

Near Elimination of Varicella Deaths in the US After Implementation of the Vaccination Program



WHAT'S KNOWN ON THIS SUBJECT: The impact of the 1-dose varicella vaccination program on varicella deaths has been documented for the early stages of program implementation. During the first 6 years of the program, deaths for which varicella was listed as the underlying cause declined 66% overall and $\geq 74\%$ for people younger than 50 years.



WHAT THIS STUDY ADDS: Our study documents the impressive impact on varicella mortality of the 1-dose US vaccination program: a decline of 88% overall and 96% among subjects younger than 50 years. With the current 2-dose program, there is potential that these most severe outcomes could be eliminated.

abstract

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OBJECTIVE: Varicella has been preventable by vaccination in the United States since 1995. Previous studies reported a 66% decline in mortality rate during the first 6 years of the program. Since then, vaccination coverage has increased substantially. We updated the analysis of US varicella mortality for 2002–2007 and assessed the impact of the first 12 years of the US varicella vaccination program on varicella deaths.

METHODS: National data on deaths for which varicella was listed as an underlying or contributing cause were obtained from the Mortality Multiple Cause-of-Death records from the US National Center for Health Statistics. We calculated the age-adjusted and age-specific mortality rates for 2002–2007 and trends since the prevaccine years.

RESULTS: During the 12 years of the mostly 1-dose US varicella vaccination program, the annual average mortality rate for varicella listed as the underlying cause declined 88%, from 0.41 per million population in 1990–1994 to 0.05 per million population in 2005–2007. The decline occurred in all age groups, and there was an extremely high reduction among children and adolescents younger than 20 years (97%) and among subjects younger than 50 years overall (96%). In the last 6 years analyzed (2002–2007), a total of 3 deaths per age range were reported among children aged 1 to 4 and 5 to 9 years, compared with an annual average of 13 and 16 deaths, respectively, during the prevaccine years.

CONCLUSIONS: The impressive decline in varicella deaths can be directly attributed to successful implementation of the 1-dose vaccination program. With the current 2-dose program, there is potential that these most severe outcomes of a vaccine-preventable disease could be eliminated. *Pediatrics* 2011;128:214–220

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KEY WORDS

varicella mortality, varicella deaths, varicella vaccine, NCHS, vaccine-preventable disease

ABBREVIATIONS

ICD—*International Classification of Diseases*

CDC—Centers for Disease Control and Prevention

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The United States had more than a decade of experience with a routine 1-dose childhood varicella vaccination program (since 1995) before a routine second dose was recommended in 2006.¹ The 1-dose program targeted children aged 12 to 18 months and also included catch-up vaccination of susceptible older children and adolescents. During 1997–2007, the national coverage for 1 dose of varicella vaccine among children aged 19 to 35 months increased from 27% to 90%.² The impact of the 1-dose program has been documented for different periods.^{3–6} Varicella incidence declined by ~90% during the first 10 years of the program in 2 varicella-active surveillance sites, where vaccine coverage reached 92% and 94% in 2005.³ Using different baseline and postprogram implementation intervals, varicella-related hospitalizations declined more than 65% to 88% during the 1-dose program.^{4,6} The rate of deaths for which varicella was listed as the underlying cause declined by 66% between 1990–1994 (average annual deaths: 105) and 1999–2001 (average annual deaths: 39).⁵ The reduction in mortality rate was 74% or higher for all age groups younger than 50 years; the greatest declines were among children aged 1 to 4 years (92%) and 5 to 9 years (89%).

Monitoring severe outcomes of disease, such as hospitalizations and deaths, is an important component of evaluating the impact of the varicella vaccination program. It is important to understand deaths in detail as they become rare; individual deaths may serve as sentinel events for the failure of the vaccine program and/or needed policy change. We updated the analysis of varicella mortality in the United States from 2002 through 2007 and summarize the impact of the first 12 years of the US varicella vaccination program on varicella deaths.

