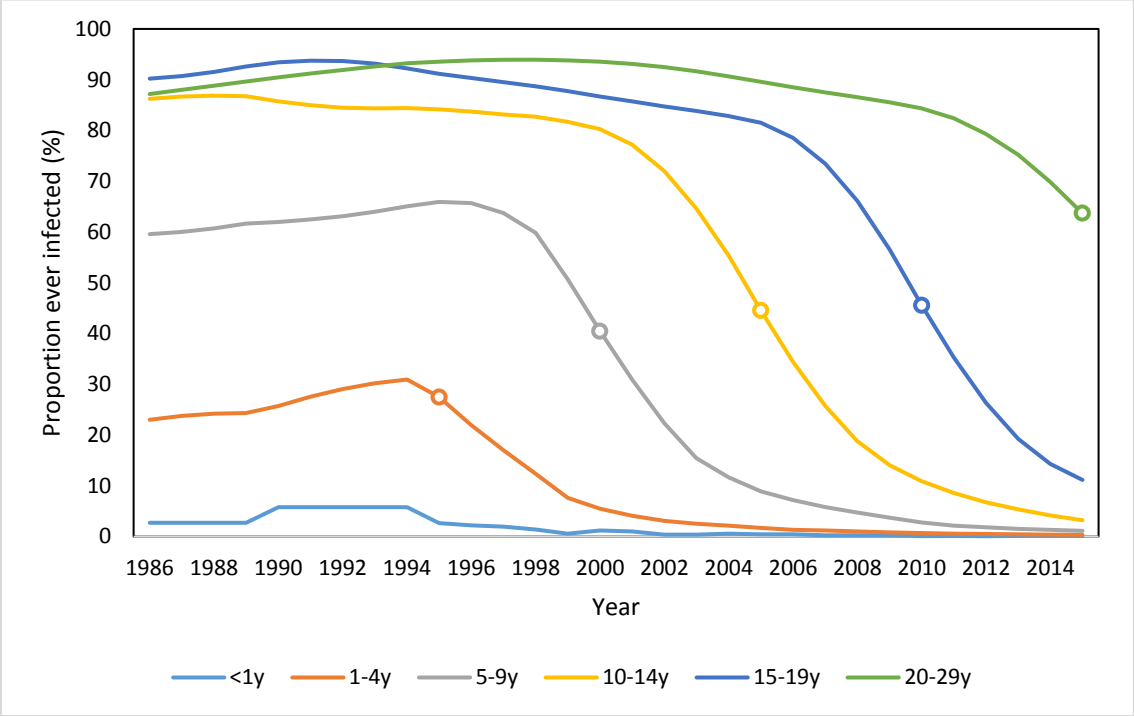

Figure 1. Proportion of individuals in the population to have ever reported varicella infection, by age cohort – United States, 1986-2015. Open circles indicate the first year persons in each age cohort were eligible to receive one routine dose of varicella vaccine in 1995 (at 12-15 months of age). A catchup campaign for children aged 1-12 years was implemented in 1995 as well, but minimal coverage levels (<12%) were achieved for children within this age range.

