HHS Public Access

Author manuscript

Pediatrics. Author manuscript; available in PMC 2019 March 26.

Published in final edited form as:

Pediatrics. 2017 March ; 139(3): . doi:10.1542/peds.2016-2536.

Safety of Second-Dose Single-Antigen Varicella Vaccine

John R. Su, MD, PhD, MPH[a], **Zanie Leroy, MD, MPH**[b], **Paige W. Lewis, MSPH**[a], **Penina Haber, MPH**[a], **Mona Marin, MD**[c], **Jessica Leung, MPH**[c], **Emily Jane Woo, MD, MPH**[d], and **Tom T. Shimabukuro, MD, MPH, MBA**[a]

[a]Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Disease

[b]School Health Branch, Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion

[c]Epidemiology Branch, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

[d]Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Springs, MD

Abstract

BACKGROUND AND OBJECTIVE: In 2006, routine 2-dose varicella vaccination for children was recommended to improve control of varicella. We assessed the safety of second-dose varicella vaccination.

METHODS: We identified second-dose single-antigen varicella vaccine reports in the Vaccine Adverse Event Reporting System during 2006 to 2014 among children aged 4 to 18 years. We analyzed reports by age group (4–6 and 7–18 years), sex, serious or nonserious status, most common adverse events (AEs), and whether other vaccines were administered concomitantly with varicella vaccine. We reviewed serious reports of selected AEs and conducted empirical Bayesian data mining to detect disproportional reporting of AEs.

RESULTS: We identified 14 641 Vaccine Adverse Event Reporting System reports after second-dose varicella vaccination, with 494 (3%) classified as serious. Among nonserious reports, injection site reactions were most common (48% of children aged 4–6 years, 38% of children aged 7–18 years). The most common AEs among serious reports were pyrexia (31%) for children aged

Address correspondence to John R. Su, MD, PhD, MPH, Immunization Safety Office, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS D-26, Atlanta, GA 30333. ezu2@cdc.gov.

Dr Su conceptualized and performed the later descriptive analysis and interpretation of data, and drafted the initial manuscript; Dr Leroy conceptualized and performed the preliminary descriptive analysis and interpretation of data; Ms Lewis performed the query and retrieval of data from the Vaccine Adverse Event Reporting System database; Ms Haber assisted in conceptualization of the descriptive analysis and interpretation of data; Dr Marin and Ms Leung assisted in conceptualization of the descriptive analysis and interpretation of data, and provided expertise on the epidemiology of varicella and the varicella vaccination program; Dr Woo performed and interpreted the disproportionality analysis, and assisted with the descriptive analysis and interpretation of data; Dr Shimabukuro assisted in conceptualization of both preliminary and later descriptive analyses and interpretation of data; and all authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

4 to 6 years and headache (28%) and vomiting (27%) for children aged 7 to 18 years. Serious reports of selected AEs included anaphylaxis (83), meningitis (5), encephalitis (16), cellulitis (52), varicella (6), herpes zoster (6), and deaths (7). One immunosuppressed adolescent was reported with vaccine-strain herpes zoster. Only previously known AEs were reported more frequently after second-dose varicella vaccination compared with other vaccines.

CONCLUSIONS: We identified no new or unexpected safety concerns for second-dose varicella vaccination. Robust safety monitoring remains an important component of the national varicella vaccination program.

In 1995, the US Food and Drug Administration licensed live attenuated varicella vaccine and approved its use in persons aged ≥12 months to prevent varicella [1]; the Advisory Committee on Immunization Practices subsequently recommended routine childhood administration of a single dose of varicella vaccine. After implementation of this recommendation, substantial declines in cases, hospitalizations, and deaths related to varicella were observed in the United States. [2–5] However, outbreaks of varicella continued, despite routine 1-dose vaccination. [6] In 2006, the Advisory Committee for Immunization Practices recommended a routine 2-dose childhood schedule for varicella vaccination, with the first dose given at ages 12 to 15 months, a second dose at ages 4 to 6 years, and “catch-up” 2-dose vaccination for other persons without evidence of immunity. [7]

Available data indicate that single-dose varicella vaccination is safe and well tolerated. In a prelicensure clinical trial, injection site reactions were common, but mild and self-limited.[8] During 1995 through 2005, the most commonly reported adverse events (AEs) to the Vaccine Adverse Events Reporting System (VAERS) were fever, rash, and injection site reactions. [9] In a clinical trial comparing 1 vs 2 doses of varicella vaccine, no serious AEs related to vaccination were reported. [10]

Limited published data exist on the safety of second-dose varicella vaccination in children after implementation of the 2006 recommendation. To address this need, we analyzed reports after the second dose of single-antigen varicella vaccine that were submitted to VAERS from 2006 through 2014 in children aged 4 to 18 years.