METHODS

We obtained data on varicella deaths for 1990–2007 from the national vital statistics system using the Mortality Multiple Cause-of-Death public-use records from the US National Center for Health Statistics. Causes of death were coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) for 1990–1998 and the ICD-10 for 1999–2007. A death from varicella was defined as a death for which a varicella diagnosis (ICD-9 code 052 and ICD-10 code B01) was listed on the death certificate.

To allow for direct comparison with previous (through 2001) US varicella mortality studies,^{5,7} we stratified the analyses according to underlying and contributing cause and according to age group. The classification as underlying or contributing cause of death is provided by the National Center for Health Statistics and performed according to a computer algorithm on the basis of the conditions listed on the death certificate. An underlying cause of death is considered to be the disease or injury that initiated the chain of events that led directly to death, whereas other significant conditions that unfavorably influenced the course of the events but were not related to the immediate cause of death are listed as contributing causes.⁸ We first updated the analysis of deaths for the new data (2002–2007). We calculated mortality rates according to age using US Census populations with bridged race categories released by National Center for Health Statistics.⁹ Because the number of deaths for 2002–2007 was low, age-specific mortality rates are reported for age-groups younger than 20 years, 20 to 49 years, younger than 50 years, and 50 years or older. We reanalyzed varicella deaths reported during 1990–2001 according to these age groups. Age-adjusted mortality rates were standardized to the

2000 census population to account for changes in the age distribution of the population over time. In the rate analysis of the new data, we grouped the years into 2 periods, 2002–2004 and 2005–2007. We considered 1990–1994 as representative of the prevaccine years. Test for trends and 95% confidence intervals for rates were calculated under the assumption that deaths followed a Poisson distribution and using the SAS 8.2 (SAS Institute, Inc, Cary, NC). *P* values of <.05 were considered statistically significant.

People at high risk for severe varicella were considered to be those who had listed the following conditions: cancer; HIV infection or AIDS; immune deficiencies; and pregnancy (conditions that also represent contraindications to vaccination¹). A diagnosis of pregnancy was listed on 3 records (1 for underlying and 2 for contributing causes), 1 each in 1990, 1991, and 1997. To define varicella-associated complications, we considered the conditions most commonly complicating varicella: secondary bacterial infections; pneumonia; complications affecting central nervous system; and hemorrhagic conditions.^{10,11}

We also searched for the presence of concurrent herpes zoster diagnoses (ICD-9 code 053 and ICD-10 code B02). For all age groups and all years (1990–2007) these records represented 4.6% (52 of 1131) of deaths for which varicella was listed as the underlying cause and 12.6% (71 of 562) of those in which varicella was a contributing cause. More than two-thirds of the records were for subjects aged 50 years or older. We conducted the analysis for mortality rates and trends by age groups and year groups, with and without the records with herpes zoster diagnoses and the trends were identical for both scenarios. We present the findings with records with concurrent herpes zoster diagnoses included for

TABLE 1 Annual Varicella-Related Deaths in the United States, According to Underlying and Contributing Cause, 1990–2007

