Effectiveness Over Time of Varicella Vaccine

Marietta Vázquez, MD
Philip S. LaRussa, MD
Anne A. Gershon, MD
Linda M. Niccolai, PhD
Catherine E. Muehlenbein, MPH
Sharon P. Steinberg
Eugene D. Shapiro, MD

Context Reports of outbreaks of varicella in highly immunized groups have increased concern about the effectiveness of varicella vaccine.

Objective To assess whether the effectiveness of varicella vaccine is affected either by time since vaccination or by age at the time of vaccination.

Design Case-control study conducted from March 1997 through June 2003.

Setting Twenty different group practices in southern Connecticut.

Participants Case subjects, identified by active surveillance of all practices, consisted of 339 eligible children 13 months or older who were clinically diagnosed as having chickenpox and who also had a polymerase chain reaction (PCR) test result that was positive for varicella-zoster virus DNA. For each case subject, 2 controls were selected, matched by both age and pediatric practice.

Main Outcome Measures The effectiveness of the vaccine, especially the effects of time since vaccination and age at the time of vaccination, adjusted for possible confounders.

Results Although the adjusted overall effectiveness of the vaccine was 87% (95% confidence interval, 81%-91%; $P<.001$), there was a substantial difference in the vaccine's effectiveness in the first year after vaccination (97%) and in years 2 to 8 after vaccination (84%, $P=.003$). The vaccine's effectiveness in year 1 was substantially lower if the vaccine was administered at younger than 15 months (73%) than if it was administered at 15 months or older (99%, $P=.01$), although the difference in effectiveness overall for children immunized at younger than 15 months was not statistically significantly different than for those immunized at 15 months or older (81% vs 88%, $P=.17$). Most cases of chickenpox in vaccinees were mild.

Conclusions Although varicella vaccine is effective, its effectiveness decreases significantly after 1 year, although most cases of breakthrough disease are mild. If administered at younger than 15 months, the vaccine's effectiveness was lower in the first year after vaccination, but the difference in effectiveness was not statistically significant for subsequent years.

JAMA. 2004;291:851-855 www.jama.com

THE LIVE, ATTENUATED VARICELLA vaccine developed by Takahashi in 1974 was approved in the United States in 1995 and is recommended for routine administration to healthy children at 12 to 18 months of age and to older children who have not yet had chickenpox.[1,2] Previously, we reported that the overall effectiveness of the vaccine in clinical practice was good (85%), at least during the first few years after vaccination.[3] However, recent reports[4,5] of outbreaks of chickenpox in groups with substantial (73% and 80%) rates of immunization, as well as studies[6] of immunized children with breakthrough infections, have increased concern about the current recommendations for administration of the vaccine.

We now report additional results from an ongoing case-control study on the influence of age at the time of vaccination and the time since vaccination on the vaccine's effectiveness. This study includes, with additional analyses, the 202 polymerase chain reaction (PCR)–positive cases and the 40 PCR-negative cases and their matched controls from the previous report[3] of the vaccine's effectiveness.

See also Patient Page.

METHODS

A complete description of the methods has been published previously.[3] Subjects were children 13 months to 16 years of age with no contraindications to vaccination with varicella vaccine. Both potential cases and potential controls who previously had chickenpox (determined by both interview and review of medical records) were excluded, since varicella vaccine is not recommended for such children. Both

Author Affiliations: Departments of Pediatrics (Drs Vázquez and Shapiro and Ms Muehlenbein) and Epidemiology and Public Health (Drs Niccolai and Shapiro) and the Children's Clinical Research Center (Dr Shapiro), Yale University School of Medicine, New Haven, Conn; and Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY (Drs LaRussa and Gershon and Ms Steinberg).
Financial Disclosures: Dr LaRussa is the recipient of a contract from Merck & Co to perform a varicella-specific PCR assay on blinded samples from recipients of varicella vaccine who have had adverse events potentially related to vaccination. Dr Gershon has received research support for a basic science project from Merck & Co. Drs Shapiro and Gershon served as consultants at a 1-day meeting on vaccine cost-effectiveness sponsored by Merck & Co.
Corresponding Author: Eugene D. Shapiro, MD, Department of Pediatrics, Yale School of Medicine, 333 Cedar St, PO Box 208064, New Haven, CT 06520-8064 (Eugene.Shapiro@Yale.edu).

potential cases and potential controls who had received the vaccine in the preceding 4 weeks were excluded from the study. In this population, 99% of families in the practices had a telephone and no potential case or control was excluded because he/she did not have a telephone.