METHODS

Data Source

VAERS is a national spontaneous reporting system for monitoring AEs that occur after receiving US-licensed vaccines.[11] VAERS accepts reports from health care providers, vaccine manufacturers, vaccine recipients, and others; data collected include signs and symptoms that are coded by using Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs).[12] MedDRA PTs are not medically confirmed diagnoses and a VAERS report may be assigned >1 MedDRA PT. Reports are classified as serious based on the Code of Federal Regulations if 1 or more of the following is reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability. [13] Because of these criteria, reported signs and symptoms that are clinically severe do not necessarily mean a report will be classified as a serious report. For serious reports, additional information is routinely requested from a variety of sources (eg, the reporter, care

providers), including medical records. Serious reports from manufacturers typically do not provide medical records to VAERS personnel (manufacturers review such records before reporting to VAERS). For nonmanufacturer serious reports, medical records are routinely requested and made available to VAERS personnel.

Descriptive Analysis

We searched the VAERS database for reports after single-antigen varicella vaccination in children aged 4 to 18 years who were vaccinated in the United States from July 1, 2006, through December 31, 2014 (among reports received by Centers for Disease Control and Prevention through June 30, 2015). We intended to capture reports of children receiving the routinely recommended second dose (ie, aged 4–6 years) and children receiving a "catch-up" second dose (ie, aged 7–18 years). Because accurate reporting of dose number (first or second) is inconsistently reported to VAERS and is therefore of limited value, we were compelled to use age range (4–18 years) as a surrogate marker of second-dose varicella vaccination. We excluded reports that were foreign; involved combination measles, mumps, rubella, and varicella vaccine; explicitly indicated first-dose varicella vaccine; or were missing age. The combination measles, mumps, rubella, and varicella vaccine was considered a different enough product to be beyond the scope of this analysis, particularly given its association with febrile seizure, an AE not associated with first-dose varicella vaccine. [14,15] We analyzed reports by age group (aged 4–6 years and 7–18 years), sex, serious or nonserious status, the most common MedDRA PTs, and whether other vaccines were given concomitantly with varicella vaccine. For simplicity, the MedDRA PTs "injection site erythema," "injection site swelling," "injection site warmth," "injection site pain," "injection site induration," and "injection site pruritus" were consolidated under the single term "injection site reactions."

Review of Prespecified Conditions

Centers for Disease Control and Prevention physicians (J.S. and Z.L.) reviewed serious reports and their associated available medical records for the following prespecified conditions (selected because of clinical significance [9,16]): anaphylaxis, meningitis, encephalitis, cellulitis, varicella, herpes zoster (HZ), and death (Table 1). The Brighton Collaboration case definition was applied to reports of anaphylaxis (Table 5).[17] (Brighton Collaboration case definitions are frequently used in pharmacovigilance and include numerical categories to describe diagnostic certainty.)

Disproportionality Analysis

We used empirical Bayesian (EB) data mining to identify AEs that were reported more frequently than expected after the second dose of varicella vaccine (compared with other vaccines) in VAERS, adjusting for age, sex, and the year in which reports were received.[18] By evaluating each AE after each vaccine (a vaccine-AE pair) throughout VAERS, data mining can identify vaccine-AE pairs that are reported more (or less) frequently than expected. We used published criteria to identify AEs that were reported at least twice as frequently as would be expected after varicella vaccine (ie, lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05] >2). [19]

RESULTS

Descriptive Analysis

From July 1, 2006, through December 31, 2014, we identified 14 641 reports received by VAERS involving second-dose varicella vaccination; 494 (3%) were serious (Table 2). The percentage of serious reports was similar regardless of age group or if other vaccines were administered concomitantly. Other vaccines were given concomitantly with varicella vaccine in 89% of reports among children aged 4 to 6 years, and 69% among children aged 7 to 18 years. Among children aged 4 to 6 years, the vaccines most commonly given with varicella vaccine were combination measles-mumps-rubella vaccine (MMR) (n = 5096, 86%) and combination diphtheria, tetanus toxoid, and acellular pertussis, either alone or as a combination with inactivated polio vaccine (n = 4954, 84%). Among children aged 7 to 18 years, the vaccines most commonly given with varicella vaccine were combination tetanus toxoid, diphtheria, and acellular pertussis (n = 2749, 50%) and meningococcal conjugate vaccine (n = 2639, 48%); in 1789 (33%) reports, varicella; combination tetanus toxoid, diphtheria, and acellular pertussis vaccine; and meningococcal conjugate vaccines were all administered concomitantly.