| | Varicella as the Underlying Cause | | | | | | | | Varicella as the Contributing Cause | | |
|----------------------------|-----------------------------------|--------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-------------------------------------|--------------------------|------------------------|
| | 1990–1994 ^{a,b} | 1999–2001 ^{b,c} | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 1990–1994 ^{a,b} | 1999–2001 ^{b,c} | 2002–2007 ^b |
| No. of deaths per year | 105 | 39.3 | 32 | 16 | 19 | 13 | 18 | 14 | 39.6 | 26.7 | 19.3 |
| No. (%) of deaths per year | | | | | | | | | | | |
| Age | | | | | | | | | | | |
| <1 y | 8.8 (8.4) | 1.7 (4.3) | 1 (3.1) | 1 (6.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (7.6) | 0.7 (2.6) | 0.2 (0.9) |
| 1–4 y | 13.2 (12.6) | 1.3 (3.3) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (7.7) | 0 (0.0) | 1 (7.1) | 5.2 (13.1) | 0.7 (2.6) | 0.5 (2.6) |
| 5–9 y | 15.6 (14.9) | 2 (5.1) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) | 1 (5.6) | 0 (0.0) | 3.2 (8.1) | 2.3 (8.6) | 0.3 (1.7) |
| 10–19 y | 10.4 (9.9) | 3.3 (8.4) | 1 (3.1) | 0 (0.0) | 1 (5.3) | 0 (0.0) | 2 (11.1) | 0 (0.0) | 2.2 (5.6) | 1 (3.7) | 0.3 (1.7) |
| 20–49 y | 35.6 (33.9) | 9.7 (24.7) | 12 (37.5) | 5 (31.3) | 4 (21.1) | 4 (30.8) | 4 (22.2) | 2 (14.3) | 11.6 (29.3) | 7 (26.3) | 2.3 (12.1) |
| ≥50 y | 21.4 (20.4) | 21.3 (54.2) | 18 (56.3) | 10 (62.5) | 11 (57.9) | 8 (61.5) | 11 (61.1) | 11 (78.6) | 14.4 (36.4) | 15 (56.2) | 15.7 (81.0) |
| Gender | | | | | | | | | | | |
| Male | 55.4 (52.8) | 21.3 (54.2) | 20 (62.5) | 10 (62.5) | 11 (57.9) | 7 (53.8) | 13 (72.2) | 6 (42.9) | 24.8 (62.6) | 14.7 (55.1) | 10.3 (53.4) |
| Female | 49.6 (47.2) | 18 (45.8) | 12 (37.5) | 6 (37.5) | 8 (42.1) | 6 (46.2) | 5 (27.8) | 8 (57.1) | 14.8 (37.4) | 12 (44.9) | 9 (46.6) |
| Race | | | | | | | | | | | |
| White | 78.6 (74.9) | 34 (86.4) | 24 (75.0) | 14 (87.5) | 17 (89.5) | 11 (84.6) | 17 (94.4) | 13 (92.7) | 28.8 (72.7) | 22.3 (83.5) | 16.3 (84.5) |
| Black | 19.2 (18.3) | 4.7 (11.9) | 5 (15.6) | 2 (12.5) | 1 (5.3) | 1 (7.7) | 1 (5.6) | 1 (7.1) | 8.8 (22.2) | 4 (15.0) | 2.2 (11.2) |
| Other | 7.2 (6.9) | 0.7 (1.7) | 3 (9.4) | 0 (0.0) | 1 (5.3) | 1 (7.7) | 0 (0.0) | 0 (0.0) | 2 (5.1) | 0.3 (1.1) | 0.8 (4.3) |
| Ethnic group | | | | | | | | | | | |
| Non-Hispanic | 87.6 (83.4) | 35.7 (90.7) | 29 (90.6) | 13 (81.3) | 14 (73.7) | 11 (84.6) | 15 (83.3) | 11 (78.6) | 34.2 (86.4) | 25 (93.6) | 18.2 (94.0) |
| Hispanic | 14.8 (14.1) | 3.7 (9.3) | 3 (9.4) | 3 (18.7) | 5 (26.3) | 2 (15.4) | 3 (16.7) | 3 (21.4) | 4.4 (11.1) | 1.3 (4.9) | 1.2 (6.0) |

^a Data are from Meyer et al.⁷

^b Numbers are averages.

^c Data are from Nguyen et al.⁵

the following reasons: the misclassification can be in either direction and we did not want to miss true varicella-related deaths; the number of records with concurrent herpes zoster diagnoses per year was low; in our analysis the trends were not affected by their inclusion or exclusion; and the previous analyses did not exclude them.

RESULTS

Mortality Rates

Varicella as the Underlying Cause of Death

During 2002–2007, varicella was listed as the underlying cause of death in 112 records (Table 1). During this period, the annual average number of deaths was the lowest ever reported, with 22 deaths during 2002–2004 and 15 during 2005–2007. The average age-adjusted mortality rate attributed to varicella as an underlying cause of death declined by 88%, from 0.41 per million population (95% confidence interval: 0.38–0.45) in 1990–1994 to 0.05 per million population (95% confidence interval: 0.04–0.06) in 2005–

2007 ($P < .001$) (Fig 1). During 2002–2007, there continued to be no racial differences in mortality rates, as achieved for the first time during 1999–2001.

