

ORIGINAL ARTICLE

Decline in Mortality Due to Varicella after Implementation of Varicella Vaccination in the United States

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ABSTRACT

BACKGROUND

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Varicella disease has been preventable in the United States since 1995. Starting in 1999, active and passive surveillance data showed sharp decreases in varicella disease. We reviewed national death records to assess the effect of the vaccination program on mortality associated with varicella.

METHODS

Data on deaths for which varicella was listed as an underlying or contributing cause were obtained from National Center for Health Statistics Multiple Cause-of-Death Mortality Data for 1990 through 2001. We calculated the numbers and rates of death due to varicella according to age, sex, race, ethnic background, and birthplace.

RESULTS

The rate of death due to varicella fluctuated from 1990 through 1998 and then declined sharply. For the interval from 1990 through 1994, the average number of varicella-related deaths was 145 per year (varicella was listed as the underlying cause in 105 deaths and as a contributing cause in 40); it then declined to 66 per year during 1999 through 2001. For deaths for which varicella was listed as the underlying cause, age-adjusted mortality rates dropped by 66 percent, from an average of 0.41 death per 1 million population during 1990 through 1994 to 0.14 during 1999 through 2001 ($P < 0.001$). This decline was observed in all age groups under 50 years, with the greatest reduction (92 percent) among children 1 to 4 years of age. In addition, by the period from 1999 through 2001, the average rates of mortality due to varicella among all racial and ethnic groups were below 0.15 per 1 million population, as compared with rates ranging from 0.37 per 1 million for whites to 0.66 per 1 million for other races in the period from 1990 through 1994.

CONCLUSIONS

The program of universal childhood vaccination against varicella in the United States has resulted in a sharp decline in the rate of death due to varicella.

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DISEASE DUE TO INFECTION WITH VARICELLA has been preventable by vaccine in the United States since 1995. During the 25 years before the varicella vaccine was licensed (1970 through 1994), rates of death for which varicella was the underlying cause fluctuated from 47 to 138 deaths per year, or 0.29 to 0.46 death per 1 million population. In the era before the vaccine was available, the age distribution of deaths shifted; from 1970 through 1974, most deaths (80 percent) occurred among persons younger than 20 years of age, but from 1990 through 1994, most deaths (54 percent) were among adults 20 years of age or older. Throughout the years from 1970 through 1994, however, the highest mortality rates were consistently among children younger than one year (range, 1.1 to 3.6 per 1 million population). In all age groups, most deaths (89 percent of deaths among children and 75 percent of deaths among adults from 1990 through 1994) occurred in persons without associated high-risk conditions.¹

After implementation of the universal childhood varicella vaccination program in 1995,^{2,3} the incidence of disease declined by 71 to 84 percent by 2000 in areas with active surveillance and by 67 to 82 percent by 2001 in areas with passive surveillance.^{4,5} To measure the effect of varicella vaccine on mortality rates, we reviewed national death records from 1990 through 2001. In contrast to previous studies of varicella-related mortality, which examined only the deaths for which varicella was listed as the underlying cause, our study assessed all varicella-related deaths, including those for which varicella was listed as a contributing cause.

METHODS

Data on deaths due to varicella in the United States were obtained from National Center for Health Statistics Multiple Cause-of-Death Mortality Data for 1990 through 2001. Causes of death were coded according to the 9th and 10th revisions of the *International Classification of Diseases* (ICD-9⁶ and ICD-10⁷) for the periods from 1990 through 1998 and 1999 through 2001, respectively. For this analysis, a death from varicella was defined as a death for which varicella (ICD-9 code 052 and ICD-10 codes B01.0 through B01.9) was classified as the underlying cause or a contributing cause of death as determined through the use of a computer algorithm that evaluated all condition codes and the order in

which they were listed.⁸ The underlying cause of death was classified as the disease or injury that initiated the chain of events that led directly to death. Other conditions listed were classified as contributing causes.

Analyses were stratified according to whether varicella was the underlying or a contributing cause, age group (<1, 1 to 4, 5 to 9, 10 to 19, 20 to 49, or ≥50 years), and period (1990 through 1994, 1995 through 1998, or 1999 through 2001). We calculated mortality rates according to age, sex, race, ethnic background, and birthplace with the use of population estimates from the National Center for Health Statistics and the U.S. Census Bureau.^{9–11} Age-adjusted mortality rates were standardized with the use of 2000 population estimates to account for changes in the age distribution of the population over time. Tests for trend and 95 percent confidence intervals for mortality rates were calculated on the basis of a Poisson distribution with the use of SAS statistical software, version 8.2. P values of less than 0.05 were considered to indicate statistical significance.