The case group consisted of children with chickenpox, identified by active surveillance, who received medical care at the 20 participating pediatric practices in southern Connecticut. Investigators were notified of all patients in each practice who either called the practice because of symptoms and signs presumed to be chickenpox or came to the physicians' offices because of an illness thought to be chickenpox.

On approximately the third to fifth day of the illness, a research assistant visited the home of each patient with chickenpox and conducted a brief interview with the parent to ascertain demographic information, pertinent medical history, risk factors, and whether the child attended school or day care. The severity of the illness was assessed based on a modified version of a clinical scale used in previous clinical trials of varicella vaccine that takes into account the number and type of lesions (eg, vesicular, hemorrhagic), the height of the fever, the presence of systemic signs, and a subjective assessment of how ill the child was.[3] A score of 7 or lower was considered mild disease, scores of 8 to 15 were considered moderately severe disease, and scores of 16 or higher were considered severe disease.

A vesicular lesion was gently unroofed with a capillary tube that was also used to collect vesicular fluid. Material also was obtained by swabbing the underlying skin with a cotton-tipped swab. A PCR assay was performed on all specimens to detect the presence of DNA of varicella-zoster virus (VZV).[7] Specimens were coded so that the technicians and the investigators who performed and interpreted the PCR tests were blind to whether the subject had received varicella vaccine. For PCR, assay results were considered positive if the specimen was positive for DNA of VZV and all negative controls in that batch were negative. The test results were considered negative if the specimen was negative for DNA of VZV, all positive controls in that batch were positive, and the specimen was positive for β-globin (indicating the presence of amplifiable human DNA in the specimen). However, if the specimen was negative for both DNA of VZV and β-globin, it was considered an inadequate sample.

We selected 2 controls who had not had chickenpox for each case subject, matched by both date of birth (±1 month) and source of primary care. Controls were selected from a list of potential controls by using a table of random numbers to select the order in which potential controls were contacted. The medical records of the subjects (both cases and controls) were reviewed, and all information about previous immunizations and about significant medical illnesses was recorded. Records of all health care practitioners (including previous practitioners) were checked. Antecedent vaccination was defined as written documentation that varicella vaccine had been received at least 4 weeks before focal time (date of onset of varicella for each case, used for both cases and their matched controls). Only written documentation of receipt of vaccines was accepted as evidence of prior immunization.

The effectiveness of a vaccine, defined as the proportionate reduction in the risk of infection among vaccinees that was attributable to vaccination, is calculated with data from clinical trials as follows: (1 – relative risk [RR]).[8] In matched case-control studies in which the controls are matched individually to the cases, the standard measure of association is the matched odds ratio (OR). Since for this type of study the matched OR closely approximates the RR that would be observed in a clinical trial,[9] the matched OR can be substituted for the RR in the above equation and the vaccine's effectiveness is estimated as follows: (1 – matched OR).

Data were analyzed primarily with SAS/STAT statistical software version 8.2 for Windows.[10] Matched ORs, with both their associated statistical significance (assessed with the maximum-likelihood χ^2 test for matched triplets) and their 95% confidence intervals (CIs) were calculated with the use of conventional techniques.[11] The vaccine's effectiveness was estimated directly from the above equation. Conditional logistic regression was used to calculate matched ORs for the effects of time since vaccination and age at the time of vaccination, as well as to adjust for effects of possible confounders, including sex, race, attendance at group day care, asthma, use of steroids, and receipt of varicella vaccine within 28 days after receiving the measles-mumps-rubella (MMR) vaccine.[12] In all calculations of ORs in the multivariable models, the unvaccinated group was the reference group. Three separate conditional logistic regression models were run: one to assess the effect of time since vaccination (a dummy-coded variable), one to assess the effect of age at the time of vaccination (also a dummy-coded variable), and one to assess the interaction between age and time since vaccination. A *t* test was used to assess the statistical significance of differences between groups in continuous variables such as age, whereas the χ^2 test was used to assess the statistical differences between categorical values. All *P* values are 2-sided. Results were considered statistically significant if the 2-tailed *P* value was $<.05$.