Varicella deaths declined in all age-groups (Fig 2 and Table 1). During 2005–2007, compared with 1990–1994, the age-specific mortality rates declined by 97% (from 0.65 to 0.02 per million population; $P < .0001$)

among children and adolescents younger than 20 years, by 90% (from 0.30 to 0.03 per million population; $P < .0001$) among adults aged 20 to 49 years, and by 67% (from 0.33 to 0.11 per million population; $P < .0001$) among adults aged 50 years or older. As a consequence of the different decline in rates according to age group, the proportion of deaths among adults aged 50 years or older increased rela-

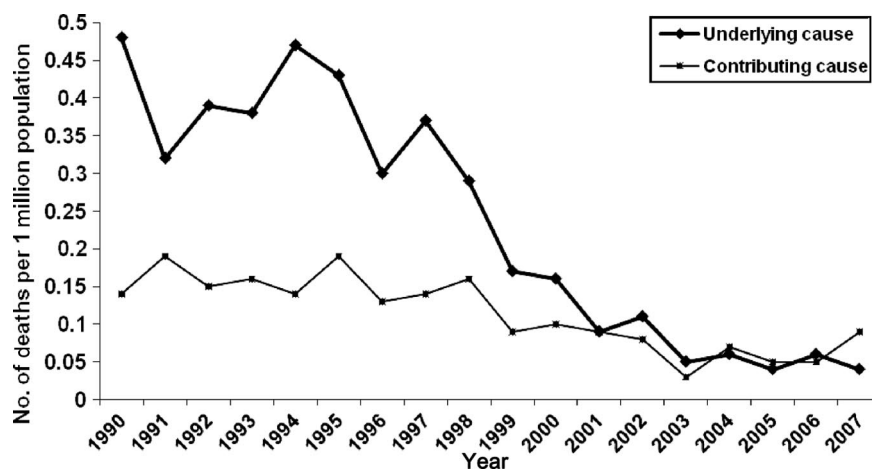


FIGURE 1 Varicella-related mortality rates in the United States, 1990–2007 (age adjusted to the 2000 US population).

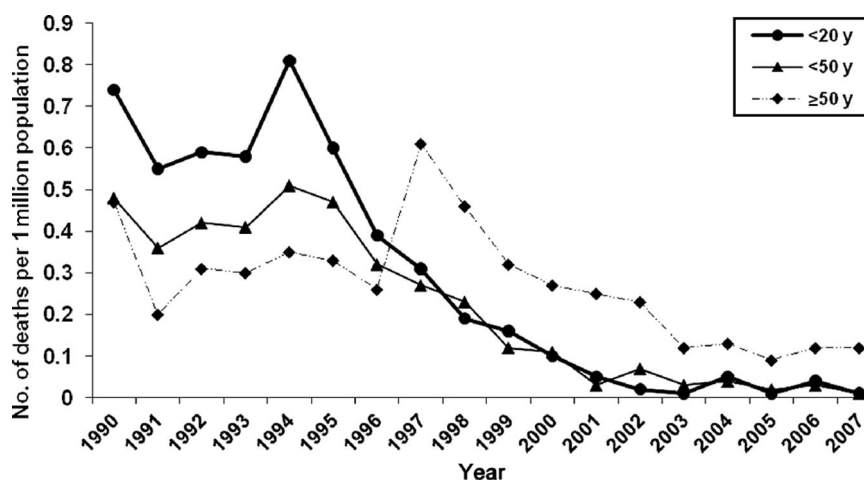


FIGURE 2 Annual age-specific mortality rates for varicella listed as the underlying cause, United States, 1990–2007.

tive to that of children during 2002–2007 compared with the prevaccine years. In 2002–2007, children and adolescents younger than 20 years accounted for 11% of the total deaths with varicella listed as the underlying cause compared with 46% in the prevaccine years, whereas adults aged 50 years or older accounted for 62% of deaths compared with 20% in the prevaccine years.