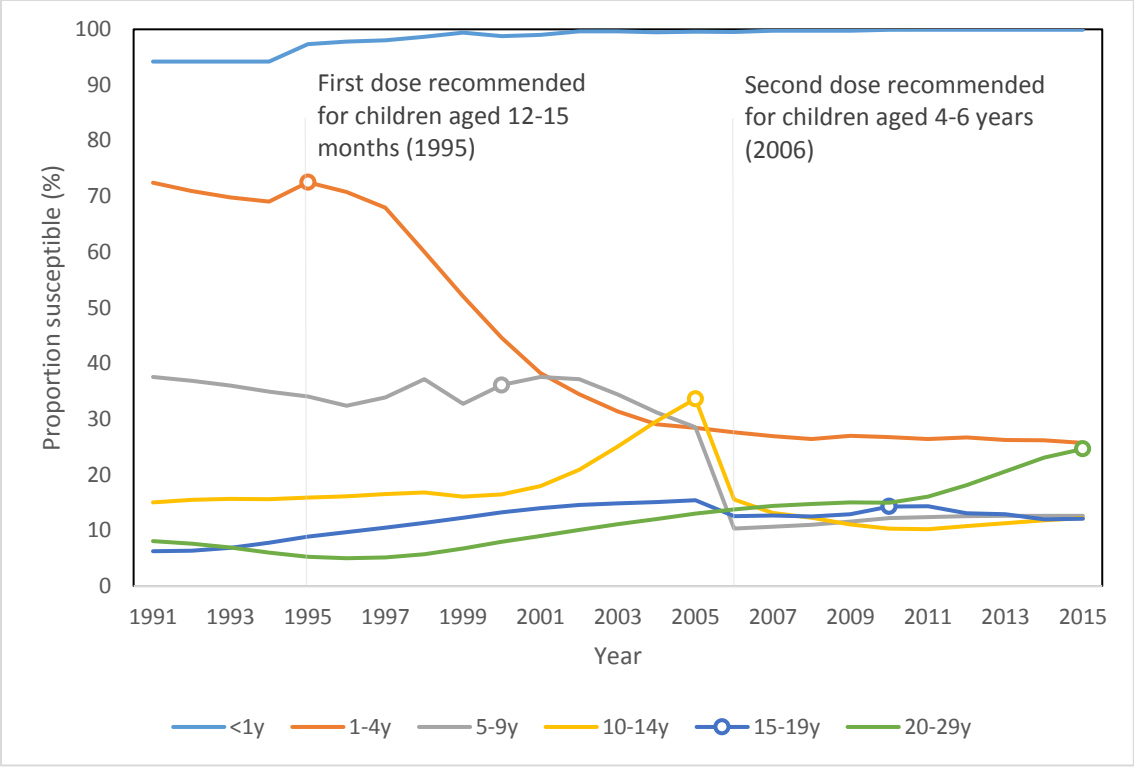

Figure 2. Proportion of individuals susceptible to varicella infection, by age cohort – United States, 1991-2015. Open circles indicate the first year persons in each age cohort were eligible to receive one routine dose of varicella vaccine in 1995 (at 12-15 months of age). A catchup campaign for children aged 1-12 years was implemented in 1995 as well, but minimal coverage levels (<12%) were achieved for children within this age range. Protection from maternal antibodies among infants is not accounted for here.