Trends were examined for preexisting conditions that increased the likelihood of severe varicella infection, varicella-associated complications, and seasonality (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). For the analysis of preexisting conditions, we classified persons according to conditions that may increase the risk of severe varicella infection. Persons at high risk were defined as those with conditions for which vaccination is contraindicated — specifically, cancer, human immunodeficiency virus (HIV) infection or the acquired immunodeficiency syndrome (AIDS), and immune deficiencies.^{2,3} We examined the proportion of persons with other conditions, who were considered at moderate risk because of either the underlying condition or its treatment (e.g., asthma, systemic lupus erythematosus, cystic fibrosis, rheumatoid arthritis and associated conditions, diabetes, and scleroderma). Since only 6 percent of persons had conditions that put them at moderate risk, and since including them with persons for whom no high-risk conditions were recorded did not affect the overall results, we classified them as not being at high risk.

Varicella-associated complications were defined as conditions known to occur as a result of varicella infection, such as pneumonia, complications affecting the central nervous system, hemorrhagic con-

ditions, and secondary infections. Seasonal trends were assessed through examination of the number and proportion of deaths due to varicella according to the month during which the deaths occurred.

RESULTS

Numbers and rates of deaths due to varicella fluctuated between 1990 and 1998, then steadily declined starting in 1999 (Fig. 1). From 1990 through 2001, 1465 death records listed varicella as the underlying cause or a contributing cause of death. Varicella-related deaths averaged 145 per year from 1990 through 1994 and declined to 66 per year from 1999 through 2001. The average age-adjusted rate of death due to varicella as both an underlying cause and a contributing cause dropped by 59 percent, from 0.56 per 1 million population in 1990 through 1994 to 0.23 in 1999 through 2001 ($P<0.001$). For deaths for which varicella was listed as the underlying cause, mortality rates dropped by 66 percent, from an average of 0.41 per 1 million population from 1990 through 1994 to 0.14 per 1 million from 1999 through 2001 ($P<0.001$), with the lowest observed rate occurring in 2001 (0.09).

MORTALITY RATES

Varicella as the Underlying Cause

Between 1990 and 2001, there were 1019 deaths for which varicella was listed as the underlying cause. The annual number of deaths decreased from 124 in 1994 to 26 in 2001. Children and adolescents younger than 20 years accounted for 380 (37 percent) of these deaths (Table 1). Infants consistently had the highest rates of death throughout the study period (range, 0.25 to 2.8 deaths per 1 million). Death rates declined in all age groups younger than 50 years (Fig. 2). In the period from 1999 through 2001, as compared with 1990 through 1994, the greatest reduction (92 percent) in average age-specific mortality rates occurred among children one to four years of age (from 0.84 to 0.07 death per 1 million, $P<0.001$), followed by reductions of 89 percent among children five to nine years of age (from 0.87 to 0.10 per 1 million, $P<0.001$) and 78 percent among infants less than 1 year of age (from 2.28 to 0.51 per 1 million, $P<0.001$). For those 10 to 19 years and 20 to 49 years of age, the reductions were 75 percent (from 0.28 to 0.07 per 1 million, $P<0.001$) and 74 percent (from 0.31 to 0.08 per 1 million, $P<0.001$), respectively. In contrast, death rates did not decline for persons 50 years of age or older. Average mortality rates for the period from 1990 through 1994 ranged from 0.19 per 1 million among persons born in the United States to 0.66 per 1 million among persons from ethnic groups other than non-Hispanic or Hispanic. By 1999 through 2001, reductions of 61 to 89 percent, according to race, ethnic background, and birthplace, resulted in average mortality rates ranging from 0.07 among U.S.-born persons and persons of racial groups other than black or white to 0.15 among whites and non-Hispanics (Table 2).

Varicella as a Contributing Cause

Between 1990 and 2001, there were 446 deaths for which varicella was listed as a contributing cause. The annual number of deaths declined from 51 in 1995 to 26 in both 1999 and 2001 ($P=0.02$). Although the age-specific trend was not statistically significant, average reductions in the rate of death in 1999 through 2001, as compared with that in 1990 through 1994, were statistically significant for younger age groups. Reductions among those younger than 50 years of age ranged from 38 percent to 78 percent, with the greatest reduction occurring among children 1 to 4 years of age (from

