Incremental Effectiveness of Second Dose Varicella Vaccination for Outbreak Control at an Elementary School in Philadelphia, Pennsylvania, 2006

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Background: In 2006, the Philadelphia Department of Public Health conducted an investigation of a varicella outbreak at an elementary school in which second-dose vaccination for outbreak control (VOC) was implemented. We evaluated the effectiveness of this intervention.

Methods: Self-administered questionnaires collected varicella disease and vaccination information. Students eligible for second-dose VOC were 1-dose vaccine recipients without prior varicella disease. A breakthrough varicella case was defined as a maculopapulovesicular rash in a student with onset >42 days after 1-dose vaccination without other apparent cause. Vaccine effectiveness was evaluated using survival analysis techniques and analyzed by vaccine status (first dose versus second dose). Multivariable Cox proportional hazard models were used to identify statistical interactions and adjust for confounders.

Results: The questionnaire response rate was 92% (342/370). Of the 286 eligible students, 187 (65%) received a second-dose VOC. The crude attack rate was 9/187 (5%) among second-dose VOC recipients; 43/99 (43%) among 1-dose recipients, and 5/6 (83%) among unvaccinated students. Second-dose VOC recipients had milder rashes, compared with 1-dose or unvaccinated students. The adjusted incremental second-dose vaccine effectiveness was 76% (95% confidence interval: 44%–90%) for students with classroom exposure. Incremental effectiveness was similar (79%) when we extended the immune response time from 4 days to 7 days after second-dose VOC.

Conclusions: Second-dose VOC resulted in a substantial reduction in varicella incidence for students with classroom exposure. Until high rates of routine second-dose vaccine coverage are achieved, clinicians should consider second-dose VOC an appropriate intervention to reduce disease transmission in institution-based outbreaks.

Key Words: varicella outbreak, varicella vaccination, vaccine effectiveness

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Since introduction of the 1-dose varicella vaccination program in the United States, rates of varicella disease, hospitalizations, and deaths have declined by approximately 90%.[1–4] Despite these achievements, varicella continues to occur endemically at low levels.[2] In recent years, varicella outbreaks have frequently occurred in elementary schools with high (>96%) 1-dose varicella vaccine coverage. In these outbreaks, overall attack rates have ranged from 11% to 17% (40% in certain classrooms) and have resulted in multiple waves of illness.[5–8] To better control disease transmission among institution-based populations with high 1-dose vaccine coverage, the Advisory Committee on Immunization Practices (ACIP) recommended second-dose varicella vaccination for outbreak control (VOC) in June 2005.[9] One year later, ACIP expanded this recommendation to universal 2-dose varicella vaccination for children at school-entry age and for catch-up vaccination among older persons who were previously vaccinated.

Vaccine coverage estimates from Philadelphia suggest that uptake of 2-dose varicella vaccination has been low to moderate, with rates ranging from 35% to 55% among children aged 4 to 8 years and 22% to 29% among older children aged 9 to12 years (2008 Philadelphia Department of Public Health (PDPH) Division of Disease Control Annual Report). As of September 2009, only 22 states require a second dose for school entry. With the majority of children in the United States still not optimally vaccinated, outbreaks among 1-dose vaccines remain a possibility, and second-dose VOC continues to be a potential public health intervention. Although 1-dose varicella vaccination is an effective outbreak intervention in school settings with a high proportion of unvaccinated students,[10] the effectiveness of second-dose varicella VOC has not been formally evaluated.

In fall 2006, PDPH was notified of a large outbreak of breakthrough varicella in an elementary school with high 1-dose varicella vaccine coverage. PDPH recommended second-dose VOC to reduce disease transmission. PDPH conducted an epidemiologic investigation to determine the extent of the outbreak and to assess the incremental effectiveness of second-dose VOC.