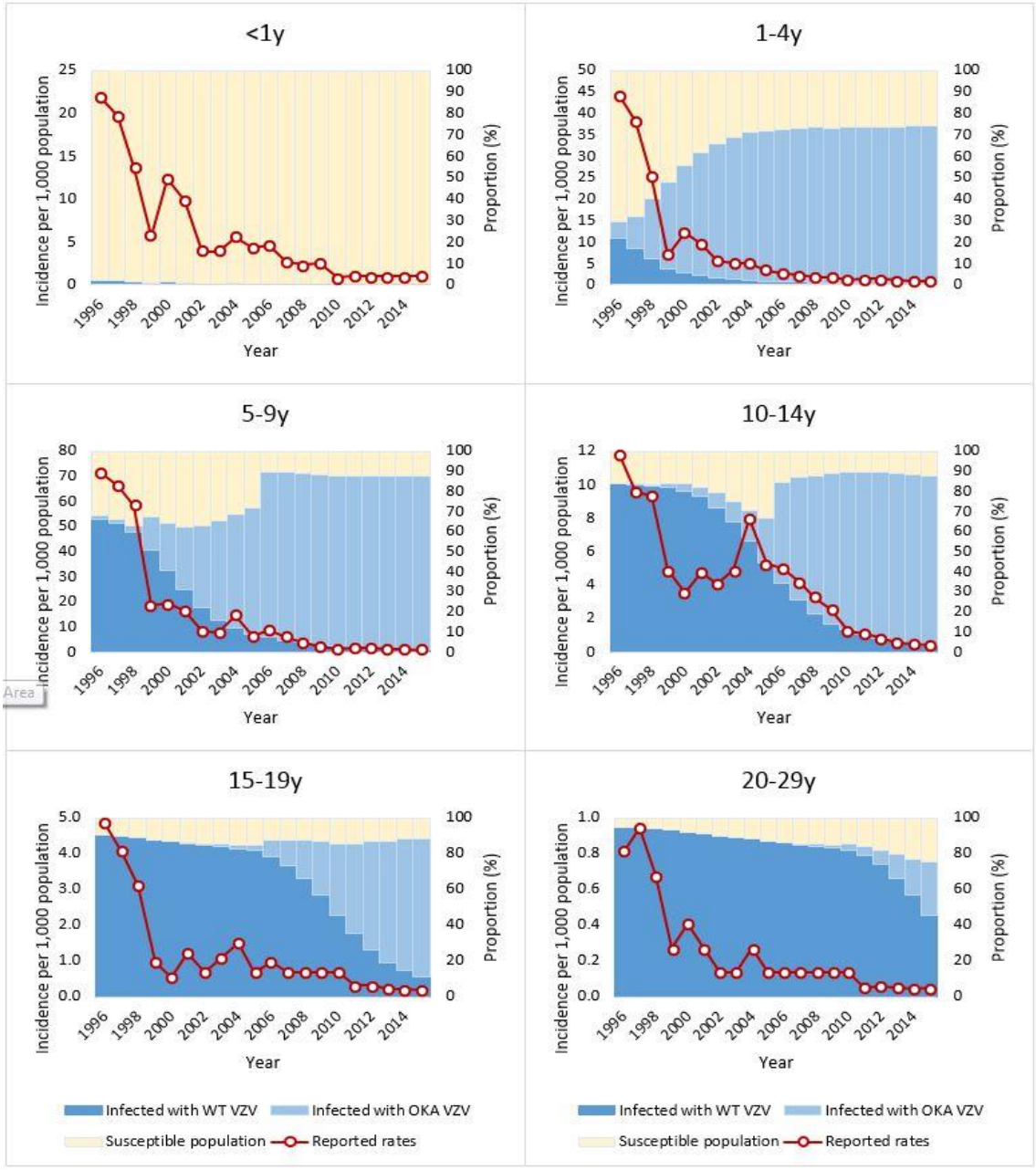

Figure 3. Varicella incidence and estimates of population susceptibility over time, by age cohort – United States, 1996-2015. Individuals "infected with OKA VZV" have received one or two doses of varicella vaccine; vaccine failure is taken into account. Many states set daycare and school requirements for varicella vaccination in 1999 and a routine second dose of vaccine was recommended in 2006. Protection from maternal antibodies among infants is not accounted for here.