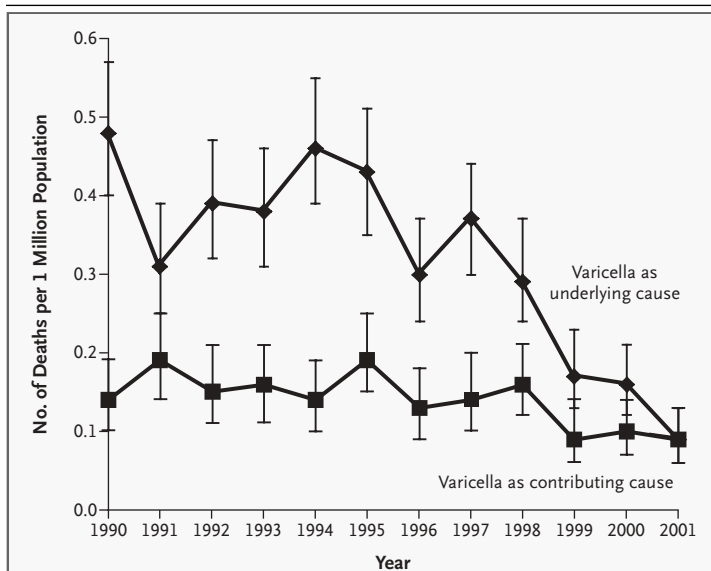


Figure 1. Varicella-Related Mortality Rates in the United States, 1990–2001.

The rates are for deaths with varicella reported as the underlying cause or a contributing cause, with adjustment for age according to population data for 2000. I bars indicate 95 percent confidence intervals.

0.32 to 0.07 death per 1 million, $P < 0.001$), followed by reductions of 67 percent among children 10 to 19 years of age ($P = 0.02$) and 66 percent among infants ($P = 0.01$). Average mortality rates according to sex, race, ethnic background, and birthplace were 27 to 81 percent lower in 1999 through 2001 than in 1990 through 1994 (Table 2).

DEATHS ASSOCIATED WITH PREEXISTING CONDITIONS

Varicella as the Underlying Cause

Among deaths for which varicella was listed as the underlying cause, high-risk conditions were listed on 97 (18 percent) of the 525 records in the period from 1990 through 1994 and 17 (14 percent)

Table 1. Annual Varicella-Related Deaths in the United States, According to Whether Varicella Was the Underlying Cause or a Contributing Cause, 1990–2001.

