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Changing Epidemiology of Varicella Outbreaks in the United States during the Varicella Vaccination Program, 1995—2019

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Abstract

We describe the changing epidemiology of varicella outbreaks informed by past and current active and passive surveillance in the United States by reviewing data published during 1995–2015 and analyzing new data from 2016 to 2019. Varicella outbreaks were defined as ≥ 5 varicella cases within 1 setting and ≥ 1 incubation period. During the 1-dose varicella vaccination program (1995–2006), the number of varicella outbreaks declined by 80% (2003–2006 vs 1995–1998) in 1 active surveillance area where vaccination coverage reached 90.5% in 2006. During the 2-dose program, in 7 states with consistent reporting to the Centers for Disease Control and Prevention, the number of outbreaks declined by 82% (2016–2019 vs 2005–2006). Over the entire program (1995–2019), outbreak size and duration declined from a median of 15 cases/outbreak and 45 days duration to 7 cases and 30 days duration. The proportion of outbreaks with <10 cases increased from 28% to 73%. During 2016–2019, most (79%) outbreak cases occurred among unvaccinated or partially vaccinated persons eligible for second-dose vaccination, highlighting the potential for further varicella control.

Routine childhood varicella vaccination has been recommended in the United States since 1995 [1]. The initial 1-dose program attained high vaccine coverage among children 19–35 months of age (90% in 2007) and reduced varicella cases, hospitalizations, and deaths by 71%–90% [2–4]. However, 1-dose vaccine effectiveness of ~82% (most outbreak investigations reported effectiveness of 71%–89%) [1, 5, 6] was insufficient to prevent varicella outbreaks, which continued to occur in highly vaccinated school populations [7, 8]. These outbreaks, though smaller and less frequent than during the pre-vaccine era, disrupted school activities and placed a burden on health departments to investigate and implement control measures [9, 10]. In 2007, the US varicella vaccine policy was updated from 1-dose to a routine 2-dose vaccine schedule at ages 12–15 months and 4–6 years to further reduce the burden of varicella and prevent outbreaks [1]. Two doses of varicella vaccine offer increased protection (vaccine effectiveness of 92%–95%) [1, 5].

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At the start of the U.S. varicella vaccination program, national varicella surveillance was not in place. Additionally, the National Notifiable Diseases Surveillance System used since 2000 for case surveillance remains inadequate for outbreak surveillance because of challenges with linking outbreak-associated cases [11]. Therefore, varicella outbreaks have been monitored through a combination of active and passive outbreak surveillance. In this paper, we review published data on varicella outbreaks during 1995–2015 and provide an update with new data from 2016–2019. We harnessed a variety of surveillance systems to describe the changing epidemiology of varicella outbreaks from the early 1-dose program through the mature 2-dose varicella vaccination program.

Methods

1995–2005, Active surveillance

Because varicella was not a nationally notifiable disease in 1995, the Centers for Disease Control and Prevention (CDC) established varicella active case-based surveillance at three areas (Antelope Valley, CA; West Philadelphia, PA; Travis County, TX), with one area, Antelope Valley (population ~284,000 in 1995) also conducting outbreak surveillance [12, 13]. Approximately 300 reporting sites were recruited in each surveillance area, including schools, daycares, healthcare providers, hospitals, public health clinics, universities, correctional facilities, and homeless shelters; sites reported bi-weekly, even when no cases were identified. Surveillance staff conducted case investigations through telephone interviews with each patient or guardian and medical records were reviewed for all serious varicella-related complications or hospitalizations.