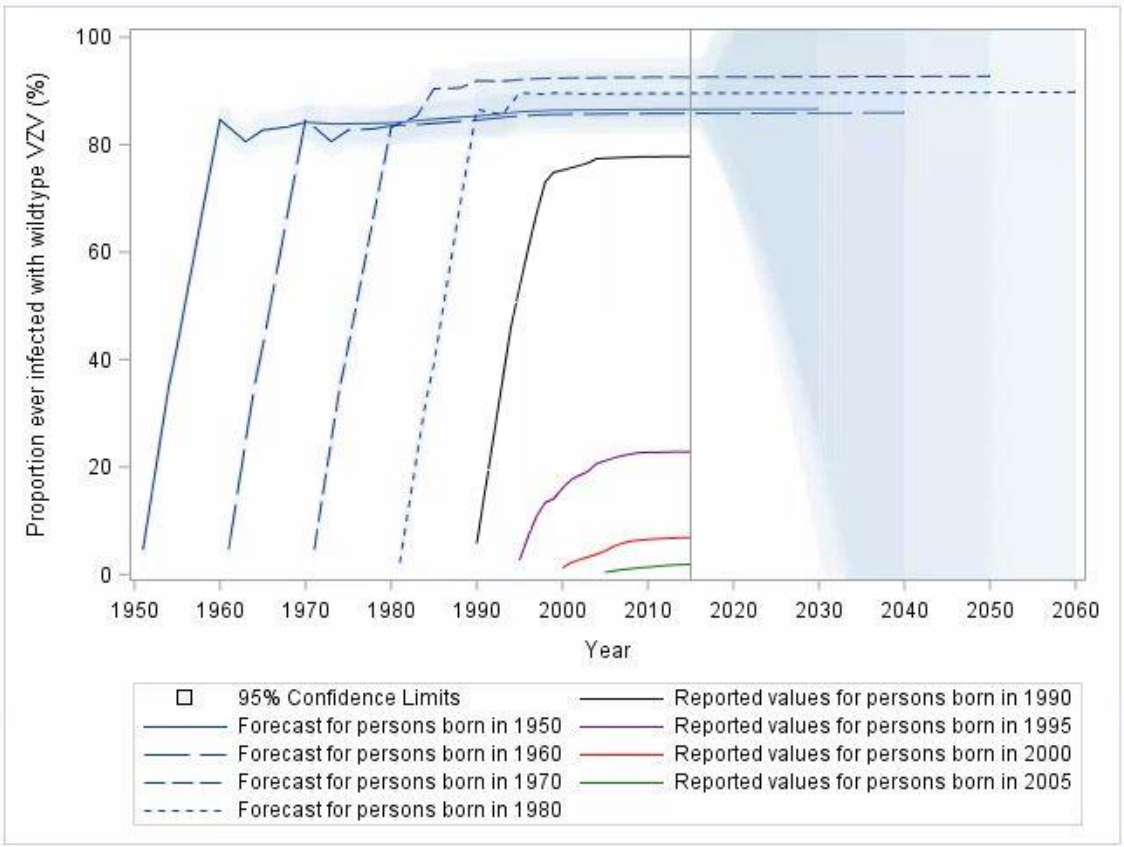

Figure 4. Autoregressive integrated moving-average (ARIMA) models to forecast the proportion of persons reporting previous or current varicella infection for the years 2016-2060, by select year of birth in the United States. Reference line at the year 2015, when most recent data were available. Persons born in 1990 were eligible for one-dose varicella vaccine catchup campaigns, persons born in 1995 were eligible for one routine dose of vaccine, and persons born in 2000 and 2005 were eligible for a second routine dose of vaccine. Forecasts for persons born during 1990-2005 are not shown due to limited (<40) observations.