As a strategy to assess whether there might have been bias introduced in the selection of the controls, we compared the proportion of subjects who had received the MMR vaccine among both the cases and the controls.[3] Since the MMR vaccine should have been administered at approximately the same age as the varicella vaccine and it should have no effect on the risk of developing varicella, we expected that there would be no significant difference between the cases and the controls in the proportions who had received the MMR

vaccine. A significant difference could indicate that selection bias may have been a problem (since this may be a marker for use of medical care).

We also performed an analysis in which we assessed the vaccine's effectiveness for potential cases whose PCR test results were negative (ie, children who did not have chickenpox by our definition). If, using the same methods, the study showed that the vaccine's effectiveness in preventing PCR-positive varicella was good but the vaccine was not effective in preventing PCR-negative potential cases of varicella, it would be strong evidence that the results were not attributable to bias (since all potential cases and controls were selected in the same manner).[3] The study was approved by Yale's Human Investigation Committee; written informed consent was obtained from case parents and oral informed consent was obtained from control parents (written assent was obtained from the case subject when appropriate).

Table 1. Characteristics of Children With Chickenpox and Their Matched Controls

Characteristic	No. (%) of Children*		*P* Value
	Children With Chickenpox (n = 339)	Controls (n = 669)	
Age, mo			
Mean (SD)	76 (32.9)	75 (32.6)	.73
Median	72	72	
Range	14-190	14-190	
Female	162 (48)	366 (55)	.04
White race	288 (85)	575 (86)	.67
Weekday location			
School	230 (68)	466 (70)	.64
Day care	82 (24)	145 (22)	
Home	27 (8)	58 (9)	
Asthma	15 (4)	37 (6)	.45
Used steroids	5 (1)	9 (1)	.87
Received varicella vaccine	122 (36)	470 (70)	<.001
Vaccinated ≤12 mo earlier	4 (3)	84 (18)	<.001
Vaccinated at <15 mo	35 (29)	89 (19)	.02
Received varicella vaccine within 28 days of MMR vaccine	1 (1)	4 (1)	.59
Received MMR vaccine	338 (99)	668 (99)	.99

Abbreviation: MMR, measles-mumps-rubella.
*Data are number (percentage) of children unless otherwise indicated. The denominators for "vaccinated ≤12 mo earlier" and "vaccinated at <15 mo" are the number of vaccinated children in the groups (122 children with chickenpox and 470 controls).

RESULTS

From March 1997 through June 2003, of the 634 potential case subjects contacted who were eligible for the study, 530 (84%) were enrolled. Of the others, a sample for PCR could not be obtained from 30 (5%) and 74 (12%) refused to participate. For the potential case subjects who were enrolled, the results of the PCR assay were positive in 364 (69%), negative in 124 (23%), and indeterminate in 42 (8%). Of the 1164 potentially eligible controls who were reached, 80 (7%) refused to participate. Information was complete for the case and at least 1 matched control for 339 matched case-control groups in which the results of the PCR assays in the potential case subjects were positive. Data from these subjects formed the basis for the analyses of the effectiveness of the vaccine.

Characteristics of the subjects included in the analyses of the vaccine's effectiveness are shown in TABLE 1. Cases and controls were similar in demographic characteristics but differed in receipt of varicella vaccine and in the proportions vaccinated at younger than 15 months and at 12 months or less before the onset of varicella in the case subjects. The numbers of cases who were enrolled each year (1997-2003) who were included in the analyses were 75, 71, 68, 48, 33, 43, and 1, respectively. The results of the unadjusted estimate of the overall effectiveness of the vaccine are shown in TABLE 2. Of the 339 case-control groups, 330 had 2 matched controls and 9 had 1 matched control. The overall effectiveness of the vaccine was 87% (OR, 0.13 [95% CI, 0.09-0.20]; $P<.001$). The effectiveness was virtually unchanged after controlling for potential confounders (sex, race, location of care during the day, history of asthma, use of corticosteroids, and receipt of varicella vaccine within 28 days after being immunized with the MMR vaccine). Chickenpox was significantly more severe in unvaccinated children (mean [SD] and median [interquartile range] severity scores, 7.3 [3.1] and 8 [4-9], respectively) than in vaccinated children (mean [SD] and median [interquartile range] severity scores, 4.5 [2.2] and 3 [3-5], respectively) ($P<.001$). Of the 122 vaccinated case subjects, 106 (87%) had mild varicella compared with 98 (45%) of the 217 unvaccinated case subjects ($P<.001$). The rash was mostly vesicular in 37 (30%) of the vaccinated cases compared with 126 (58%) of the unvaccinated cases ($P<.001$). The vaccine's overall effectiveness against moderate or severe disease was 98% (95% CI, 93%-99%; $P<.001$) and was not significantly different if the child was vaccinated at 15 months or younger.