Among children aged 4 to 6 years, nonserious reports of AEs after second-dose varicella vaccination most commonly reported injection site reactions (n = 3102, 48%) and erythema (n = 953, 15%) (Table 3); similarly, among children aged 7 to 18 years, injection site reactions (n = 2919, 38%) and erythema (n = 1589, 21%) were most commonly reported (Table 4). For serious reports of AEs after second-dose varicella vaccination, the most commonly reported AEs among children aged 4 to 6 years were pyrexia (n = 78, 31%) and injection site reactions (n = 63, 25%); among children aged 7 to 18 years, headache (n = 67, 28%) and vomiting (n = 65, 27%) were most commonly reported.

Review of Serious Reports for Prespecified Conditions

Anaphylaxis—We identified 83 serious reports of anaphylaxis after second-dose varicella vaccination; other vaccines were administered concomitantly with varicella vaccine in 69 (83%) of these reports. Fifty-eight reports (52 with medical records available) described children aged 4 to 6 years; 39 (67%) met Brighton Level 1 criteria (the highest level of diagnostic certainty), 13 (22%) met Brighton Level 2, 1 (2%) met Brighton Level 3, and 5 (9%) did not meet the Brighton case definition (which is summarized in Table 5). Twenty-five reports (22 with medical records available) described children aged 7 to 18 years; 13 (52%) met Brighton Level 1 criteria, 9 (36%) met Brighton Level 2, 0 (0%) met Brighton Level 3, and 3 (12%) did not meet the Brighton case definition. Past medical histories of anaphylaxis, asthma, atopic dermatitis, or allergies to eggs and/or medications were noted in 29 (50%) reports for children aged 4 to 6 years; 4 of these 29 reports described a history of anaphylaxis (2 of whom experienced anaphylaxis after vaccines: 1 after MMR, 1 after influenza vaccine [type unspecified]). Of the 10 (40%) reports for children aged 7 to 18 years with such histories, 4 had a history of anaphylaxis: 2 after MMR, 1 after influenza vaccine (type unspecified), and 1 after products containing gelatin, including vaccines (types not available for review). No report described a patient with a positive rechallenge (eg,

experiencing anaphylaxis after receiving a vaccine, then receiving the same vaccine and subsequently experiencing anaphylaxis again).

Regardless of age group or other concomitantly administered vaccines, median time to onset was 5 to 10 minutes after vaccination. None of the reports described children with a history of anaphylactic reaction after a previous dose of varicella vaccine.

Meningitis and Encephalitis—We identified 5 serious reports of meningitis (4 with medical records available) after second-dose varicella vaccination among 5 children aged 4, 5 (2 children), 14, and 15 years. Among the children aged 4 years and 5 years (2 children), median time from vaccination to onset of meningitis was 1 day (range 1–7 days); for the children aged 14 and 15 years, time from vaccination to onset of meningitis was 15 days and 6 days, respectively. None of the meningitis reports described laboratory evidence of varicella-zoster virus (VZV) (eg, by serologic testing, polymerase chain reaction (PCR), or viral culture), and all were based on physician diagnosis.

We identified 16 serious reports of encephalitis after second-dose varicella vaccination, 6 among children aged 4 to 6 years and 10 among children aged 7 to 18 years; medical records were available for all 16 reports. Median reported onset was 6 days (range: 0–17 days) after vaccination among children aged 4 to 6 years, and 12 days (range: 0 to 63 days) after vaccination among children aged 7 to 18 years. No reports of encephalitis described laboratory evidence of VZV; diagnoses were based on imaging studies and physician diagnosis. Five reports described acute demyelinating encephalomyelitis (ADEM) diagnosed by magnetic resonance imaging.

Cellulitis—We identified 83 serious reports of cellulitis after second-dose varicella vaccination; 52 reports (46 with medical records available) described cellulitis on the limb on which the varicella vaccine was administered. For these 52 reports, median time from vaccination to onset was the day after vaccination (range 0–5 days), regardless of age group or whether varicella vaccine was administered alone or with other vaccines. Site of varicella vaccination was available for 47 of 52 reports, and included the left arm (15), right arm (17), left thigh (10), and right thigh (5). Of 36 children who received varicella vaccine concomitantly with other vaccines, 31 (86%) received varicella vaccine and at least 1 other vaccine in the same limb.