METHODS

Outbreak Setting

On November 2, 2006, PDPH received reports of 18 suspected varicella cases in an elementary school. On November 8, PDPH received laboratory confirmation of varicella-zoster virus (VZV) infection in 1 of these students. The outbreak occurred in a

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private, nonsectarian school in Philadelphia with 370 students and 64 staff. Students were organized in 6 academic units that included prekindergarten through grade 8 students. Classrooms were separated by partitions that did not extend from floor to ceiling. Students intermingled during 4 specialty courses, and in the cafeteria and hallways. During the 2006–07 academic year, the city of Philadelphia required evidence of varicella immunity (1-dose vaccination or parental report of history of disease) for students entering kindergarten through grade 11.

Outbreak-Control Measures

On November 2, a notification letter was sent to parents informing them of the outbreak and recommending VOC. PDPH recommended that students without a varicella history visit their healthcare provider to receive their first or second dose, as appropriate. Parents also were informed that publicly funded vaccinations were available for students without adequate insurance at their provider's office or at a PDPH health center through the Vaccines for Children Program. No vaccination clinics were offered by PDPH or the school; students were vaccinated at individual appointments made with their healthcare providers. PDPH recommended that school officials exclude from school students and staff experiencing any varicelliform rash illness until their lesions crusted over.

Epidemiologic Investigation

PDPH initiated an epidemiologic investigation involving case finding, contact tracing, and lesion-specimen collection. A retrospective cohort study was conducted using self-administered questionnaires mailed to all staff and students' parents 1 month after the outbreak ended; a second questionnaire was mailed a month later to parents who did not respond. Questionnaires collected information regarding demographic characteristics, underlying medical conditions, prior VZV infections, rash illnesses since the start of the school year, attendance at school, participation in after-school activities, and VZV exposures outside of school. We ascertained varicella vaccination dates from healthcare provider records, PDPH's immunization database, school records or parents' report, in this order of preferred sources. PDPH staff conducted telephone interviews with parents of cases by using the Varicella Active Surveillance Project's Case Investigation Questionnaire that collects information about clinical manifestations, diagnosis, treatment, VZV exposures, and household transmission.[1] The National VZV Laboratory at the Centers for Disease Control and Prevention performed polymerase chain reaction testing of clinical samples.[11,12]

The outbreak investigation protocol was reviewed by the human subject committees at PDPH and the Centers for Disease Control and Prevention and was determined to be public health practice, not research.

Study Definitions

A case of varicella was defined as acute maculopapulovesicular rash without other apparent cause in an unvaccinated student or staff member occurring after September 8, 2006 (first day of school year). A case of breakthrough varicella was defined as a varicella-like rash with onset >42 days after 1-dose varicella vaccination.[13]

Students were classified as 1-dose recipients if they had received only 1 dose of varicella vaccine before the start of the school year. For our main analyses, we classified students as second-dose VOC recipients beginning 4 days after receiving their second-dose VOC, given the rapid immune response after booster vaccination identified in previous studies.[14–16] Incremental vaccine effectiveness was defined as the additional reduction in varicella disease experienced by dose VOC recipients, relative to 1-dose vaccine recipients.

Varicella exposures were assessed by setting. Classroom exposures were quantified by calculating the number of infectious cases within their academic unit. Infectious period for each case began 2 days before rash onset and lasted until the day they were excluded from attending school. Exposures during after-school activities were similarly determined. Household exposures were dichotomously categorized (present or absent).

Data Analysis

Analyses were restricted to students who attended school during the outbreak, had no prior varicella disease history, and whose parents completed the questionnaire. Because 98% (63/64) of staff had been born before 1980 and reported disease histories, we excluded staff from all vaccine effectiveness analyses. However, cases of varicella and herpes zoster among any excluded persons were included in certain analyses as sources of disease exposure.

Descriptive analyses of the student population and outbreak-related cases were performed. χ^2 test and Fisher exact tests were used to compare proportions for categorical variables by vaccination status, and Wilcoxon rank-sum tests were used to compare medians for continuous variables, assuming non-normal distributions.