2005–2019, Passive and active surveillance

Starting in 2005, some health departments initiated varicella outbreak surveillance. During 2005–2012, 9 states reported to CDC annually aggregate varicella outbreak data collected through passive surveillance [14]. During 2012–2015, 10 jurisdictions (state and local health departments) conducted active surveillance for varicella outbreaks in 300 schools in each jurisdiction through CDC's Epidemiology and Laboratory Capacity (ELC) program [15]. Jurisdictions submitted aggregate data to CDC, including zero-event reporting. In August 2015, the ELC program was extended to provide nationwide passive varicella outbreak surveillance which included jurisdictions disseminating information to public health partners (e.g., schools, physician offices, hospitals) to raise awareness of varicella case and outbreak reporting requirements and providing training and education to collect case and outbreak data. In jurisdictions where varicella was not a reportable condition (n=10), varicella outbreaks were reported through mandates for reporting of outbreaks of all etiologies. Reporting sources varied by jurisdiction and included healthcare providers, school (or other facility) nurses, and parents. Jurisdictions sent CDC quarterly data on varicella cases (including zero-reporting) from outbreaks and clusters, including data on transmission setting, age, rash onset dates, number of skin lesions, vaccination status of patients, prior disease history, laboratory-confirmation [16] and whether patients were hospitalized or developed complications. Vaccination status was obtained by the jurisdiction from provider and school records and electronic immunization registries.

Definitions

Jurisdictions refer to 50 state and 6 local (large metropolitan area) health departments that report public health surveillance data to CDC. Varicella was defined as an illness with acute onset of diffuse (generalized) maculopapulovesicular rash without other apparent cause [17]. Varicella outbreaks were defined by CDC as ≥ 5 varicella cases occurring within one setting and ≥ 1 incubation period (21 days) [16]. Since 2005, information was also obtained on varicella clusters, defined as 3–4 varicella cases in one setting and within ≥ 1 incubation period [15]. We used previously reported definitions of severity [13, 15, 18]: mild (<50 skin lesions), moderate (50–499 lesions), and severe (≥ 500 lesions or a reported complication or hospitalization). We defined partially-vaccinated patients as those aged ≥ 5 years who had received only one dose of vaccine.

Analysis

Varicella outbreak data during 1995–2015 have been previously summarized [13–15, 18]. One report [14] used a definition of ≥ 3 cases, so we reanalyzed those data using an outbreak definition of ≥ 5 cases for that timeframe (2005–2012). For 2016–2019, we conducted a descriptive analysis of outbreak and cluster data; for case-level analyses, since demographic and clinical characteristics of outbreak- and cluster-associated patients were similar, we report results with the two categories combined. We used χ^2 -square and linear regression tests to evaluate numeric and categorical variables, respectively, and the Cochran Armitage trend test to examine proportions over time. Two-sided p -values <0.05 were considered statistically significant. SAS 9.4 (SAS Institute Inc., Cary, NC) was used for analysis.

Results

Outbreak characteristics, 1995–2019

In the vaccination program's early years (1995–1998), 236 varicella outbreaks were reported from the Antelope Valley, CA active surveillance area; by the end of the 1-dose period (2003–2006) the number of outbreaks reported from Antelope Valley was 47, an 80% decline [13]. Vaccine coverage there reached 90.5% in 2006. During the early 2-dose period (2007–2010), 12 outbreaks were reported from Antelope Valley (95% decline from 1995–1998). Active surveillance was discontinued in 2010 because the low number of cases made it impractical to further monitor the program.

During the 2-dose period, outbreak surveillance relied on passive surveillance in 9 states (2005–2012, [14]), active surveillance in 10 sentinel jurisdictions (2012–2015, [15]), and nationwide passive surveillance in 56 jurisdictions (2016–2019). During 2016–2019, 49 (88%) of 56 jurisdictions reported varicella data to CDC (including zero-reporting); 48 (98%, 44 states and 4 local jurisdictions) reported ≥ 1 outbreak. These jurisdictions reported a total of 316 varicella outbreaks (median 4 outbreaks per jurisdiction, interquartile range [IQR], 2–11). From 1995–1998 to 2016–2019, outbreak duration and size declined from a median of 45 to 30 days and 15 to 7 cases per outbreak; size and duration have been relatively stable since 2010 [Table 1]. The proportion of outbreaks with <10 cases increased from 28% in 1995–1998 to 37% by the end of the 1-dose period (2005–2006) and to 73%

in 2016–2019. In 7 states with continuous reporting from the end of the 1-dose period, the number of outbreaks declined 82%, from 381 in 2005–2006 to 82 in 2016–2019.