The vaccine's effectiveness in the first year after vaccination was 97%, which decreased to 86% in the second year after vaccination and to 81% in years 7 to 8 after vaccination (TABLE 3). The difference between the effectiveness in year 1 and year 2 was statistically significant ($P=.007$), as it was between year 1 and each of the subsequent years. However, the differences between the effectiveness in year 2 and in each subsequent year (including years 7-8) were not statistically significantly different ($P=.63$). The trend for the decrease in

the vaccine's effectiveness with time was not linear. Consequently, we combined the estimates of the vaccine's effectiveness for years 2 through 8 (Table 3).

The vaccine's effectiveness in the first year after vaccination was substantially lower if the vaccine was administered when the child was younger than 15 months than if the child was 15 months or older at the time of vaccination (73% vs 99%, $P=.01$), although the difference in the effectiveness for these age groups was not statistically significant either for years 2 to 8 or overall (TABLE 4). For comparison, the results for all children in the study (vaccinated at ≥12 months) are also included in Table 4. Among vaccinees who developed chickenpox, the disease was mild in 88% of those vaccinated at younger than 15 months and in 81% of those vaccinated at 15 months or older ($P=.30$). The vaccine's effectiveness in year 1 vs years 2 to 8 was also significantly different if the child was 15 months or older at the time of vaccination but not if the child was younger than 15 months at the time of vaccination.

Although there was a substantial difference in the proportions of cases and controls who had received varicella vaccine, all but 1 case and 1 control had received the MMR vaccine, initial administration of which is recommended at approximately the same age as for the varicella vaccine (Table 1). There were 113 potential cases for whom the PCR test result was negative and for whom information about the potential case and at least 1 matched control was complete. Of these, 98 (87%) of the 113 PCR-negative potential cases and 182 (81%) of their 225 matched controls had received varicella vaccine. The matched OR was 1.44. The effectiveness of the vaccine against PCR-negative potential cases (1 – matched OR) was –56% and was not significantly different than 0% (95% CI, –197% to 18%; $P=.18$). Both of these analyses suggest that bias did not have a substantial effect on the results of this study.

Table 2. Overall Effectiveness of Varicella Vaccine*

No. of Vaccinated Matched Controls per Case	Cases, No.	Matched Controls, No.	
		Vaccinated	Unvaccinated
Vaccinated Cases			
0	6	0	11
1	27	27	25
2	89	178	0
Unvaccinated Cases			
0	50	0	97
1	69	69	66
2	98	196	0

*Matched odds ratio = 0.13 (95% confidence interval, 0.09-0.20). Unadjusted vaccine effectiveness = 87% (95% confidence interval, 80%-91%), $P<.001$.

Table 3. Effectiveness of the Varicella Vaccine by Time Since Vaccination*

Years Since Vaccination	No. Vaccinated		Effectiveness, % (95% CI)	*P* Value
	Cases	Controls		
1†	4	84	97 (91-99)	<.001
2	22	108	86 (76-92)	<.001
3	26	92	83 (69-90)	<.001
4	24	68	81 (62-90)	<.001
5	24	65	84 (67-93)	<.001
6	13	33	82 (54-93)	<.001
7-8	9	20	81 (40-94)	.005
2-8†	118	386	84 (76-89)	<.001

Abbreviation: CI, confidence interval.
*Results are adjusted for sex, race, attendance at group day care, asthma, use of steroids, and receipt of varicella vaccine within 28 days after receiving the measles-mumps-rubella vaccine. The *P* values in the table refer to whether the adjusted estimates of the vaccine's effectiveness are statistically significantly different than 0%.
†Difference in overall effectiveness in year 1 vs years 2 to 8 (97% vs 84%; $P = .003$).