We initially calculated unadjusted incidence rates, stratified by vaccine status, following standard methods.[17] For these calculations, the at-risk period for each student began on October 13, 2006, (infectious start date of the first case) and ended on the rash onset date for students who developed varicella, or December 16, 2006, for students who did not (final day when the last infectious student attended school and could be a source of disease exposure). For those students who received a second-dose VOC, transition to second-dose VOC status was set at 4 days after receipt of dose 2. In other words, the second-dose VOC recipients contributed to the person-time for incidence in the 1-dose group up until 4 days after receipt of dose 2. The incidence for second-dose VOC recipients represented time at-risk and disease occurrence beginning 5 days after receipt of second-dose VOC. To assess the validity of the choice of 4 days for response to second-dose VOC, we performed a sensitivity analysis extending the assumed anamnestic immune response time from 4 days to 7 and 10 days after second-dose VOC.

Multivariable Cox proportional hazards (PH) models were then developed to determine risk-adjusted incremental reduction in varicella disease among students who received a second-dose VOC, compared with students who received only 1 dose.[18] Both second-dose VOC and disease exposure were treated as time-dependent covariates. In other words, for students who received a second-dose VOC, disease exposure was quantitatively assessed separately for the time period before and after their transition to second-dose VOC status. To account for potential residual confounding caused by changing exposure levels over time, the time scale for the Cox PH models was the calendar date, rather than number of days from study inception.[18] We assessed for statistical interaction between vaccine status and 7 other candidate effect modifiers: classroom exposure, household exposure, exposures occurring during after-school activities, herpes zoster exposure, other community VZV exposures, time since 1-dose vaccination (<4.5, 4.5–6.6, 6.7–8.8, or >8.8 years), and age at 1-dose vaccination (12–15 months or >15 months). Because statistical interaction between vaccine status and classroom exposure was identified, we created a separate model, limited to students with classroom exposure, in which we adjusted for possible confounding by the 6 remaining variables.[19] In all PH regression models,

statistical significance was determined by using the likelihood ratio test, with a level of significance of $P < 0.05$. Incremental effectiveness of second-dose VOC was calculated by using Yule and Greenwood's formula: 1 minus relative risk.[20] In our study, relative risk refers to the incidence rate of breakthrough varicella among second-dose VOC recipients, compared with 1-dose recipients, and was estimated by using the hazard ratio. All analyses were conducted by using SAS v9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Epidemiologic Investigation

Questionnaire response rate was 92% (342/370) for students and 100% (64/64) for staff. Of the 342 students, 296 (86%) attended school during the outbreak and had no reported varicella history. Among these, 6 (2%) were unvaccinated, 286 (97%) were 1-dose recipients, and 4 (1%) were 2-dose recipients before the outbreak. Only 2% reported preexisting medical conditions (asthma or eczema) that might have affected disease transmission or immune response to vaccination. No students reported immunocompromizing conditions or taking immunosuppressive medication. We excluded from further analyses all staff, 45 (13%) students reporting history of disease, and 1 student who transferred to the school after the outbreak had ended.

The outbreak began October 13, 2006 (Fig. 1), corresponding to the start of the infectious period of the first cases and lasted for 64 days until December 16, 2006. Among the 286 students eligible for second-dose VOC, a total of 187 (65%) received a second-dose VOC. A total of 57 cases of varicella were identified. The crude attack rate was 5/6 (83%) among unvaccinated children; 43/99 (43%) among 1-dose recipients; and 9/187 (5%) among second-dose VOC recipients. Crude attack rates were highest among students in kindergarten (43%) and the grades 1 and 2 academic unit (38%) and ranged from 3% to 11% among students in other grade levels. No cases were identified among the 4 students who received a second vaccine dose prior to the outbreak.

The 2 initial cases experienced predominantly papular rashes, with <50 lesions and were afebrile. Cases among second-dose VOC recipients tended to have less severe rashes (signified by the proportion of students reporting >50 skin lesions and vesicular rash) compared with unvaccinated or 1-dose recipients (Table 1). Although a higher proportion of second-dose VOC cases reported fever compared with 1-dose cases, this difference was not statistically significant ($P = 0.26$). Disease was diagnosed by healthcare providers significantly more among cases who were 1-dose recipients compared with cases who were second-dose VOC recipients (81% versus 44%; $P = 0.03$). Disease among four 1-dose cases was laboratory confirmed as wild-type VZV. No hospitalizations or complications occurred. No cases were prescribed antibiotics or antiviral medication.