Most reported outbreak-associated varicella cases occurred in school-aged children aged 5–14 years (range, 62% to 96%) [13–15][Table 1]. The proportion of patients with varicella in outbreak settings who were vaccinated (at least one dose) increased from 2% in 1995–1998 to 66%–80% in 2005–2012 and decreased to 25% in 2016–2019. Since 2012, most varicella cases have occurred in unvaccinated or 1-dose vaccinated patients (72% in 2012–2015) or unvaccinated or partially vaccinated among vaccine-eligible persons (79% in 2016–2019). Information on disease severity and complications was available during 1995–2005 and 2012–2019. The proportion of moderate and severe varicella cases (> 50 skin lesions) decreased from 65% in 1995–1998 to 47% in 2016–2019; 9% of outbreak-associated patients had a reported complication in 1995–1998 and 1% in 2016–2019.

During 2016–2019, the most common transmission settings were schools (41%), followed by daycares (19%) and households (16%). Fourteen percent of outbreaks occurred in correctional or detention facilities, with 43% of these occurring in 2019; only 2% of outbreaks were reported in colleges. Overall, 122 (39%) outbreaks were laboratory confirmed, with a median of 2 cases confirmed in each outbreak [Supplementary Table 1].

For 2016–2019, we examined the relationship between vaccination status of the index case and outbreak size and duration. Vaccination status of the index patient did not affect outbreak size (median=6–7 cases) but did affect outbreak duration. Outbreak duration was shorter when the index patient was vaccinated with either one or two doses compared with when the index patient was unvaccinated or had prior disease history (20–21 days vs. 31–33 days; $p=0.049$). In outbreaks with an unvaccinated index patient, a higher proportion of outbreak patients were unvaccinated (83%) compared with when the index patient was vaccinated (33%) or had disease history (64%) ($p<0.001$).

Patient characteristics, 2016–2019

A total of 5,135 patients were associated with varicella outbreaks or clusters during 2016–2019. Most were aged 5–9 (1,670, 32%) or 1–4 (1,222, 24%) years [Supplementary Table 1]. The median age was 7 years (IQR, 3–12) and remained stable over time, ranging between 6 and 8 years. From 2016 to 2019, the proportion of outbreak/cluster-associated patients aged 15–19 years increased from 3% to 6% and proportion of patients aged ≥ 20 years increased from 10% to 24% ($p<0.010$); 67% of 15–19 year-olds and 72% of ≥ 20 year-olds were reported from correctional or detention facilities in 2019. Among 4,310 patients with information on both age and vaccination status and excluding those with prior disease history, 3,124 (72%) were unvaccinated (315 [10%] aged <1 year and 2,809 [90%] aged ≥ 1 years), 650 (15%) vaccinated with 1 dose (321 [49%] aged 1–4 years and 329 [51%] aged ≥ 5 years), and 536 (12%) vaccinated with 2 doses. Among 3,994 (78%) patients aged ≥ 1 year with known vaccination status, age, number of doses and without prior disease history, 3,138 (79%) were not age-appropriately vaccinated, including 2,809 unvaccinated and 329 partially vaccinated; this proportion increased from 76%–78% in 2016–2018 to 85% in 2019 ($p<0.001$).

Among 3,657 (71%) patients with disease severity data available, 1,532 (42%) had mild disease, 1,936 (53%) had moderate disease, and 189 (5%) had severe disease. A higher proportion of vaccinated patients than unvaccinated patients had mild disease (68% vs. 33%, $p<0.001$). Among those aged ≥ 1 year, partially vaccinated patients also were more likely to have mild disease compared with unvaccinated patients (41% vs 23%, $p<0.001$). Among vaccinated patients, a higher proportion of 2-dose vaccinated patients had mild disease compared with 1-dose vaccinated patients (78% vs. 61%; $p<0.001$). Among 189 patients with severe disease, 74 (39%) were hospitalized or had a complication and the rest had ≤ 500 lesions (105 unvaccinated, 6 1-dose and 4 2-dose vaccine recipients). A total of 45 (1%) patients were hospitalized, mostly (28, 62%) unvaccinated while 18% (8) were vaccinated [Supplementary Table 1]. There were 29 patients (0.6%) with a reported complication but not hospitalized, among whom most (21, 72%) were also unvaccinated [Supplementary Table 1]. The proportion of hospitalized patients did not differ by vaccination status (0.9% unvaccinated and partially vaccinated, 0.7% vaccinated, $p>0.6$).