Table 4. Effectiveness of the Varicella Vaccine by Time Since Vaccination and Age at the Time of Vaccination*

Effectiveness	Age at Time of Vaccination, mo			*P* Value, <15 vs ≥15 mo
	≥12	<15	≥15	
Year 1, % (95% CI)	97 (91 to 99)	73 (–43 to 95)	99 (93 to 100)	.01
P value†	<.001	.12	<.001	
Years 2-8, % (95% CI)	84 (76 to 89)	81 (62 to 90)	85 (77 to 90)	.47
P value†	<.001	<.001	<.001	
P value, year 1 vs years 2-8	.003	.71	.007	
Overall, % (95% CI)	87 (81 to 91)	81 (64 to 90)	88 (82 to 92)	.17
P value†	<.001	<.001	<.001	

Abbreviation: CI, confidence interval.
*Results are adjusted for sex, race, attendance at group day care, asthma, use of steroids, and receipt of varicella vaccine within 28 days after receiving the measles-mumps-rubella vaccine.
†The *P* values refer to whether the adjusted estimates of the vaccine's effectiveness are statistically significantly different than 0%.

COMMENT

This study indicates that at least through the first 8 years after vaccination, the overall effectiveness of live, attenuated varicella vaccine remains good, although breakthrough varicella is not rare. Most vaccinated children who develop chickenpox have mild disease, regardless of their age at the time of vaccination or the time since vaccination, at least up to 7 to 8 years after vaccination (ie, the vaccine's effectiveness against moderate to severe disease is excellent throughout the period of the study).

However, there is a substantial, statistically significant decrease in the vac-

cine's overall effectiveness in the second year after vaccination, after which the decrease in the vaccine's effectiveness is not statistically significant, at least through years 7 to 8 after vaccination. We do not know the explanation for this phenomenon, although it is consistent with observations in other studies[4-6] that the risk of breakthrough infection increases over time. Presumably, this is a result of waning immunity in a proportion of immunized children in addition to occasional primary vaccine failure.[13] Although the breakthrough infections are usually mild, such infections nevertheless may place the child at higher risk of subsequently developing zoster and may result in spread of varicella to susceptible contacts.[4,13]

The vaccine's effectiveness in the first year after vaccination is substantially lower in children who are vaccinated at younger than 15 months. This is consistent with other reports[4-6] that have indicated that children vaccinated at younger than 15 months are at increased risk of breakthrough infection. Changing the age at which immunization with varicella vaccine is begun from 12 to 15 months might alleviate this problem. However, the improved effectiveness of the vaccine would have to be balanced against both the risk of leaving such children unvaccinated for these 3 months and the risk that some children might not return for vaccination in a timely manner. Alternatively, administering a second dose of the vaccine might also solve both this problem and the problem of waning immunity.[13,14] More data are needed about the effect of a second dose of the vaccine on duration of immunity to varicella.

Because this is a nonexperimental study, bias may have affected the results. However, the analyses that showed both that there was no difference in the proportions of cases and of controls who had received MMR vaccine and that the vaccine was not effective against potential cases with a PCR result that was negative (even though both these cases and their matched controls were selected in the same manner as were the PCR-positive cases and their matched controls) suggest that bias did not have an important effect. The study was conducted only in private practices, although the racial distribution of the population was similar to that of the entire state of Connecticut. The vaccine had only been in routine use in this country for up to 7 to 8 years at the time the analyses were performed, so the effect of longer duration since vaccination could not be assessed. In addition, during much of the study period varicella was still circulating widely, and subclinical infection and boosting of vaccine-induced immunity through natural exposure likely occurred to some extent. As the incidence of varicella continues to diminish, boosting of immunity through natural exposure will become increasingly rare.

It is clear that the incidence of varicella in the United States is decreasing as a result of the widespread use of varicella vaccine.[15,16] Nevertheless, in the United States, deaths from varicella and other complications in immunocompetent persons still occur and will continue to occur until the infection is eliminated.[17] It is important to monitor closely the incidence of varicella and the effectiveness of the vaccine over time to determine if a booster dose is needed to improve its effectiveness.