Incremental Effectiveness of Second-Dose Vaccination for Outbreak Control

The unadjusted incidence rate was 4.9 cases/1000 person-days for 1-dose recipients and 1.4 cases/1000 person-days for second-dose VOC recipients. Before beginning the multivariable analyses, we examined whether the number of classroom exposures had a linear association with the log-hazard of disease occurrence.[21] Because no linear association was identified, we analyzed classroom exposure as a categorical variable (present versus absent). In multivariable analyses, there were no statistically significant interactions between vaccine status and 6 of the 7 candidate variables tested. A statistically significant interaction was identified between vaccine status and classroom exposure ($P < 0.0001$), suggesting that second-dose VOC was effective only for students with classroom exposure. Thus, receiving second-dose VOC was not associated with varicella incidence for students with no classroom exposure. However, incidence was extremely low among these students (1 case occurring in a 1-dose recipient and none in second-dose VOC recipients). In further analyses, we excluded the time periods during which a student had no classroom exposure (51 students). Of these, 1 student was a 1-dose recipient and 50 students were second-dose VOC recipients.

Among students with classroom exposure, second-dose VOC was significantly associated with lower incidence of varicella disease (adjusted hazard ratio = 0.24; 95% confidence interval [CI]: 0.10–0.56). Incremental effectiveness of second-dose VOC was 76% (95% CI: 44%–90%). Our sensitivity analyses demonstrate that incremental effectiveness was similar when we extended the anamnestic immune response time from 4 days to 7 days after second-dose VOC (Table 2). Although the confidence intervals overlapped when compared with our main model, the incremental effectiveness increased to 94% when we assumed a 10-day delay between second-dose VOC administration and second-dose VOC immune status.

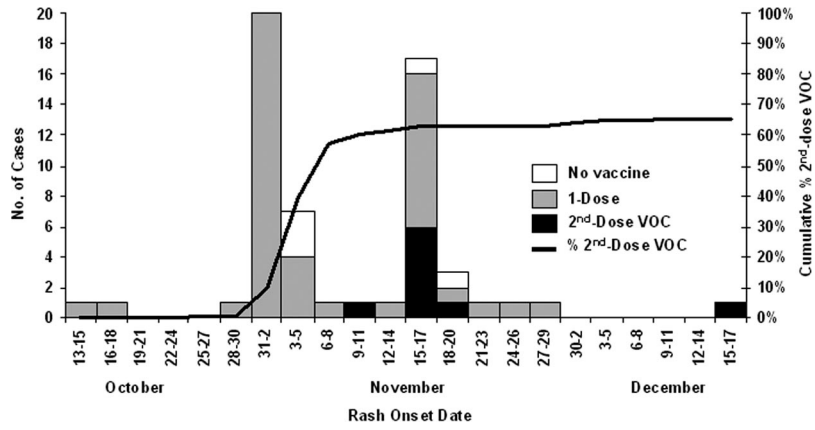

FIGURE 1. Number of cases by rash onset date and the cumulative percent of students receiving second dose vaccination for outbreak control (VOC) (n = 57)*. *The 2 peaks of the epidemic curve are 14 days apart, which corresponds to the known incubation period for varicella.