Varicella—We identified 6 serious reports of varicella disease after second-dose varicella vaccination in children aged 7, 11, 16, and 18 (3 children) years (medical records available for 5 reports). Median time to onset was 21 days (range 17–51 days) after vaccination. Three children were diagnosed by PCR (1 child had wild-type VZV; genotyping results were not available for the other 2 children). Of these 6 children, 3 were immunocompromised when diagnosed (for whom time to onset ranged from 22–51 days after vaccination): 1 child had congenital HIV infection, with a CD4 count of 6 and a viral load >90 000 copies/mL; another had juvenile rheumatoid arthritis and was taking anakinra, leflunomide, methotrexate, and thalidomide at the time of diagnosis; and the third had Crohn’s disease and was taking methotrexate and prednisone at the time of diagnosis.

HZ—We identified 6 serious reports of HZ (medical records available for 3 reports) after second-dose varicella vaccination in children aged 10, 13, 14, 15, and 16 (2 children) years; the children aged 16 years were reported with both varicella and HZ, but were diagnosed with disseminated HZ. Onset ranged from 10 days to 7 years after vaccination. Five children were VZV-positive by PCR, with genotyping data available for 1 child: a girl aged 15 years with a history of dermatomyositis, who began mycophenolate and prednisone 3 weeks before onset of HZ, who had vaccine-strain VZV.

Deaths—We identified 7 reported deaths after second-dose varicella vaccination (Table 2). Ages ranged from 4 to 18 years. The median time from vaccination to death was 2 days (range <1–22 days). Cause of death from autopsy reports and/or death certificates were available for 6 reports: asphyxiation, febrile seizure, accidental drowning, influenza B sepsis, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura secondary to Shiga toxin (+) *Escherichia coli*, and viral myocarditis. Significant chronic medical problems were common among these children, such as a history of congenital heart malformations and seizure disorder. No deaths were attributed to wild-type or live-attenuated (vaccine-strain) VZV.

Disproportionality Analysis

EB data mining revealed an EB05>2 for the following MedDRA PTs, indicating that they were reported at least twice as frequently for varicella vaccine compared with other vaccines: “varicella post vaccine,” “varicella,” and “rash, vesicular.”

DISCUSSION

Varicella vaccination has been a safe and effective tool in reducing illness and death in the United States from varicella. [2–4] Serious reports to VAERS of AEs after varicella vaccination are rare, with 5% of reports after the first dose,[9] and 3% of reports after the second dose (in this analysis) being serious. The proportion of serious reports, including prespecified AEs in our analysis, were similar for both children aged 4 to 6 years (receiving their second dose on schedule) and aged 7 to 18 years (receiving a catch-up dose). The data here are reassuring: commonly reported AEs (eg, injection site reactions, pyrexia) were previously described in postlicensure monitoring, [9] and no unexpected safety concerns were identified. The only AEs reported more frequently after second-dose varicella vaccination (compared with other vaccines) were known, previously characterized AEs of varicella vaccination, and are listed on the product package insert or in other guidance. [1,16]

Most (89%) serious reports of anaphylaxis met either Brighton Level 1 or 2 criteria, indicating good evidence for the diagnoses of anaphylaxis. [17] Anaphylaxis has been reported with varicella vaccine previously. [1,20,21] In a 2011 report on vaccine AEs, the Institute of Medicine concluded that varicella vaccine can cause anaphylaxis rarely, [16] a conclusion supported by the small proportion of reported anaphylaxis here (110 reports, or 0.75%).

Meningitis after varicella vaccination (either from wild-type or vaccine-strain VZV) has been reported rarely. [9,22] In our review, no serious reports of meningitis after second-dose varicella vaccination could be conclusively attributed to VZV, and meningitis after second-

dose varicella vaccination (7 cases, or 0.05% of 14 641 total reports) was reported with a frequency comparable to that after first-dose varicella vaccination (39 cases, or 0.15% of 25 306 total reports).[9] Encephalitis and demyelinating conditions like ADEM have been described after administration of vaccines, including varicella vaccine. [23–28] However, there is insufficient evidence to accept or reject a causal relationship between varicella vaccination and ADEM.[16]