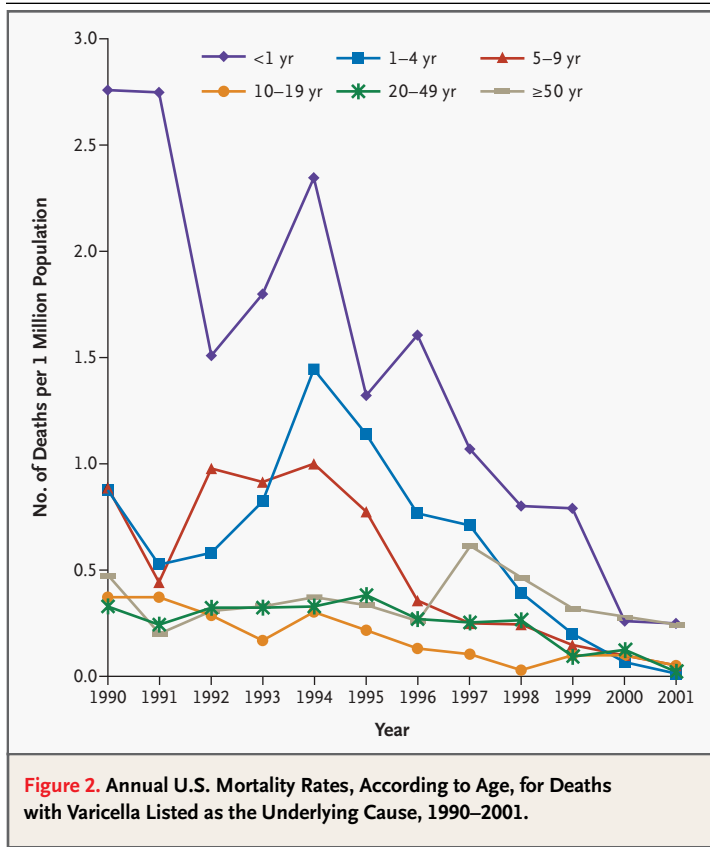
Variable	Varicella as Underlying Cause									Varicella as Contributing Cause*		
	1990–1994*†	1995	1996	1997	1998	1999	2000	2001	1990–1994	1995–1998	1999–2001	
No. of deaths	105	115	81	99	81	48	44	26	39.6	42.0	26.7	
	<i>number of deaths per year (percent)</i>											
Age												
<1 yr	8.8 (8.4)	5 (4.3)	6 (7.4)	4 (4.0)	3 (3.7)	3 (6.3)	1 (2.3)	1 (3.8)	3.0 (7.6)	3.0 (7.1)	0.7 (2.6)	
1–4 yr	13.2 (12.6)	18 (15.7)	12 (14.8)	11 (11.1)	6 (7.4)	3 (6.3)	1 (2.3)	0	5.2 (13.1)	4.8 (11.4)	0.7 (2.6)	
5–9 yr	15.6 (14.9)	15 (13.0)	7 (8.6)	5 (5.1)	5 (6.2)	3 (6.3)	2 (4.5)	1 (3.8)	3.2 (8.1)	2.5 (6.0)	2.3 (8.6)	
10–19 yr	10.4 (9.9)	8 (7.0)	5 (6.2)	4 (4.0)	1 (1.2)	4 (8.3)	4 (9.1)	2 (7.7)	2.2 (5.6)	2.0 (4.8)	1.0 (3.7)	
20–49 yr	35.6 (33.9)	46 (40.0)	33 (40.7)	31 (31.3)	32 (39.5)	11 (22.9)	15 (34.1)	3 (11.5)	11.6 (29.3)	14.0 (33.3)	7.0 (26.2)	
≥50 yr	21.4 (20.4)	23 (20.0)	18 (22.2)	44 (44.4)	34 (42.0)	24 (50.0)	21 (47.7)	19 (73.1)	14.4 (36.4)	15.8 (37.6)	15.0 (56.2)	
Sex												
Male	55.4 (52.8)	59 (51.3)	54 (66.7)	53 (53.5)	49 (60.5)	25 (52.1)	28 (63.6)	11 (42.3)	24.8 (62.6)	23.3 (55.5)	14.7 (55.1)	
Female	49.6 (47.2)	56 (48.7)	27 (33.3)	46 (46.5)	32 (39.5)	23 (47.9)	16 (36.4)	15 (57.7)	14.8 (37.4)	18.8 (44.8)	12.0 (44.9)	
Race												
White	78.6 (74.9)	88 (76.5)	56 (69.1)	79 (79.8)	65 (80.2)	43 (89.6)	36 (81.8)	23 (88.5)	28.8 (72.7)	32.5 (77.4)	22.3 (83.5)	
Black	19.2 (18.3)	24 (20.9)	23 (28.4)	17 (17.2)	11 (13.6)	5 (10.4)	8 (18.2)	1 (3.8)	8.8 (22.2)	8.5 (20.2)	4.0 (15.0)	
Other‡	7.2 (6.9)	3 (2.6)	2 (2.5)	3 (3.0)	5 (6.2)	0	0	2 (7.7)	2.0 (5.1)	1.0 (2.4)	0.3 (1.1)	
Ethnic group												
Non-Hispanic	87.6 (83.4)	96 (83.5)	68 (84.0)	87 (87.9)	70 (86.4)	47 (97.9)	39 (88.6)	21 (80.8)	34.2 (86.4)	35.5 (84.5)	25.0 (93.6)	
Hispanic	14.8 (14.1)	16 (13.9)	13 (6.0)	12 (12.1)	11 (13.6)	1 (2.1)	5 (11.4)	5 (19.2)	4.4 (11.1)	6.3 (15.0)	1.3 (4.9)	
Born in United States§	90.2 (85.9)	106 (92.2)	72 (88.9)	86 (86.9)	66 (81.5)	42 (87.5)	38 (86.4)	21 (80.8)	33.8 (85.4)	37.3 (88.8)	24.3 (91.0)	
<20 yr	45.8 (43.6)	45 (39.1)	28 (34.6)	24 (24.2)	15 (18.5)	13 (27.1)	7 (15.9)	3 (11.5)	12.6 (31.8)	11.8 (28.1)	4.3 (16.1)	
20–49 yr	29.8 (28.4)	42 (36.5)	29 (35.8)	26 (26.3)	23 (28.4)	9 (18.8)	12 (27.3)	1 (3.8)	9.4 (23.7)	12.3 (29.3)	6.3 (23.6)	
≥50 yr	14.6 (13.9)	19 (16.5)	15 (18.5)	36 (36.4)	28 (34.6)	20 (41.7)	19 (43.2)	17 (65.4)	11.8 (29.8)	13.3 (31.7)	13.7 (51.3)	
Born outside United States§	14.6 (13.9)	9 (7.8)	9 (11.1)	13 (13.1)	14 (17.3)	6 (12.5)	6 (13.6)	4 (15.4)	5.0 (12.6)	4.5 (10.7)	2.3 (8.6)	
<20 yr	2.2 (2.1)	1 (0.9)	2 (2.5)	0	0	0	1 (2.3)	1 (3.8)	0.8 (2.0)	0.5 (0.1)	0.3 (1.1)	
20–49 yr	5.6 (5.3)	4 (3.5)	4 (4.9)	5 (5.1)	9 (11.1)	2 (4.2)	3 (6.8)	1 (3.8)	1.8 (4.5)	1.8 (4.3)	0.7 (2.6)	
≥50 yr	6.8 (6.5)	4 (3.5)	3 (3.7)	8 (8.1)	5 (6.2)	4 (8.3)	2 (4.5)	2 (7.7)	2.4 (6.1)	2.3 (5.5)	1.3 (4.9)	