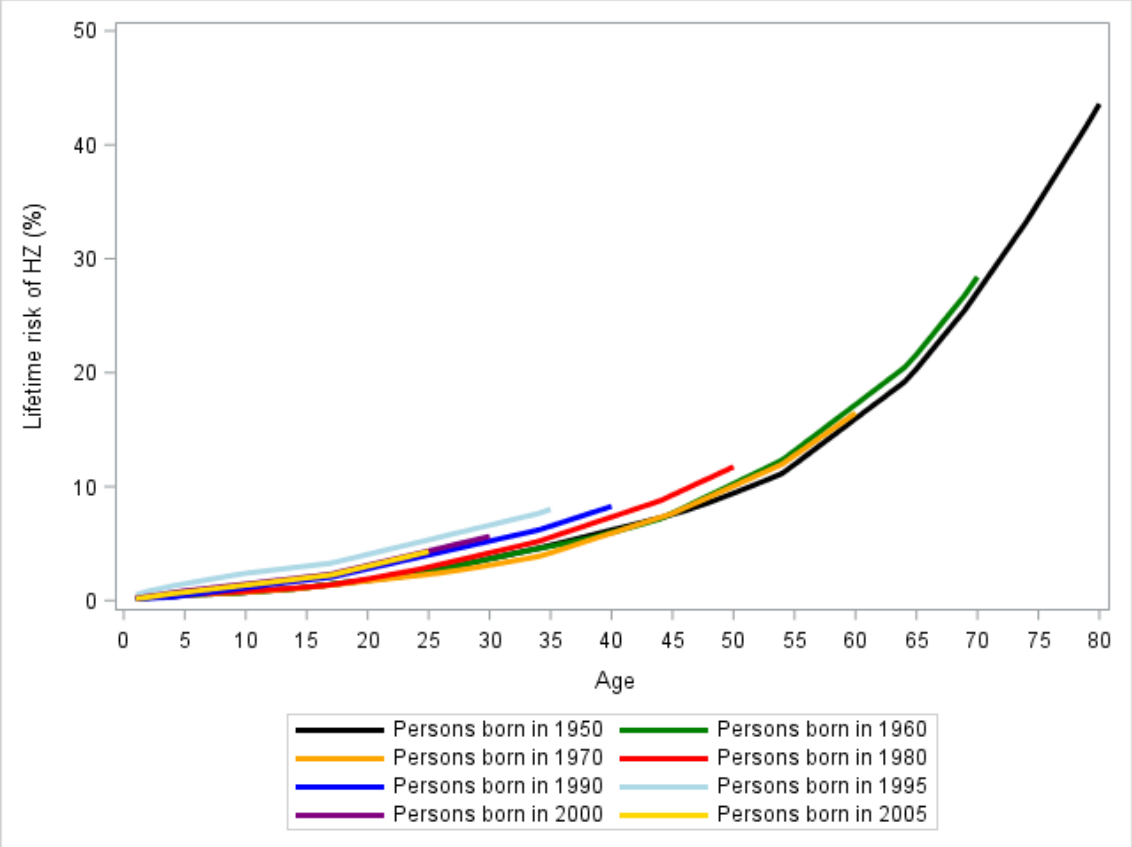

Figure 5. Estimated proportion of individuals in the U.S. population that will ever report herpes zoster (HZ) infection, by birth cohort. 15-year forecasts for all birth cohorts are included here.