Cellulitis is a known AE that occurs after varicella vaccination. [1,9] A previous report suggested that cellulitis might be dependent on where the vaccine was injected [29]; the data here showed no such association. Cellulitis and cellulitis-like reactions can be difficult to distinguish from local reactions that involve pain, swelling, and erythema.[30]

Our analysis indicated a frequency of reported varicella and HZ after second-dose vaccination comparable with first-dose vaccination. [9] Almost half of serious reports of varicella and/or HZ after second-dose varicella vaccination occurred among immunosuppressed children; only 1 had vaccine-strain VZV (the 15-year-old girl with dermatomyositis). Such infections are a known complication of administering live virus vaccines to immunosuppressed children (in whom live virus vaccines are usually contraindicated) [1,9]; guidelines exist to help inform decisions about using live virus vaccines in this population. [31] Some experts suggest use of live virus vaccines (such as varicella vaccine) be deferred until 3 months after cessation of chemotherapy, and use in HIV-positive persons might be deferred until stable antiretroviral therapy, a good CD4 response, and maximal viral suppression have been achieved.[32] The absence of serious reports of varicella and HZ among children aged 4 to 6 years in this analysis might reflect changing demographics of varicella infection in the United States. [33]

Review of deaths reported to VAERS after second-dose varicella vaccination does not suggest a causal relationship with vaccination. Six of the 7 reported deaths occurred within 6 days of vaccination; the average incubation period of VZV is 14 days. Many of the reported deaths described patients with preexisting medical conditions that possibly increased the risk of premature death. Although 1 death (boy aged 12 years) was attributed to viral myocarditis, no evidence suggested VZV was involved.

Our analysis has limitations. VAERS is a passive reporting system, and subject to limitations such as underreporting, reporting biases, inconsistent data quality and completeness, changes in reporting over time, and lack of an unvaccinated comparison group. [9,11] We used age range (4–18 years) as a surrogate measure of second-dose varicella vaccination, so some reports in this analysis are assumed to be the second dose. Without denominator data (eg, doses of second-dose varicella vaccine administered), we are unable to calculate true rates of AEs after vaccination and estimate relative risk by using VAERS data. For these and other reasons, we generally cannot determine if reported AEs to VAERS are causally related to second-dose varicella vaccination. [11] Despite these limitations, VAERS remains a valuable tool for detecting unusual or unexpected patterns of reported AEs that might indicate vaccine safety concerns requiring further evaluation. [34,35] Our analysis detected no such concerns.

CONCLUSIONS

The safety data on second-dose varicella vaccination are reassuring; reported AEs after second-dose varicella vaccination were mild, self-limiting, and similar in reported frequency to AEs after first-dose vaccination,[9] with no new or unexpected safety concerns. Routine 2-dose vaccination with varicella vaccine has further reduced morbidity from varicella, [36,37] with >140 million doses of varicella vaccine distributed through the United States as of 2013. [38] Continued robust safety monitoring remains an important component of the national varicella vaccination program.

ACKNOWLEDGMENTS

The authors thank Drs Karen R. Broder and Maria V. Cano for their contributions to and review of this analysis and manuscript.

FUNDING: No external funding.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the US Food and Drug Administration. Mention of a product or company name does not constitute endorsement by the Centers for Disease Control and Prevention or the US Food and Drug Administration.

ABBREVIATIONS

ADEM	acute demyelinating encephalomyelitis
AE	adverse event
EB	empirical Bayesian
HZ	herpes zoster
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles-mumps-rubella vaccine
PCR	polymerase chain reaction
PT	Preferred Term
VAERS	Vaccine Adverse Event Reporting System
VZV	varicella-zoster virus

REFERENCES

1. Food and Drug Administration. Varivax prescribing information Published 1995. Available at: www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142812.pdf. Accessed November 14, 2016
2. Guris D, Jumaan AO, Mascola L, et al. Changing varicella epidemiology in active surveillance sites--United States, 1995–2005. J Infect Dis 2008;197(suppl 2):S71–S75 [PubMed: 18419413]
3. Nguyen HQ, Jumaan AO, Seward JF. Decline in mortality due to varicella after implementation of varicella vaccination in the United States. N Engl J Med 2005;352(5):450–458 [PubMed: 15689583]