TABLE 1. Spectrum of Illness for Outbreak-Associated Cases of Varicella According to Vaccine Status

Clinical Characteristic	Unvaccinated (n = 5)	1 Dose (n = 43)	Second-Dose VOC (n = 9)	*P*
>50 lesions, %*	100	21	0	0.33
Primarily vesicular rash, %*†	33	12	0	0.57
Fever, %*	60	33	56	0.26
Rash duration days, median (range)‡	6 (3–11)	4 (1–10)	4 (2–7)	0.47
Missed school days, median (range)‡	3 (2–5)	2 (0–5)	2 (0–3)	0.42
Healthcare provider-diagnosed illness, %*	60	81	44	0.03
Complications, %*	0	0	0	1.0

*P value calculated by using Fisher exact test comparing 1-dose versus second-dose VOC.
†Cases with missing information excluded (Unvaccinated: n = 3, 1 dose: n = 41).
‡P value calculated by using Wilcoxon rank sum test comparing 1-dose versus second-dose VOC.

TABLE 2. Incremental Effectiveness of Second-Dose VOC at Varying Immune-Response Times

	Response Time		
		Sensitivity Analysis	
	4 Days	7 Days*	10 Days†
1-dose cases, n	42	42	46
Crude 1-dose incidence rate, cases/1000 person days	4.9	4.6	4.9
Second-dose VOC cases, n	9	7	2
Crude second-dose incidence rate, cases/1000 person days	1.4	1.2	0.4
Adjusted hazard ratio, (95% CI)‡	0.24 (0.10–0.56)	0.21 (0.08–0.51)	0.06 (0.02–0.27)
Adjusted incremental effectiveness second-dose VOC, (95% CI), %‡	76 (44–90)	79 (49–92)	94 (73–98)

*Under this assumption, 2 second-dose VOC cases were excluded from analysis because they did not have classroom exposure.
†Under this assumption, 5 students among whom disease developed 8–9 d after second-dose VOC were categorized as 1-dose cases. Of these 1 case without classroom exposure was excluded from the analysis.
‡The following variables were included in multivariable analysis but are not presented in the table: classroom exposure, household exposure, exposures occurring during after-school activities, exposure to children experiencing herpes zoster, community varicella exposures, time since first varicella vaccination, and age at first varicella vaccination.

DISCUSSION

This study presents the first data to describe the benefit of second-dose VOC after exposure to varicella in an outbreak setting. Our principal finding was that second-dose VOC reduced varicella incidence by 76% (95% CI: 44%–90%) for students with classroom exposure. We did not detect increased protection among students without classroom exposure. One possible explanation is that the benefit of second-dose VOC is only evident when the likelihood of infection is higher. What mattered was not the number of classroom-based exposures or whether an exposure occurred during after-school activities but whether a classroom-based exposure occurred at all. This implies that classroom exposure contains a certain combination of elements—confined space, nature of student interaction, or duration of exposure—that enhances varicella transmission.

Our finding of 76% incremental effectiveness for second-dose VOC differs from the only effectiveness estimate for the 2-dose varicella vaccination regimen reported to date. Gould et al. reported an incremental effectiveness of 28% during an outbreak among children in an Arkansas elementary school.[22] Because second-dose VOC had been administered in an earlier outbreak (7 months before the outbreak that was investigated), their finding is more representative of the incremental field effectiveness of routine 2-dose varicella vaccination, rather than the incremental effectiveness of second-dose VOC. Moreover, 2-dose vaccine coverage was lower (39%) in the Arkansas outbreak compared with our study (65%), and the analyses did not account for classroom exposure. While it is possible that higher 2-dose coverage would have resulted in a higher incremental 2-dose vaccine effectiveness during the Arkansas outbreak, it is also likely that, similar to the estimates for 1-dose varicella vaccine, 2-dose varicella vaccine effectiveness estimates will fall within a range, and several postlicensure studies will be needed to better understand the field protection provided by the second-dose varicella vaccination regimen.[23]

We are also the first to describe delivery of second-dose VOC by primary-care providers. This approach is consistent with ACIP immunization recommendations and supports the concept of the medical home.[24] Parker et al. described school-based vaccination clinics to be challenging and resource intensive to implement.[7] In contrast, our experience illustrates that provider-based vaccination can be effective when access to care and ample parent and physician cooperation is present. Our data support existing ACIP recommendations encouraging clinicians to consider second-dose VOC to reduce disease transmission in outbreaks. Clinicians contemplating use of second-dose VOC can consider it as analogous to postexposure prophylaxis (PEP) applied to an outbreak setting. Both interventions aim to modify or avert disease after exposure and are likely to be most effective when administered as early as possible after exposure. However, VOC can be administered beyond PEP's 5-day restriction and protects against repeated outbreak-associated exposures.