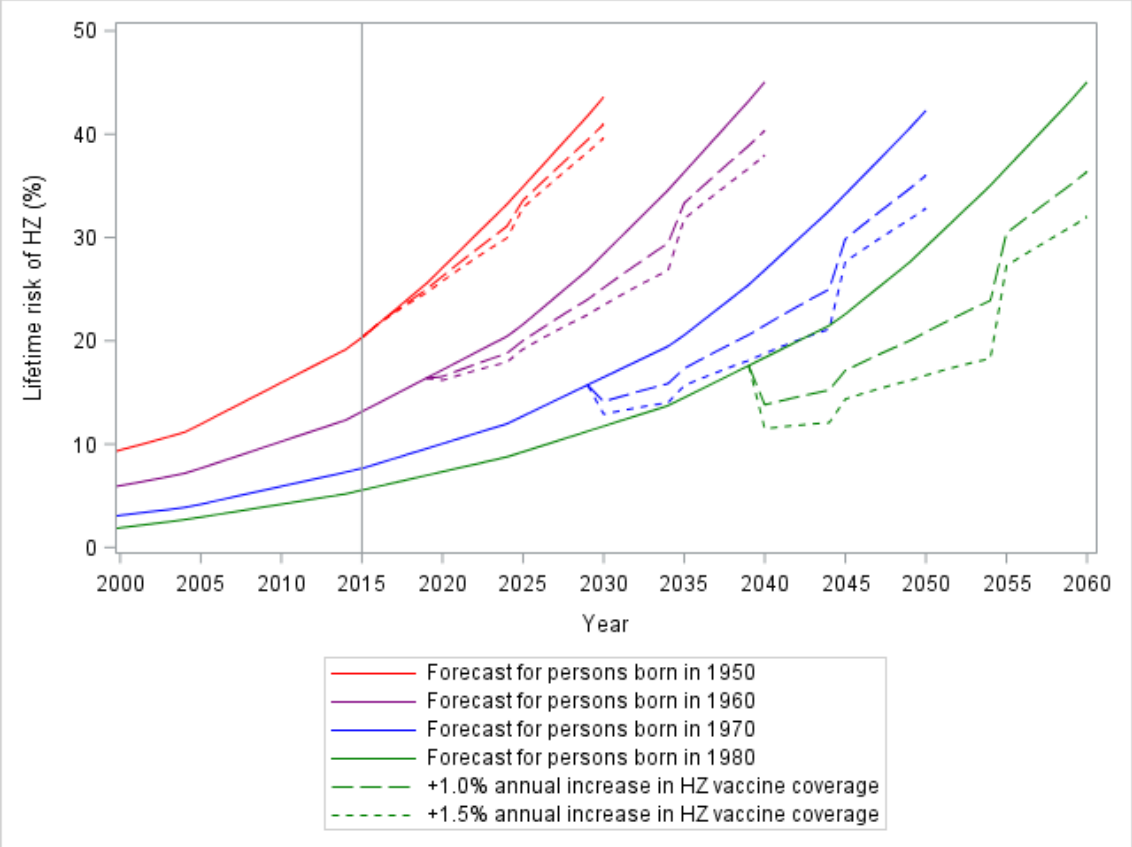

Figure 6. Lifetime risk of herpes zoster (HZ) in different scenarios of HZ vaccine uptake, by birth cohort in the United States. Solid lines represent a static vaccine uptake scenario, in which coverage remains at 33% among adults aged ≥60 years from 2016 onward. In a "+1% annual increase" scenario, coverage among adults aged ≥60 years starts at 33% (2016) and would reach 50% coverage in 2033 and 75% coverage in 2057. In a "+1.5% annual increase" scenario, coverage among adults aged ≥60 years starts at 33% (2016) and would reach 50% coverage in 2025 and 75% coverage in 2037. Reference line at the year 2015, when most recent data were available.

Chapter III: Public Health Implications & Future Directions

Our study has significance for real world decision-making. First, our forecasted values highlight the importance of high population immunity from vaccines and, namely, how childhood vaccination programs may have a substantial impact on reducing burden of disease for adults and others unvaccinated in the community. Our data also allow individuals to identify their risk of VZV infection and reactivation by year of birth. Second, this study highlights the need for ongoing, active surveillance of age-specific incidence, which can help to determine whether varicella and zoster vaccine waning is occurring (and if so, when). These data have important programmatic implications for both varicella and herpes zoster vaccination policy and for cost-effectiveness evaluation. Third, we show that VZV status and susceptibility has changed over time among age cohorts in the U.S. population; these changes have clinical implications on how each age cohort will experience varicella and herpes zoster. Lastly, the caveats of this study highlight how much we still don't know about VZV boosting and reactivation.

In the scientific community, concerns have been raised that reduction in varicella and circulating VZV would increase the incidence of herpes zoster, since VZV boosts the host's cell-mediated immunity and protects against reactivation (i.e., the "exogenous boosting hypothesis") (89). Our data indicate that this theory is unlikely to be the sole reason why herpes zoster incidence increased since we observed these increases to stabilize once high vaccination coverage was reached and circulation of wild-type VZV was subsequently low (approximately five years after the program was implemented [2000], coverage reached about 70% among children). Several studies from other countries agree with our claim, since they document increases in age-specific herpes

zoster incidence in settings of no or limited varicella vaccination programs (90-92). Moreover, the exogenous boosting hypothesis is not supported by U.S. studies, which also report recent plateauing in zoster incidence and/or an increase in the interval between varicella and subsequent herpes zoster (53,58,70).

Altogether, reasons for reactivation of latent VZV are not fully understood. The pre-vaccine increase is probably multifactorial and includes better surveillance methods, increasing numbers of elderly people and immunosuppressed individuals due to medication use, and rising stress levels (93). Risk factors for causing reactivation of VZV are less understood and may include comorbid chronic conditions, trauma, psychological stress, race, and family history (94). Understanding the pathophysiology of VZV will be critical for deciding whom to target for zoster vaccination and treatment strategies. Ongoing and sensitive surveillance of herpes zoster, like the VASP of the CDC, is needed to detect and understand changes in zoster epidemiology as cohorts of children vaccinated against varicella begin to enter adulthood.

Future research should consider the application of other and more complex models to predict the potential short- and long-term effects of varicella and zoster vaccination. For example, a study in Norway quantified the impact of a range of alternative immunization options against varicella and herpes zoster using a dynamic mathematical model (95). Brisson et al. developed a deterministic age-structured model that fits 1- and 2- dose vaccine efficacy, varicella force of infection, and zoster incidence in order to examine the potential impact of alternative varicella vaccination programs on varicella and zoster incidence (96). A transmission model could be calibrated to prevaccine data, validated against early post-vaccine data, and then used to predict future

incidence as long as vaccination coverage was available (78). Despite uncertainties that are inherent in predicting rates in the long term, these types of models could provide valuable insights for national policy and decision-making in regards to national zoster vaccination strategies in the near future.