4. Seward JF, Watson BM, Peterson CL, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. JAMA 2002;287(5):606–611 [PubMed: 11829699]
5. Marin M, Meissner HC, Seward JF. Varicella prevention in the United States: a review of successes and challenges. Pediatrics 2008;122(3). Available at: www.pediatrics.org/cgi/content/full/122/3/e744
6. Lopez AS, 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(6). Available at: www.pediatrics.org/cgi/content/full/117/6/e1070
7. Marin M, Güris D, Chaves SS, Schmid S, Seward JF; Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2007;56(RR-4):1–40
8. Weibel RE, Neff BJ, Kuter BJ, et al. Live attenuated varicella virus vaccine. Efficacy trial in healthy children. N Engl J Med 1984;310(22):1409–1415 [PubMed: 6325909]
9. 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 [PubMed: 18419393]
10. 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(1):49–54 [PubMed: 8684876]
11. Varricchio F, Iskander J, Destefano F, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. Pediatr Infect Dis J 2004;23(4):287–294 [PubMed: 15071280]
12. MedDRA. Medical Dictionary for Regulatory Activities Available at: www.meddra.org. Accessed January 19, 2016
13. Food and Drug Administration. Code of Federal Regulations Title 21 Published 2015. Available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=310.305. Accessed January 19, 2016
14. Klein NP, Fireman B, Yih WK, et al.; Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010;126(1). Available at: www.pediatrics.org/cgi/content/full/126/1/e1
15. Rowhani-Rahbar A, Fireman B, Lewis E, et al. Effect of age on the risk of fever and seizures following immunization with measles-containing vaccines in children. JAMA Pediatr 2013;167(12):1111–1117 [PubMed: 24126936]
16. Institute of Medicine. Varicella Virus Vaccine. Adverse effects of Vaccines: Evidence and Causality Washington, DC: The National Academies Press; 2012:239–292
17. Bonhoeffer J, Kohl K, Chen R, et al.; The Brighton Collaboration. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). Vaccine 2002;21(3–4):298–302 [PubMed: 12450705]
18. DuMouchel W Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat 1999;53:177–190
19. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf 2002;25(6):381–392 [PubMed: 12071774]
20. Ozaki T, Nishimura N, Muto T, et al. Safety and immunogenicity of gelatin-free varicella vaccine in epidemiological and serological studies in Japan. Vaccine 2005;23(10):1205–1208 [PubMed: 15652662]
21. Sakaguchi M, Yamanaka T, Ikeda K, et al. IgE-mediated systemic reactions to gelatin included in the varicella vaccine. J Allergy Clin Immunol 1997;99(2):263–264 [PubMed: 9042057]
22. Pahud BA, Glaser CA, Dekker CL, Arvin AM, Schmid DS. Varicella zoster disease of the central nervous system: epidemiological, clinical, and laboratory features 10 years after the introduction of the varicella vaccine. J Infect Dis 2011;203(3):316–323 [PubMed: 21177308]

23. Centers for Disease Control and Prevention. Adverse events following vaccination Published 2015. Available at: www.cdc.gov/vaccines/pubs/pinkbook/mening.html#reactions. Accessed February 1, 2016
24. Huber S, Kappos L, Fuhr P, Wetzel S, Steck AJ. Combined acute disseminated encephalomyelitis and acute motor axonal neuropathy after vaccination for hepatitis A and infection with Campylobacter jejuni. J Neurol 1999;246(12):1204–1206 [PubMed: 10653319]
25. Joyce KA, Rees JE. Transverse myelitis after measles, mumps, and rubella vaccine. BMJ 1995;311(7002):422
26. Rosenberg GA. Meningoencephalitis following an influenza vaccination. N Engl J Med 1970;283(22):1209 [PubMed: 4394376]
27. Chouliaras G, Spoulou V, Quinlivan M, Breuer J, Theodoridou M. Vaccine-associated herpes zoster ophthalmicus [correction of opthalmicus] and encephalitis in an immunocompetent child. Pediatrics 2010;125(4). Available at: www.pediatrics.org/cgi/content/full/125/4/e969
28. Wise RP, Salive ME, Braun MM, et al. Postlicensure safety surveillance for varicella vaccine. JAMA 2000;284(10):1271–1279 [PubMed: 10979114]
29. Walter EB, Snyder MA, Clements DA, Katz SL. Large injection site reactions after a second dose of varicella vaccine. Pediatr Infect Dis J 2008;27(8):757–759 [PubMed: 18574438]
30. Lapphra K, Scheifele D. Vaccination site reaction or bacterial cellulitis? Paediatr Child Health 2009;14(4):245 [PubMed: 20357923]
31. Centers for Disease Control and Prevention. General recommendations on immunization Published 2015. Available at: www.cdc.gov/vaccines/pubs/pinkbook/genrec.html. Accessed February 2, 2016
32. Tamma P Vaccines in immunocompromised patients. Pediatr Rev 2010;31(1):38–40 [PubMed: 20048039]
33. Leung J, Lopez AS, Blostein J, et al. Impact of the US two-dose varicella vaccination program on the epidemiology of varicella outbreaks: data from nine states, 2005–2012. Pediatr Infect Dis J 2015;34(10):1105–1109 [PubMed: 26186103]
34. Centers for Disease Control and Prevention (CDC). Intussusception among recipients of rotavirus vaccine--United States, 1998–1999. MMWR Morb Mortal Wkly Rep 1999;48(27):577–581 [PubMed: 10428095]
35. Centers for Disease Control and Prevention (CDC). Withdrawal of rotavirus vaccine recommendation. MMWR Morb Mortal Wkly Rep 1999;48(43):1007 [PubMed: 10577495]
36. Leung J, Bialek SR, Marin M. Trends in varicella mortality in the United States: data from vital statistics and the national surveillance system. Hum Vaccin Immunother 2015;11(3):662–668 [PubMed: 25714052]
37. Leung J, Harpaz R. Impact of the maturing varicella vaccination program on varicella and related outcomes in the United States: 1994–2012. J Pediatric Infect Dis Soc 2016;5(4):395–402 [PubMed: 26407276]
38. Willis E, Marko A, Marin M, et al. Pregnancy registry for varicella-zoster virus-containing vaccines: 18-year summary of pregnancy outcomes. Paper presented at: IDWeek; October 8–12, 2014; Philadelphia, PA Abstract 1048