Varicella as the Contributing Cause

During 2002–2007, 116 death records had varicella listed as the contributing cause of death for an average of 19.3 deaths annually (Table 1). Adults younger than 50 years accounted for 19% of deaths compared with 64% of deaths during the prevaccine years. The average age-adjusted mortality rate attributed to varicella as a contributing cause declined by 63% from 1990–1994 to 2005–2007 ($P < .001$) (Fig 1). The decline was greatest among children and adolescents younger than 20 years (94%), followed by adults aged 20 to 49 years (80%), and was considerably lower among those aged 50 years or older (18%) (rates available from the authors).

Deaths Associated With Preexisting Medical Conditions

Among deaths for which varicella was the underlying cause, high-risk preexisting medical conditions were listed on 12 (11%) of 112 records in 2002–2007, compared with 14% in 1999–2001 and 19% in 1990–1994. All 12 high-risk conditions were neoplastic ($n = 9$ leukemia or lymphoma; $n = 3$ solid organ tumors). All deaths among children and adolescents younger than 20 years ($n = 12$) occurred in those without high-risk conditions (as defined in the “Methods”), although in 3 instances there were listed conditions that could put a person at high risk (chronic myeloproliferative disease; myelodysplastic syndrome, unspecified; and immunodeficiency, unspecified), but insufficient information was available to ascertain the degree of immunocompromise. Among adults aged 20 to 49 years, 2 (6%) deaths occurred in those with high-risk conditions, whereas for those aged 50 years or older, 10 (15%) deaths occurred among those with high-risk conditions. Among deaths for which varicella was the contributing cause, high-risk preexisting medical conditions were

listed on 56 (48%) of 116 records in 2002–2007. These conditions were cancer ($n = 52$) and HIV infection and AIDS ($n = 4$). The most frequent conditions reported as underlying cause of death were cancer (41%) and secondary bacterial infection (14%) among subjects younger than 50 years and cancer (43%) and cardiovascular diagnoses (21%) among adults aged 50 years or older.

Complications

Among deaths for which varicella was the underlying cause, at least 1 varicella-associated complication was listed on 90 (80%) of 112 records in 2002–2007. By age group, the proportion of deaths with listed complications was similar (range: 77%–83%). Also, this proportion was similar with that reported during 1999–2001. During 2002–2007, the most common complications were secondary bacterial infection among children and adolescents younger than 20 years (67%) and pneumonia among adults aged 20 to 49 years (58%) and aged 50 years or older (36%).

Among deaths for which varicella was the contributing cause, a varicella-associated complication was listed on 50 (43%) of 116 records in 2002–2007, with similar proportions by age group. Secondary bacterial infection and pneumonia were the most common complications, reported in 19% and 16%, respectively, of all deaths.

DISCUSSION

During the 12 years of the mostly 1-dose US varicella vaccination program, the mortality rate attributed to varicella as the underlying cause declined by 88% compared with the prevaccine years. The decline occurred in all age groups, with an extremely high reduction among children and adolescents younger than 20 years (97%) and among those younger than 50 years

overall (96%). Most of the deaths (89%) continued to occur among those without apparent contraindications to vaccination and were therefore potentially preventable. Unlike the previous report (through 2001), we also found a decline in deaths attributed to varicella listed as the contributing cause of death. Our findings exceed the reduction in mortality modeled in cost-effectiveness analyses before or in the early stages of the implementation of the varicella vaccination program^{12,13} and indicate the potential for a higher-than-anticipated benefit of a fully implemented 1-dose program. However, this should be interpreted bearing in mind that varicella causes few deaths and that the main benefit of the vaccination program comes from a reduction of lost work and medical care associated with cases and severe complications. Nevertheless, varicella deaths are a powerful reminder of the importance of vaccination for prevention.