Author Contributions: As principal investigator, Dr Shapiro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Vázquez, LaRussa, Gershon, Shapiro.
Acquisition of data: Vázquez, LaRussa, Gershon, Steinberg.
Analysis and interpretation of data: Vázquez, LaRussa, Gershon, Niccolai, Muehlenbein, Shapiro.
Drafting of the manuscript: Vázquez, Shapiro.
Critical revision of the manuscript for important intellectual content: Vázquez, LaRussa, Gershon, Niccolai, Muehlenbein, Steinberg, Shapiro.
Statistical expertise: Vázquez, Niccolai, Muehlenbein, Shapiro.
Obtained funding: Gershon, Shapiro.
Administrative, technical, or material support: LaRussa.
Supervision: Vázquez, LaRussa, Gershon, Shapiro.
Funding/Support: This work was supported in part by grants R01-AI41608, R01-AI 24021, and K24-AI01703 from the National Institute of Allergy and Infectious Diseases and by the Yale Children's Clinical Research Center grant MO1-RR06022, General Clinical Research Centers Program, National Center for Research Resources, National Institutes of Health, Bethesda, Md. Dr Vázquez was supported in part by the Robert Wood Johnson Minority Medical Faculty Development Program.
Role of the Sponsor: The National Institute of Allergy and Infectious Diseases and the Yale Children's Clinical Research Center did not participate in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.
Acknowledgment: We are grateful for the efforts of Valerie Parcells, RN, who visited the case subjects and collected much of the data.

REFERENCES

1. Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T, Isomura S. Live vaccine used to prevent the spread of varicella in children in hospital. *Lancet.* 1974;2:1288-1290.
2. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 1996;45(RR-11):1-36.
3. Vázquez M, LaRussa PS, Gershon AA, Steinberg SP, Freudigman K, Shapiro ED. The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med.* 2001;344:955-960.
4. Galil K, Lee B, Strine T, et al. Outbreak of varicella at a day-care center despite vaccination. *N Engl J Med.* 2002;347:1909-1915.
5. Galil, K, Fair E, Mountcastle N, Britz P, Seward J. Younger age at vaccination may increase risk of varicella vaccine failure. *J Infect Dis.* 2002;186:102-105.
6. Verstraeten T, Jumaan AO, Mullooly JP, et al. A retrospective cohort study of the association of varicella vaccine failure with asthma, steroid use, age at vaccination, and measles-mumps-rubella vaccination. *Pediatrics.* 2003;112:e98-e103.
7. LaRussa P, Lungu O, Hardy I, Gershon A, Steinberg S, Silverstein S. Restriction fragment length polymorphism of polymerase chain reaction products from vaccine and wild-type varicella-zoster virus isolates. *J Virol.* 1992;66:1016-1020.
8. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field: further observations. *Epidemiol Rev.* 1988;10:212-241.
9. Cornfield J. A method of estimating comparative rates from clinical data: application for cancers of the lung, breast, and cervix. *J Natl Cancer Inst.* 1950-51;11:1269-1275.
10. SAS Institute Inc. *SAS OnlineDoc.* Version 8. Cary, NC: SAS Institute Inc; 1999.
11. Abramson JH, Gahlinger PM. *Computer Programs for Epidemiologists PEPE v. 4.0.* Salt Lake City, Utah: Sagebrush Press; 2001:113-118.
12. Breslow NE, Day NE. *Statistical Methods in Cancer Research, Vol. 1: The Analysis of Case-Control Studies.* Lyon, France: World Health Organization; 1980.
13. Gershon AA. Varicella vaccine—are two doses better than one? *N Engl J Med.* 2002;347:1962-1963.
14. Watson B, Boardman C, Laufer D, et al. Humoral and cell-mediated immune responses in healthy children after one or two doses of varicella vaccine. *Clin Infect Dis.* 1995;20:316-319.
15. Seward JF, Watson BM, Peterson CL, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. *JAMA.* 2002;287:606-611.
16. Decline in annual incidence of varicella—selected states, 1990-2001. *MMWR Morb Mortal Wkly Rep.* 2003;52:884-885.
17. Varicella-related deaths—United States, 2002. *MMWR Morb Mortal Wkly Rep.* 2003;52:545-547.