WHAT'S KNOWN ON THIS SUBJECT:

Single-dose vaccination for varicella has proven safe with no unexpected adverse events. A 2-dose vaccination schedule for varicella vaccine was recommended in 2006.

WHAT THIS ANALYSIS ADDS:

We identified no unexpected safety concerns. All adverse events reported to the Vaccine Adverse Event Reporting System after the second dose of varicella vaccine were described previously, with frequencies comparable to those occurring after the first dose of varicella vaccine.

TABLE 1

MedDRA PTs Used to Identify Prespecified Conditions

Prespecified Conditions	MedDRA PTs
Anaphylaxis	Anaphylactic shock; anaphylactic reaction; anaphylactoid reaction; anaphylactoid shock
Meningitis	Meningitis; meningism; meningitis, viral; meningitis, aseptic
Encephalitis	Encephalitis; encephalopathy; myelitis; encephalomyelitis; encephalitis post immunization; encephalitis, viral; encephalitis post varicella; meningoencephalitis, viral
Cellulitis	Cellulitis, staphylococcal; cellulitis, streptococcal; cellulitis; administration site cellulitis; injection site cellulitis; injection site necrosis; vaccination site necrosis; myositis; infective myositis; muscle abscess; gas gangrene; post procedural cellulitis; application site cellulitis; cellulitis enterococcal; cellulitis, gangrenous; cellulitis, pasteurella; soft tissue debridement
Varicella	Varicella; varicella post vaccine; varicella-zoster gastritis; varicella-zoster esophagitis; varicella-zoster pneumonia; varicella immunization; varicella virus test positive; varicella zoster virus infection
HZ	HZ; HZ, cutaneous, disseminated; HZ, disseminated; HZ infection, neurologic; HZ meningitis; HZ meningoencephalitis; HZ meningomyelitis; HZ necrotizing retinopathy; HZ oticus; HZ pharyngitis; ophthalmic HZ
Death[a]	Died

[a]Also included reports where the checkbox for “Patient died” was checked in Box 8 of the VAERS form.

TABLE 2

Characteristics of Second-Dose Varicella Vaccination Reports Submitted to VAERS, 2006–2014