The 97% decline in mortality rates for which varicella is listed as the underlying cause of death among children and adolescents younger than 20 years is a direct consequence of the varicella vaccination program implemented in 1995, either through individual protection afforded by vaccination or through herd immunity effects. The 1-dose vaccination program focused initially on children aged 12 to 18 months; nationwide, coverage among children aged 19 to 35 months increased progressively from 27% in 1997 to 76% in 2001 and 90% in 2007.² With the aging of the child cohorts and implementation of elementary, middle, and high school requirements for varicella vaccine, high vaccination rates also were reached among adolescents aged 13 to 17 years (76% in 2007).¹⁴ As children and adolescents bore more than 90% of the US varicella disease burden in the prevaccine era,¹⁵ the de-

cline in varicella disease³ and the associated decline in varicella deaths can be directly attributed to successful implementation of the vaccination program. In addition, it is likely that with a childhood vaccination program, children would be vaccinated and protected before acquiring a condition (eg, acute lymphoblastic leukemia) that would put them at risk for severe disease.

In the previous analysis of varicella deaths, 6 years into the vaccination program (1995–2001), Nguyen et al⁵ found a 66% overall reduction in the mortality rates attributed to varicella as an underlying cause, with 75% or more among all age groups younger than 20 years. Corresponding to the increase in coverage from 2001 to 2007, we describe additional declines in mortality among these age groups. For the first time, there were years in which consistently no deaths were reported in 1 or more of the age groups younger than 20 years. In the last 6 years analyzed (2002–2007), a total of 3 deaths for each age range were reported among children aged 1 to 4 and 5 to 9 years, compared with an annual average of 13 and 16 deaths, respectively, in the prevaccine years. Data for infants deserve special mention because no varicella deaths were reported for the last 4 years. Infants are not eligible for vaccination, and they are protected through high immunity in the population that leads to decreased circulation of the varicella-zoster virus and decreased opportunities for exposure to the virus.

Evidence from studies that assessed the field performance or impact of 1-dose varicella vaccination supports our finding of an impressive decline in varicella deaths. Extensive postlicensure experience has demonstrated that 1 dose of the vaccine is ~85% effective in preventing all varicella but has a much higher effectiveness

(97%–100%) for prevention of severe cases of varicella.¹⁶ In a population-based study, children vaccinated with 1 dose were 13 times less likely than unvaccinated children to have moderate or severe illness (defined as ≥ 50 skin lesions) and one-half as likely to report a complication.¹⁷ Also, vaccinated subjects were 67% less likely than unvaccinated subjects to be hospitalized, and only isolated instances of vaccinated children requiring hospitalization for varicella-related complications have been reported to date.¹⁸ In addition, data from national surveillance can be instructive. As part of national varicella surveillance, varicella deaths are reportable to the Centers for Disease Control and Prevention (CDC) by state health departments. Although substantial underreporting occurs, important detailed case investigation information, such as potential risk factors and vaccination status, are supplied by the death reports submitted to the CDC. Of 77 deaths reported to the CDC since 1997 (likely all or most also reported to the National Center for Health Statistics and were included in our analysis), only 2 occurred among 1-dose-vaccinated children (CDC, unpublished data). Both children were on steroid therapy at the time of death, and 1 child had a malignant condition.

In contrast to the previous report,⁵ we found a greater-than-expected decline (67%) in mortality with varicella listed as an underlying cause of death among adults aged 50 years or older, although to a much lesser extent than the decline among younger age groups. In the 50 years or older age group, the validity of reported varicella deaths is low (43%)¹⁹ as cases of varicella rarely occur^{20,21} because almost all adults are immune to varicella. We also documented a decline in the mortality rates with varicella listed as the contributing cause of death, primarily

among people younger than 50 years. A potential alternative explanation for these 2 findings, aside from the direct and herd immunity effect of vaccination, is a change in physician coding practices and/or the validity of varicella listed as a cause of death on death certificates (less misdiagnosis of other rashes as varicella) secondary to the reduction of varicella-zoster virus circulation and disease in the population.