Varicella was laboratory confirmed in 513 (11%) patients, increasing from 10% in 2016 to 15% in 2019 ($p<0.001$) [Supplementary Table 1]. A higher proportion of unvaccinated patients were laboratory confirmed compared with vaccinated patients (12% vs. 6%; $p<0.001$); 8% of partially vaccinated patients were laboratory confirmed.

Discussion

Since the initiation of the varicella vaccination program in 1995, the number of varicella outbreaks has continued to decline. Outbreak size and duration have also declined from a median of 15 to 7 cases/outbreak and duration from 45 to 30 days; size and duration appear to have stabilized since 2010. The proportion of outbreaks with <10 cases increased from 28% to 73% in 2016–2019..

The characteristics of varicella outbreaks during the mature 2-dose US varicella vaccination program (2016–2019), documented using nationwide varicella outbreak surveillance, support the continued impact of the 2-dose program. Three quarters of reported outbreaks consisted of <10 cases, and most lasted approximately 30 days. In states with consistent reporting of varicella outbreaks over time, an 82% decline in the number of outbreaks was observed during the 2-dose program compared with the end of the 1-dose period. During the same period, there were ongoing activities to increase awareness and reporting of varicella outbreaks, making it unlikely that the reduced number of outbreaks was due to diminished reporting over time. By 2016–2019, when transmission did occur, it most commonly resulted in clusters with only 3–4 cases rather than outbreaks (≥ 5 cases). (Supplementary Figure 1).

We report that when the index patient was unvaccinated, outbreak duration was longer, with transmission occurring in pockets of unvaccinated persons as the proportion of unvaccinated patients was higher in these outbreaks compared with outbreaks in which the index patient was vaccinated. Overall, most (79%) patients were not age-appropriately vaccinated (i.e., unvaccinated or partially vaccinated); only 12% had received 2 doses of varicella vaccine. In contrast with outbreaks during the 1-dose period when most cases were among 1-dose

vaccinated children in elementary schools, increased protection among 2-dose vaccinated persons appears to limit transmission in settings with high 2-dose coverage. Throughout the program, schools were the main varicella outbreak setting and have served as the main reporting source for outbreak surveillance. In 2016–2019, schools continued to be the main outbreak setting although the proportion of school outbreaks decreased over time; as before, outbreaks in colleges rarely occur. An increase was seen during 2016–2019 for outbreaks where transmission occurred in the household, which includes visitors who do not live in the household but who were exposed in the household, and in correctional and detention centers. When considering outbreaks and clusters together, households were the most common transmission setting. The increase in the proportion of outbreaks in correctional and detention facilities and larger proportion of cases among persons aged ≥ 20 years in 2019 can be explained by the increase in immigrant populations in 2019 in the Southern US border [19] mainly from countries in which the epidemiology of varicella is different, with higher susceptibility among young adults than the general U.S. population [20]. About 1/5 of outbreaks occurred in daycares, with small fluctuations in this proportion over time. We also found that vaccinated patients had milder disease, as measured by number of skin lesions, fewer complications or hospitalizations, than unvaccinated patients, characteristics described previously [15, 21]. Additionally, we report that 2-dose vaccinated patients had milder disease than 1-dose vaccinated patients.