* Numbers are averages; some reflect rounding.

† Data are from Meyer et al.¹

‡ This group includes Asians, American Indian or Alaska Natives, and Native Hawaiians or other Pacific Islanders, according to the 1997 race and ethnic-group standards of the U.S. Office of Management and Budget.

§ Data were not included for persons for whom birthplace or ethnic group was unknown.



of the 118 records in 1999 through 2001. Between 1990 and 2001, cancer accounted for the greatest proportion of high-risk conditions among those younger than 20 years (71 percent) and those 50 years of age or older (90 percent); HIV infection or AIDS was the most common condition (in 58 percent) among persons 20 to 49 years of age who were considered at high risk. Among persons younger than 20 years, the number of deaths listed as involving a high-risk condition averaged 5.4 per year in the period from 1990 through 1994 and 0.7 per year in 1999 through 2001; the majority of deaths occurred in persons without high-risk conditions (89 percent in 1990 through 1994 and 92 percent in 1999 through 2001). The average number of deaths was lower in 1999 through 2001 than in 1990 through 1994 both for persons at high risk and for those not at high risk in all age groups except those 20 to 49 years of age. In contrast, the average number of deaths that involved complications increased over time among adults 50 years of age or older, with the exception of deaths involving hemorrhagic complications, for which no records were listed from 1995 through 2001, and deaths involving sec-

who were not at high risk, the decline ranged from 68 percent among those 20 to 49 years of age to 89 percent among those 1 to 4 years of age.

Varicella as a Contributing Cause

Among deaths for which varicella was reported as a contributing cause, the most frequent preexisting conditions reported as the underlying cause of death in the periods 1990 through 1994 and 1995 through 1998 were HIV infection and AIDS (18 percent and 23 percent, respectively) and cancer (18 percent and 21 percent). In 1999 through 2001, cancer was the most frequent underlying cause of death (in 43 percent), followed by HIV infection and AIDS (11 percent). Overall, among persons at high risk, cancer was the most common condition for those younger than 20 years (in 50 percent) and those 50 years or older (in 92 percent), and HIV infection or AIDS accounted for 75 percent of such conditions among those 20 to 49 years of age. The average number of deaths was lower in 1999 through 2001 than in 1990 through 1994 both for persons at high risk and for those not at high risk in all age groups except infants at high risk and adults 50 years of age or older at high risk. The greatest decline occurred among children one to four years of age who were at high risk (100 percent), infants who were not at high risk (89 percent), and children one to four years of age who were not at high risk (86 percent).

COMPLICATIONS

Varicella as the Underlying Cause

Among deaths for which varicella was listed as the underlying cause, 200 (38 percent) of the 525 deaths in 1990 through 1994 and 93 (79 percent) of the 118 deaths in 1999 through 2001 had at least one varicella-associated complication. Between 1990 and 2001, the most common complication was a secondary infection among persons younger than 20 years of age (occurring in 21 percent) and pneumonia among those 20 to 49 years of age (22 percent) and those 50 years of age or older (23 percent). Among persons younger than 20 and those 20 to 49 years of age, the average number of complications declined over time, with the exception of pneumonia, the rate of which fluctuated among persons 20 to 49 years of age. In contrast, the average number of deaths that involved complications increased over time among adults 50 years of age or older, with the exception of deaths involving hemorrhagic complications, for which no records were listed from 1995 through 2001, and deaths involving sec-

Table 2. Average Varicella-Related Mortality Rates in the United States, According to Whether Varicella Was the Underlying Cause or a Contributing Cause, 1990–2001.