Our data suggest that vaccine-induced immunity can develop as early as day 5 after second-dose VOC as evidenced by the similar estimates of incremental vaccine effectiveness when assuming time-to-immunity of 4 or 7 days. This finding is consistent with an anamnestic immune response identified in other studies of 2-dose varicella vaccination.[14] Additionally, our sensitivity analyses indicate that immunity can improve with time with continued antibody proliferation and cell-mediated immunity.[25] However, other factors might have contributed to this increasing vaccine effectiveness by introducing residual confounding that was not adequately controlled in our analyses. For example, we cannot fully account for differences in exposures between vaccine groups

during the outbreak or differentiate between exposure-induced immunity and vaccine-induced immunity. Additionally, our ability to estimate immunity ≥10 days after second-dose VOC was limited because ongoing disease circulation was too limited ≥10 days later to determine any additional benefit.

Given the effectiveness, limited side effects, and long-term benefits of varicella vaccination, second-dose VOC can be a valuable intervention in institution-based outbreaks, including child care centers, healthcare facilities, homeless shelters, and residential facilities.[26,27] However, effectiveness of second-dose VOC might vary among populations with lower 1-dose vaccine coverage, outbreaks with later implementation of VOC, or those with lower VOC uptake.

This study had several limitations. Transition from 1-dose to 2-dose vaccine immunity was uncorroborated by antibody or cellular immune response testing, and the association between classification of vaccine status and the students' true immune status after second-dose VOC was inferred. Also, susceptibility to breakthrough disease and intensity of exposure might have been different by the time students transitioned to second-dose VOC status. However, the number of cases was similar between the first and second part of the outbreak. An additional concern is the possibility that some of the rashes after second-dose VOC might be vaccine related and not outbreak associated. Previous studies of vaccine-related rashes among 2-dose recipients, however, have reported rates of only 1%.[28] Finally, we identified wild-type strain among only 4 1-dose recipients. Accuracy of clinical diagnosis of breakthrough varicella is unknown because breakthrough disease often presents with modified morphology. However, misdiagnosis is unlikely to have occurred differentially between the 2 comparison groups, given the active search for cases.

As endemic transmisson of varicella continues to be a public health concern, second-dose VOC remains an available public health intervention until high rates of routine 2-dose vaccine coverage and further decreases in varicella disease and its complications are achieved.