Report Characteristics	4–6 y		7–18 y		All Ages, 4–18 y
	Varicella Vaccine Only, *n* (%)	Varicella + Other Vaccines, *n* (%)	Varicella Vaccine Only, *n* (%)	Varicella + Other Vaccines, *n* (%)	Total Reports, *n* (%)
Total reports	758	5907	2473	5503	14 641
Serious[a]	27 (4)	223 (4)	61 (2)	183 (3)	494 (3)
Boys[b]	324 (43)	2956 (50)	1040 (42)	2262 (41)	6582 (45)
Girls[b]	341 (45)	2884 (49)	1375 (56)	3198 (58)	7798 (53)
Prespecified conditions[c]					
Anaphylaxis	8 (1)	66 (1)	10 (<1)	26 (<1)	110 (1)
Meningitis	0 (0)	5 (<1)	0 (0)	2 (<1)	7 (<1)
Encephalitis	0 (0)	8 (<1)	1 (<1)	9 (<1)	18 (<1)
Cellulitis	24 (3)	334 (6)	161 (7)	209 (4)	728 (5)
Varicella	117 (15)	87 (1)	107 (4)	79 (1)	390 (3)
HZ	15 (2)	21 (<1)	34 (1)	37 (1)	107 (1)
Death	0 (0)	3 (<1)	2 (<1)	2 (<1)	7 (<1)

[a]Includes death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.

[b]Percentage of unknown sex ranged from 1% to 12%.

[c]Second-dose varicella vaccination reports of prespecified conditions classified as serious: anaphylaxis (*n* = 83, 75%), meningitis (*n* = 5, 71%), encephalitis (*n* = 16, 89%), cellulitis (*n* = 83, 11%), varicella (*n* = 6, 2%), HZ (*n* = 6, 6%); all deaths are serious reports. Of 83 serious reports of cellulitis, 52 (63%) reports were of cellulitis on the same limb on which the varicella vaccine was administered.

TABLE 3

Most Commonly Reported AEs Among Children Aged 4 to 6 Years After Second-Dose Varicella Vaccination in VAERS, 2006–2014

Severity of Report and AE Reported	Varicella Vaccine Only, *n* (%)	Varicella + Other Vaccines, *n* (%)	Total *n* (%)
Nonserious	731	5684	6415
Injection site reaction	192 (26)	2910 (51)	3102 (48)
Erythema	107 (15)	846 (15)	953 (15)
Pyrexia	60 (8)	558 (10)	618 (10)
Urticaria	42 (6)	419 (7)	461 (7)
Skin warm	36 (5)	351 (6)	387 (6)
Serious[a]	27	223	250
Pyrexia	4 (15)	74 (33)	78 (31)
Injection site reaction	4 (15)	59 (26)	63 (25)
Anaphylactic reaction	7 (26)	51 (23)	58 (25)
Cough	3 (11)	53 (24)	56 (22)
Vomiting	3 (11)	54 (24)	57(23)
Leukocytosis	2 (7)	54 (24)	56 (22)

A single report may contain more than 1 AE (ie, not mutually exclusive).

[a]Includes death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.

TABLE 4

Most Commonly Reported AEs Among Children Aged 7 to 18 Years After Second-Dose Varicella Vaccination in VAERS, 2006–2014

Severity of Report and AE Reported	Varicella Vaccine Only, *n* (%)	Varicella + Other Vaccines, *n* (%)	Total *n* (%)
Nonserious	2412	5320	7732
Injection site reaction	1060 (44)	1859 (35)	2919 (38)
Erythema	590 (25)	999 (19)	1589 (21)
Skin warm	212 (9)	429 (8)	641 (8)
Edema, peripheral	147 (6)	417 (8)	564 (7)
Pyrexia	142 (6)	412 (8)	554 (7)
Serious[a]	61	183	244
Headache	11 (18)	56 (31)	67 (28)
Vomiting	13 (21)	52 (28)	65 (27)
Nausea	7 (12)	52 (28)	59 (24)
Pyrexia	11 (18)	49 (27)	60 (25)
Leukocytosis	6 (10)	37 (20)	43 (18)

A single report may contain more than 1 AE (ie, not mutually exclusive).

[a]Includes death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.

TABLE 5

Summary of Brighton Criteria Case Definitions for Anaphylaxis[17]

For all levels of diagnostic certainty: anaphylaxis is a clinical syndrome characterized by sudden onset, rapid progression of signs and symptoms, AND involving multiple (≥2) organ systems, as follows:

Level 1 of diagnostic certainty

- ≥1 major dermatological AND
- ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion

Level 2 of diagnostic certainty

- ≥1 major cardiovascular AND ≥1 major respiratory criterion

OR

- ≥1 major cardiovascular OR respiratory criterion AND

1. ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems)

OR

2. (≥1 major dermatologic) AND (≥1 minor cardiovascular AND/OR minor respiratory criterion)

Level 3 of diagnostic certainty

- ≥1 minor cardiovascular OR respiratory criterion

AND

- ≥1 minor criterion from each of ≥2 different systems/categories

The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.