Variable	Varicella as Underlying Cause			Varicella as Contributing Cause		
	1990–1994*	1995–1998	1999–2001	1990–1994	1995–1998	1999–2001
	<i>number of deaths per 1 million (95% confidence interval)</i>					
Age						
<1 yr	2.28 (1.19–4.39)	1.33 (0.55–3.19)	0.51 (0.13–2.05)	0.76 (0.25–2.36)	0.80 (0.26–2.47)	0.26 (0.04–1.82)
1–4 yr	0.84 (0.49–1.45)	0.77 (0.44–1.36)	0.07 (0.01–0.46)	0.32 (0.13–0.78)	0.32 (0.13–0.77)	0.07 (0.01–0.46)
5–9 yr	0.87 (0.53–1.41)	0.40 (0.20–0.80)	0.10 (0.02–0.39)	0.16 (0.05–0.50)	0.15 (0.05–0.46)	0.10 (0.02–0.39)
10–19 yr	0.28 (0.15–0.52)	0.13 (0.05–0.31)	0.07 (0.02–0.23)	0.06 (0.01–0.22)	0.05 (0.01–0.21)	0.02 (0.00–0.17)
20–49 yr	0.31 (0.22–0.43)	0.30 (0.21–0.41)	0.08 (0.04–0.15)	0.10 (0.06–0.18)	0.11 (0.07–0.19)	0.06 (0.03–0.12)
≥50 yr	0.32 (0.21–0.49)	0.42 (0.29–0.60)	0.27 (0.18–0.42)	0.21 (0.13–0.36)	0.22 (0.14–0.37)	0.19 (0.12–0.32)
Sex						
Male	0.44 (0.34–0.57)	0.41 (0.31–0.53)	0.15 (0.10–0.23)	0.20 (0.13–0.30)	0.17 (0.12–0.26)	0.11 (0.07–0.18)
Female	0.38 (0.29–0.50)	0.29 (0.21–0.39)	0.13 (0.08–0.20)	0.11 (0.07–0.19)	0.14 (0.09–0.22)	0.08 (0.05–0.15)
Race						
White	0.37 (0.30–0.46)	0.32 (0.26–0.41)	0.15 (0.11–0.21)	0.14 (0.09–0.20)	0.15 (0.10–0.21)	0.10 (0.06–0.14)
Black	0.59 (0.38–0.93)	0.55 (0.35–0.86)	0.14 (0.06–0.33)	0.28 (0.15–0.54)	0.26 (0.13–0.50)	0.11 (0.04–0.29)
Other†	0.66 (0.32–1.39)	0.23 (0.08–0.73)	0.07 (0.01–0.48)	0.19 (0.05–0.76)	0.08 (0.01–0.55)	Not available‡
Ethnic group						
Non-Hispanic	0.38 (0.31–0.47)	0.33 (0.27–0.41)	0.15 (0.11–0.20)	0.15 (0.10–0.21)	0.15 (0.11–0.21)	0.10 (0.07–0.15)
Hispanic	0.61 (0.37–1.01)	0.43 (0.25–0.74)	0.11 (0.04–0.30)	0.16 (0.06–0.43)	0.20 (0.09–0.44)	0.03 (0.00–0.20)
Birthplace						
United States	0.19 (0.16–0.24)	0.17 (0.14–0.21)	0.07 (0.05–0.10)	0.07 (0.05–0.10)	0.08 (0.06–0.11)	0.05 (0.03–0.07)
Other country	0.35 (0.21–0.59)	0.23 (0.13–0.41)	0.10 (0.04–0.23)	0.12 (0.05–0.28)	0.10 (0.04–0.25)	0.04 (0.01–0.15)

* Data are from Meyer et al.¹

† This group includes Asians, American Indian or Alaska Natives, and Native Hawaiians or other Pacific Islanders, according to the 1997 race and ethnic-group standards of the U.S. Office of Management and Budget.

‡ The average number of deaths per year was too small to allow for the estimation of a rate.

ondary infections among persons at high risk, which fluctuated between zero and three deaths per year (Table 3).

Varicella as a Contributing Cause

Among deaths for which varicella was listed as a contributing cause, 70 (35 percent) of the 198 deaths in the period from 1990 through 1994 and 29 (36 percent) of the 80 deaths in 1999 through 2001 occurred among persons with at least one varicella-associated complication. From 1990 through 2001, the most common complications were secondary infections (25 percent among persons younger than 20 years of age, 15 percent among those 20 to 49, and 15 percent among those 50 or older). There was no consistent pattern according to age group in the average number of complica-

tions among persons at high risk and those not at high risk over time in this category.