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REFERENCES

1. Seward J, Watson B, Peterson C, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. *JAMA*. 2002;287: 606–611.
2. Guris D, Jumaan A, Mascola L, et al. Changing varicella epidemiology in active surveillance sites—United States, 1995–2005. *J Infect Dis*. 2008; 197(suppl 2):S71–S75.
3. Reynolds M, Watson B, Plott-Adams K, et al. Epidemiology of varicella hospitalizations in the United States, 1995–2005. *J Infect Dis*. 2008; 197(suppl 2):S120–S126.
4. Marin M, Jumaan A, Zhang J, Seward J. A decade of varicella prevention in the United States: successes and challenges. International Herpesvirus Workshop, Esturil Portugal, 2008.
5. Centers for Disease Control and Prevention. Outbreak of varicella among vaccinated children—Michigan, 2003. *MMWR.* 2004;53:389–392.
6. Lopez A, Guris D, Zimmerman L, et al. One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose. *Pediatrics*. 2006;117:e1070–e1077.
7. Parker AA, Reynolds MA, Leung J, et al. Challenges to implementing second-dose varicella vaccination during an outbreak in the absence of a routine 2-dose vaccination requirement—Maine, 2006. *J Infect Dis*. 2008; 197(suppl 2):S101–S107.
8. Tugwell BD, Lee LE, Gillette H, et al. Chickenpox outbreak in a highly vaccinated school population. *Pediatrics*. 2004;113:455–459.
9. Centers for Disease Control and Prevention. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2007;56(RR-4):1–40.
10. Hall S, Galil K, Watson BM, Seward J. The use of school-based vaccination clinics to control varicella outbreaks in two schools. *Pediatrics*. 2000;105:e17.
11. Loparev V, McCaustland K, Holloway B, et al. Rapid genotyping of varicella-zoster virus vaccine and wild-type strains with fluorophore-labeled hybridization probes. *J Clin Microbiol*. 2000;38:4315–4319.
12. Loparev VN, Argaw T, Krause PR, et al. Improved identification and differentiation of varicella-zoster virus (VZV) wild-type strains and an attenuated varicella vaccine strain using a VZV open reading frame 62-based PCR. *J Clin Microbiol*. 2000;38:3156–3160.
13. Council of State and Territorial Epidemiologists. Position Statement 99-ID-9. Vaccine preventable disease: surveillance and reporting. CSTE, 1999. Available at http://www.cste.org/ps/1999/1999-id-09.htm.
14. Watson B, Rothstein E, Bernstein H, et al. Safety and cellular and humoral immune responses of a booster dose of varicella vaccine 6 years after primary immunization. *J Infect Dis*. 1995;172:217–219.
15. Pichichero M, Voloshen T, Passador S. Kinetics of booster responses to haemophilus influenzae type B conjugate after combined diptheria-tetanus-acellcular *Pertussis haemophilus* influenzae type B vaccination in infants. *Pediatr Infect Dis J*. 1999;18:1106–1108.
16. Strebel PM, Dayan GH, Halsey NA. Measles vaccine. In: Plotkin S, Orenstein WA, Offit PA, eds. *Vaccines*. Saunders: Elsevier; 2008:353–398.
17. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:29–46.
18. Allison P. *Survival Analysis Using the SAS System: A Practical Guide*. Cary, NC: SAS Institute Inc; 1995.
19. Kleinbaum D, Kupper L, Muller K, Nizam A. *Applied Regression Analysis and Other Multivariable Methods*, 3rd ed. Pacific Grove, CA: Suxbury Press; 1998.
20. Orenstein W, Bernier R, Hinman A. Assessing vaccine efficacy in the field: further observations. *Epidemiol Rev*. 1988;10:212–241.
21. Hosmer D, Lemeshow S. *Applied Survival Analysis*. New York: John Wiley & Sons; 1999.
22. Gould PL, Leung J, Scott C, Schmid DS, Deng H, Lopez A, Chaves SS, Reynolds M, Gladden L, Harpaz R, Snow S. An outbreak of varicella in elementary school children with two-dose varicella vaccine recipients–Arkansas, 2006. *Pediatr Infect Dis J*. 2009;28:678–681.
23. Seward JF, Marin M, Vázquez M. Varicella vaccine effectiveness in the US vaccination program: a review. *J Infect Dis.* 2008 Mar 1;197(Suppl 2): S82–S89.
24. National Vaccine Advisory Committee. Standards for child and adolescent immunization practices. *Pediatrics*. 2003;112:958–963.
25. Plotkin S, Orenstein WA, Offit PA. *Vaccines*, 5th ed: Saunders: Elsevier; 2008.
26. Chaves SS, Haber P, Walton K, et al. Safety of varicella vaccine after licensure in the United States: experience from reports to the vaccine adverse event reporting system, 1995–2005. *J Infect Dis*. 2008;197(suppl 2): S170–S177.
27. Galea SA, Sweet A, Beninger P, et al. The safety profile of varicella vaccine: a 10-year review. *J Infect Dis*. 2008;197(suppl 2):S165–S169.
28. Ngai AL, Staehle BO, Kuter BJ, et al. Safety and immunogenicity of one vs. two injections of Oka/Merck varicella vaccine in healthy children. *Pediatr Infect Dis J*. 1996;15:49–54.