Over the course of the varicella vaccination program, vaccine coverage for 1 and then 2 doses has risen to high, sustained levels. Varicella 1-dose coverage rose among 19–35 month-olds from 26% in 1997 to 92.7% in 2020 [22–24]. Nationally, coverage levels are not routinely measured for the 4–6 year age group, the age recommended for routine second dose of varicella vaccination. However, evidence indicates that second dose coverage is high among children. Early in the 2-dose program, an assessment in 6 states found 2-dose coverage 80%–92% among children aged 7 years during 2006–2012 using data from Immunization Information Systems [25]. Elam-Evans et al. updated this analysis and report 2-dose coverage of 86%–100% (median: 92.8%) in this age group in the same states in 2020 [24]. Since 2015 all states have a 1-dose varicella vaccine requirement and in 2020 44 states and DC have requirements for 2 doses of varicella vaccine for school entry (36 have requirements for middle school); immunization school requirements are associated with increased vaccination coverage [24, 26–28]. Among 13–17 year-olds, varicella vaccination coverage with 2 doses reached 90.6% in 2019, up from 34.1% in 2008 [24, 29, 30]. Nevertheless, some children and adolescents remain unvaccinated providing opportunities for varicella clusters and small outbreaks.

Varicella outbreak surveillance has limitations. There were changes in the populations covered under surveillance, reporting sources, and surveillance methods (active/passive surveillance, and variables collected). Varicella outbreak surveillance has evolved from one sentinel area conducting active surveillance during the 1-dose program (1995–2006) [13, 18], to 9 states that conducted passive surveillance during the early years of the 1-dose program (2005–2012) [14], to nationwide passive surveillance during the mature 2-dose program (2016–2019). Only aggregate data were available during 2005–2015, which did not allow for case-level analyses. Passive surveillance relies on reporting of cases and outbreaks from public health partners and has underreporting and misclassification

limitations [31]. However, all states have mandates for reporting of either varicella cases (most states) or outbreaks, and jurisdictions promote reporting requirements. It is more likely that notification and reporting of individual cases would be missed rather than of outbreaks, as well as of small versus large outbreaks, which would make our estimate on the reduction in outbreak size and duration conservative. Outbreak and case surveillance practices vary by jurisdiction, so reporting might not be uniform. Laboratory confirmation of cases associated with outbreaks was limited, though it increased slightly over time; therefore, there is potential for case misclassification in either direction that could affect the number of outbreaks, size and duration. Diagnosing varicella can be challenging among vaccinated people, because disease is usually mild or atypical (may be maculopapular rash versus typical vesicular lesions) [21]. Varicella outbreak passive surveillance does not capture all case information that is collected for case-based surveillance (e.g., underlying medical conditions); additionally collected data may be incomplete, although completeness has improved over time. For example, during 2005–2009 age and vaccination status were missing for 46% and 49% of patients, respectively while during 2012–2015, number of lesions was missing for 22% of patients. By 2016–2019 7%–16% of patients had incomplete data on key variables including vaccination status, number of lesions, and hospitalization status.

Surveillance data demonstrate that the 2-dose varicella vaccination program led to declines in transmission with smaller, shorter outbreaks compared with those that occurred during the 1-dose program. Transmission from varicella cases now most commonly results in clusters with only 3–4 cases. More than half the outbreaks that do occur result in only 5–7 cases. This has implications for surveillance, which should place increasing emphasis on varicella clusters to understand evolving varicella epidemiology. Most outbreak cases occur among unvaccinated or partially vaccinated persons, creating opportunities for further prevention and control of varicella outbreaks and highlighting the importance of compliance with vaccination recommendations. Continued national varicella outbreak surveillance to monitor outbreaks and outbreak-associated case characteristics is critical for monitoring impact of the varicella vaccination program.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Varicella Outbreak and Case Characteristics during the U.S. Varicella Vaccination Program, 1995–2019

Table 1.