SEASONAL TRENDS

Varicella as the Underlying Cause

Consistent with the seasonality of varicella disease, we observed a strong seasonal pattern among deaths occurring between 1990 and 2001 for which varicella was listed as the underlying cause, particularly among persons younger than 50 years of age. In this age group, the highest number of deaths — 305 (42 percent) of 729 — occurred in late spring (March through May), and the lowest number — 51 (7 percent) — occurred in late summer and early autumn (August through October). For deaths among persons 50 years of age or older, the seasonal pattern was less pronounced, with 95 deaths (33 per-

Table 3. Varicella-Related Complications among Persons Who Died from Varicella Infection as the Underlying Cause in the United States, 1990–2001.*

Complication	Age, <20 yr		Age, 20–49 yr		Age, ≥50 yr	
	High Risk	Normal Risk	High Risk	Normal Risk	High Risk	Normal Risk
	<i>average number of complications (percent)</i>					
All						
1990–1994	2.0 (37)	18.2 (43)	2.6 (31)	11.6 (43)	1.2 (21)	4.4 (28)
1995–1998	0.5 (22)	14.3 (54)	2.5 (28)	10.3 (39)	3.0 (31)	6.8 (34)
1999–2001	0.3 (50)	5.7 (74)	1.0 (100)	7.7 (89)	3.7 (92)	12.7 (73)
Central nervous system disorder						
1990–1994	0.6 (11)	3.6 (8)	0.8 (10)	1.4 (5)	0	0
1995–1998	0	2.0 (8)	0.3 (3)	1.0 (4)	0.3 (3)	0.5 (3)
1999–2001	0.3 (50)	0.7 (9)	0.3 (33)	0.3 (4)	1.3 (33)	2.3 (13)
Pneumonia						
1990–1994	0.6 (11)	7.2 (17)	0.4 (5)	6.2 (23)	0.8 (14)	2.4 (15)
1995–1998	0.3 (11)	4.5 (17)	1.0 (11)	4.8 (18)	1.8 (18)	4.0 (20)
1999–2001	0	1.7 (22)	0.3 (33)	6.7 (77)	2.7 (67)	7.0 (40)
Secondary infection						
1990–1994	1.0 (19)	6.8 (16)	1.0 (12)	2.6 (10)	0.2 (4)	1.8 (11)
1995–1998	0	8.5 (32)	1.8 (20)	3.0 (11)	1.8 (18)	2.8 (14)
1999–2001	0	2.7 (35)	0.3 (53)	0.7 (8)	0.7 (17)	4.0 (23)
Hemorrhage						
1990–1994	0.2 (4)	3.6 (8)	0.6 (7)	2.8 (10)	0.2 (4)	0.8 (5)
1995–1998	0.3 (11)	1.0 (4)	0	2.3 (9)	0	0
1999–2001	0	0.3 (4)	0	0	0	0

* Data for the period from 1990 through 1994 are from Meyer et al.¹

cent) of 290 occurring from March through May and 51 (18 percent) from August through October. The magnitude of the seasonal pattern lessened over time (Fig. 3).

Varicella as a Contributing Cause

Seasonality among deaths for which varicella was listed as a contributing cause was less pronounced than among deaths for which varicella was listed as the underlying cause in persons younger than 50 years of age, and there was no seasonal pattern in those 50 years of age or older. Among persons younger than 50, 101 of 266 deaths due to varicella (38 percent) occurred from March through May, as compared with 38 (14 percent) from August through October. The seasonal pattern did not change with time.

DISCUSSION

An average of 145 varicella-related deaths per year occurred in the United States from 1990 through 1994, a higher number than was previously recognized, owing to the fact that reports had been based solely on deaths for which varicella was listed as the underlying cause. Since the implementation of the varicella vaccination program, varicella-related deaths have declined dramatically to the lowest level ever reported; rates of mortality due to varicella in the United States are now considerably lower than the reported rates in countries that do not have a universal vaccination program.^{12–17} Varicella-related deaths have declined among children and among adults 20 to 49 years of age, and mortality rates are similar for all racial and ethnic

groups and for persons born inside the United States and those born in other countries. However, most deaths related to varicella continue to occur among persons who do not have high-risk conditions and who are eligible for vaccination.