Our findings invite speculation regarding whether in the future varicella-related deaths in the US could be eliminated or reduced to extremely low numbers, similar to several other vaccine-preventable diseases (eg, measles, polio).^{22,23} It is clear that the 1-dose varicella vaccination program with the high coverage achieved had a major impact on varicella deaths. There is potential for the additional impact of the 1-dose program with ensuring the vaccination of eligible people without evidence of immunity because we found that most deaths occurred among those without apparent contraindications for vaccination. On the other hand, the effectiveness afforded by 1 vaccine dose does not provide sufficient herd immunity to completely interrupt community transmission of

varicella-zoster virus.¹⁶ To address this issue, a second dose of varicella vaccine was routinely recommended in the United States beginning in 2006.¹ Studies have indicated that a second dose among children produces an improved humoral and cellular immune response^{24–26} that correlates with improved protection against disease.^{24,27} Therefore, the second dose has the potential to further increase the population immunity, also providing indirect vaccine protection for people with contraindications to vaccination. High population immunity is essential to prevent the transmission of varicella-zoster virus because, unlike other vaccine-preventable diseases, aside from instances of importation there is continuous introduction of the endogenous virus from herpes zoster patients. Considering all these elements, elimination of varicella deaths could be attainable in the United States.

Our analysis was limited in several respects. Misclassification of deaths attributed to varicella was possible in either direction. However, we do not believe that misclassification could explain the trend over time. Information on medication was not available; thus, the proportion of people with immunocompromising preexisting conditions

could have been underestimated. Vaccination status also was not available, but the experience accumulated to date supports the assumption that the vast majority of the varicella deaths occurred among unvaccinated people.^{16–18} Reporting of varicella deaths among adults aged 50 years or older is less valid,¹⁹ and no additional information was available in the death certificates to allow us to make an assessment of the cause of death; therefore, we focused our analysis and discussion on people younger than 50 years.

CONCLUSIONS

Our analysis documents the impressive impact on varicella mortality of the US vaccination program, largely during a period when only 1 dose was administered. With the current 2-dose program, there is potential that these most severe outcomes of a vaccine-preventable disease could be eliminated.

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CARNAROLI ON THE MIND: “Get carnaroli rice” he said. I was having dinner at a lovely, local restaurant in Milan and by good fortune sitting immediately adjacent to a Milanese man having dinner with his niece. We were discussing Italian cooking and where to have a good meal in Milan and Parma. I had shared that I liked to cook risotto and might be purchasing some rice and parmesan cheese while visiting Parma. “Absolutely,” the man continued. “I have yet to have a good pasta or risotto meal in New York City. They either overcook the pasta or use the wrong rice.” I was paying close attention. After all, he had given me fabulous advice on my dinner selection. Both he and his niece agreed that he took his food and food preparation very seriously. I traditionally had used arborio rice when making risotto primarily because I can easily find it in Burlington while carnaroli was both expensive and had to be ordered online. What was it about carnaroli rice that made this man so passionate? According to an article in *The Guardian* (*Life and Style*: June 27, 2011), carnaroli rice, native to northern Italy, has slightly longer and thinner grains, higher starch content, and a firmer texture than arborio rice. When cooked in risotto, carnaroli rice tends to keep its shape better and as my dining companion remarked, is quite difficult to overcook. I opted not to tempt fate and ask if he adds the heated liquid bit by bit or all at once but simply recorded the name of his favorite restaurant and cheese shop in Parma. In contrast to Burlington, every small shop in Parma has a wonderful selection of different carnaroli rice. I opted to purchase a kilogram each of three different brands of locally produced carnaroli rice. On my arrival in the U.S., the customs official merely gave me a quizzical look after perusing my declaration form. As for me, while I felt a little bit like a smuggler carrying 3 kilograms of vacuum packed rice, I can’t wait to cook Risotto Milanese.

Noted by WVR, MD

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