Characteristic	Active surveillance ^a			Passive surveillance ^b			Active surveillance (schools) ^c	Nationwide surveillance
	1995–1998	1999–2002	2003–2006	2005–2006	2007–2009	2010–2012		
Outbreak Characteristics								
Outbreaks (#)	236	52	47	381	441	146	29	316
Reporting Jurisdictions (#)^d	1	1	1	7	9	9	10 ^e	48
Duration, in days (median, range)	45 (7–198)	41 (1–149)	30 (3–72)	39 (1–206)	35 (1–180)	29 (2–118)	31 (4–100)	30 (0–257)
Size, No. cases (median, range)	15 (5–124)	11 (5–56)	9 (5–45)	12 (5–96)	9 (5–131)	8 (5–66)	7 (5–31)	7 (5–257)
<10 cases	65 (28)	24 (46)	30 (64)	142 (37)	223 (51)	87 (60)	22 (76)	233 (73)
Case Characteristics								
Total Cases (#)	5409	703	499	5790	5965	1677	262	3465
Age, years (median, range)	6 (0–59)	7 (0–49)	9 (0–43)	NA	NA	NA	NA	7 (0–79)
Age Group								
<1	150 (3)	20 (3)	5 (1)	5 (0.2)	25 (1)	16 (1)	9 (3)	208 (6)
1–4	1,596 (30)	115 (16)	25 (5)	91 (3)	123 (4)	115 (7)	28 (11)	810 (23)
5–9	2,987 (55)	442 (63)	254 (51)	2,181 (76)	2,258 (66)	746 (46)	143 (55)	1,118 (32)
10–14	402 (7)	107 (15)	194 (39)	583 (20)	955 (28)	624 (38)	67 (26)	491 (14)
15–19	73 (1)	3 (0.4)	10 (2)	16 (1)	34 (1)	58 (4)	11 (4)	135 (4)
20	201 (4)	16 (2)	11 (2)	7 (0.2)	17 (1)	70 (4)	4 (2)	518 (15)
Unknown								185 (5)
Lesions (#)								
<50	1,894 (35)	287 (41)	252 (51)	NA	NA	NA	100 (49) ^f	961 (32)
50	3,515 (65)	414 (59)	242 (49)	NA	NA	NA	104 (51)	1,372 (47)
50–499	3,305 (61)	374 (53)	201 (51)	NA	NA	NA	97 (48)	1,292(44)
500	210 (4)	42 (6)	8 (2)	NA	NA	NA	7 (3)	80 (3)
Unknown				NA	NA	NA		636 (21)
Vaccinated (%)^g	79 (2)	152 (22)	294 (59)	1,820 (78)	2,938 (80)	870 (66)	110 (45)	767 (25)

Characteristic	Active surveillance ^a			Passive surveillance ^b			Active surveillance (schools) ^c	Nationwide surveillance
	1995–1998	1999–2002	2003–2006	2005–2006	2007–2009	2010–2012	2012–2015	2016–2019
1 dose ^e	NA	NA	NA	1076 (59)	1822 (62)	584 (67)	42 (38)	397 (52)
2 doses ^{e,g}	NA	NA	NA	1 (0.1)	95 (3)	209 (24)	68 (62)	278 (36)
Unknown doses	NA	NA	NA	743 (41)	1021 (35)	77 (9)	0 (0)	92 (12)
Total with available information (%)	NA	NA	NA	2,330 (40)	3,694 (62)	1,313 (78)	204 (78)	3,116 (90)
% Complications	502 (9)	39 (6)	14 (3)	NA	NA	NA	0 (0)	19 (1)

Abbreviations: NA, not available; OB, outbreak.

^aBialek et al. [13]

^bLeung et al. [14]

^cLopez et al. [15]; surveillance conducted during 3 school-years (2012–2013, 2013–2014, 2014–2015)

^dReporting jurisdictions refer to one surveillance area (Antelope Valley, CA) in 1995–2006 and state and local health departments in 2005–2019 that reported varicella outbreak surveillance data to CDC.

^eSurveillance was in >300 schools in each jurisdiction; 6 jurisdictions participated in all 3 school-years.

^fPercentages for number of lesions during 2012–2015 were calculated among 262 cases with available information.

^gProportion vaccinated was calculated among persons with available information on vaccination status. Proportion with 1, 2, or unknown doses was calculated among vaccinated cases.