The decline in mortality parallels the increased use of varicella vaccine and the decline in cases of varicella in the United States. Varicella vaccine coverage among children 19 to 35 months of age increased from 26 percent in 1997 to 76 percent in 2001, with no disparities among racial or ethnic groups.^{18,19} The greatest decline in mortality occurred among children in this age group (1 to 4 years), who are the ones targeted by the vaccination program; however, mortality (annual numbers and rates of death) also declined among infants, older children and adolescents, and adults 20 to 49 years of age, probably as the result of a combination of vaccination and herd-immunity effects.⁴ Surveillance data from selected sites have shown similar reductions in the incidence of disease and in hospitalizations since the vaccine was licensed, and the rates of national varicella-related hospitalizations have declined significantly.^{4,5,20} As anticipated, the large decline in deaths among children led to a higher proportion of varicella-related deaths among adults. This statistic should not be confused with the numbers and rates of deaths, which also declined dramatically among adults.

Underlying conditions known to increase the severity of varicella infection accounted for few of the varicella-related deaths. We expected to see a larger decline in deaths among persons not at high risk than among those at high risk, because the majority of immunocompromised persons are not eligible for vaccination; however, the opposite was found to be true in this analysis. This finding should be interpreted with certain factors in mind. First, a lack of information on immunosuppressive therapy may have led us to underestimate the prevalence of preexisting conditions. Second, persons with high-risk conditions may have received early, aggressive antiviral treatment when they contracted varicella. In contrast, a failure to recognize the potential for severe disease among persons not at high risk may have led to delays in instituting therapy. Third, a higher rate of use of varicella vaccine among close contacts of persons ineligible for vaccination might have occurred, and this may have prevented most cases of varicella and related deaths in this group through herd-immunity effects. The reduction of varicella among infants, who are not

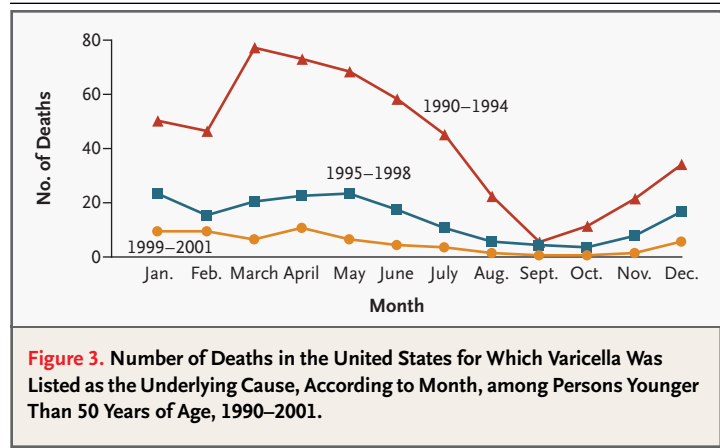


Figure 3. Number of Deaths in the United States for Which Varicella Was Listed as the Underlying Cause, According to Month, among Persons Younger Than 50 Years of Age, 1990–2001.

eligible for vaccination, is solely due to herd-immunity effects. Finally, children with acute lymphoblastic leukemia were eligible for vaccination (through a research protocol).² Moreover, in recent years, a higher proportion of children have been likely to be vaccinated before acquiring acute lymphoblastic leukemia. Nonetheless, to prevent deaths from varicella among persons with high-risk conditions, ensuring immunity through the vaccination of close contacts is recommended.^{2,3}

Varicella-related mortality rates did not decline among persons 50 years of age or older. This may be the result of deaths due to herpes zoster having been misclassified as deaths due to varicella, especially since data show that more than 99 percent of Americans in this age group have serologic evidence of infection with varicella-zoster virus and that second varicella infections are uncommon.²¹ A validation study of death certificates in the United States that listed varicella as the cause showed that less than 43 percent of the deaths among persons 50 years of age or older that were attributed to varicella were likely to have been caused by varicella, as compared with approximately 80 percent among persons younger than 50 years.²² Also, in our study, varicella infection among persons 50 years of age or older had a less pronounced seasonal pattern than did infection among younger groups.

In addition to inaccurate classifications of deaths due to varicella, there are other limitations to this study. As previously described, the use of death records, including the inadvertent omission of medical conditions, may lead to the underestimation of preexisting conditions and complications.¹ Furthermore, the available data do not permit the analysis of other factors (e.g., types of therapy) that may have

contributed to declines in varicella-related mortality. Finally, changes in the ICD codes in 1999 may have affected the estimated mortality rates. However, we do not believe that changes in coding can account for the dramatic decline in varicella-related mortality that had begun well before 1999.

Varicella-related deaths are now preventable by vaccine. The United States was the first country to implement a universal vaccination program for childhood varicella, and our analysis clearly documents the dramatic national decline in vari-

cella-related mortality for all ages, races, and ethnic groups after the increased use of vaccine. The data to date support the success of the current U.S. varicella vaccination program and should be useful for countries considering a universal varicella vaccination program to reduce varicella-related morbidity and mortality.

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