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Safety Surveillance of Varicella Vaccines in the Vaccine Adverse Event Reporting System, United States, 2006–2020

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Abstract

Background.—The Vaccine Adverse Event Reporting System (VAERS) is the United States national passive vaccine safety surveillance system. We updated the data on the safety of single-antigen varicella vaccine (VAR) and assessed the safety of combination measles, mumps, rubella, and varicella vaccine (MMRV) licensed in the United States using VAERS data.

Methods.—US VAERS reports received after administration of VAR and MMRV during 2006–2020 were identified. Reports were analyzed by vaccine type, age, seriousness, most common adverse events (AEs), and concomitant vaccines. We reviewed medical records of selected reports of AEs of special interest and conducted empirical Bayesian data mining to identify disproportionally reported AEs.

Results.—During 2006–2020, approximately 132.8 million VAR doses were distributed; 40 684 reports were received in VAERS (30.6/100 000 doses distributed), with 4.1% classified as serious (1.3/100 000 doses distributed). Approximately 35.5 million MMRV doses were distributed; 13 325 reports were received (37.6/100 000 doses distributed) with 3.3% classified as serious (1.3/100 000 doses distributed). The most common adverse health events after both VAR and MMRV were injection site reactions (31% and 27%), rash (28% and 20%), and fever (12% and

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Supplementary Data

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14%), respectively. Vaccination errors accounted for 23% of reports after VAR administration and 41% after MMRV administration, but ≥95% of them did not describe an adverse health event. AEs associated with evidence of vaccine strain varicella-zoster virus (vVZV) infection included meningitis, encephalitis, herpes zoster, and 6 deaths (all in immunocompromised persons with contraindications for vaccination). No new or unexpected AE was disproportionally reported.

Conclusions.—No new or unexpected safety findings were detected for VAR and MMRV given as recommended, reinforcing the favorable safety profiles of these vaccines. Providers should obtain specimens for viral testing and strain-typing for serious AEs if they consider vVZV as the possible causative agent.

Keywords

epidemiology; postmarketing; surveillance; varicella vaccine; vaccine safety

The routine childhood varicella vaccination program in the United States was initiated in 1995 with 1 dose recommended for children aged 12–18 months and older children offered catch up vaccination, and 2 doses recommended for susceptible persons aged ≥13 years in close contact with persons at high risk for serious complications [1]. The policy was updated in 2007 to recommend a routine 2-dose schedule for children at ages 12–15 months and 4–6 years, and a 2-dose catch-up for persons who lacked evidence of varicella immunity [1]. Two varicella vaccines have been used in the United States: a single-antigen vaccine (VAR) since 1995 for persons aged ≥12 months, and a combination measles, mumps, rubella, and varicella vaccine (MMRV) since 2005 for children aged 12 months–12 years. Both vaccines contain live attenuated varicella-zoster virus (vVZV) and are contraindicated in severely immunocompromised persons and pregnant women [1]. Varicella vaccination has substantially reduced varicella disease burden in the United States [2, 3].

The safety of a single dose of VAR was examined in the Vaccine Adverse Event Reporting System (VAERS) during the first 10 years of the program, and the safety of a second dose was evaluated among persons aged 4–18 years during the first 8 years of the 2-dose program [4–6]. These studies, along with others using the manufacturer's postmarketing safety surveillance [7–9] have demonstrated a favorable safety profile for VAR, with most adverse events (AEs) being nonserious [10]. Serious AEs (SAEs) associated with vVZV have been reported but are rare [4, 5, 9]. Studies have confirmed an association between a first dose of MMRV and febrile seizures in young children [11, 12]. We updated the analysis of VAERS reports for VAR and provide a first analysis for MMRV through 2020.

METHODS

Data Source

VAERS is the US national passive vaccine safety surveillance system coadministered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) [13]. It receives spontaneous reports of AEs following vaccination from vaccine manufacturers, health care providers, vaccine recipients, and others. Vaccination errors, whether or not describing an adverse health event, may also be reported [14]. Since 2007, reported AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA)

Preferred Terms (PTs), an internationally standardized terminology [15]. A PT is a distinct descriptor for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical, social, or family history characteristic. MedDRA PTs are not medically confirmed diagnoses, and a VAERS report may be assigned ≥1 PT. Reports are classified as serious (death, life-threatening illness, hospitalization or prolongation of existing hospitalization, permanent disability, or occurrence of a congenital anomaly) or nonserious [10]. For serious reports, medical records are routinely requested and reviewed.

Descriptive Analysis

US VAERS reports received after administration of VAR or MMRV during 2006–2020 were identified. Reports were summarized by vaccine type, age, seriousness, most common AEs, and concomitant vaccines. Similar to previous safety assessments, 2 composite categories were created by consolidating relevant PTs for injection site signs and symptoms [6] (Supplementary Material) and vaccination errors [16]. Reporting rates were calculated using doses of VAR and MMRV distributed in the United States during the study period as the denominator (CDC unpublished data).

Review of Adverse Events of Special Interest

We selected adverse events of special interest (AESI), a subset of all VAERS reports following VAR or MMRV, based on previously reported association with live vaccines and biological plausibility: death, meningitis, encephalitis, herpes zoster (HZ), and anaphylaxis. CDC co-authors (PLM, MM, JL) reviewed all reports and available medical records for AESI except for HZ, for which only serious reports (as defined above) were reviewed (there is agreement among experts that vVZV can cause HZ therefore we focused on serious reports only). Cause of death was obtained from the autopsy report, death certificate, or medical records. If testing was done, VZV was detected by polymerase chain reaction (PCR) or direct fluorescence assay (DFA), and strain-typing to distinguish vVZV from wild-type VZV was conducted using PCR.

Data Mining

We applied empirical Bayesian (EB) data mining methods [17] to identify MedDRA PTs that were disproportionally reported (ie, reported more frequently than expected compared with other vaccines in VAERS) after the administration of VAR or MMRV, adjusting for age, sex, and year of reporting. We used the published criterion of EB05 ≥ 2.0, where EB05 represents the lower bound of the 90% confidence interval surrounding the EB geometric mean [18]. An EB05 ≥ 2.0 indicates that a particular vaccine-event pair occurs at least twice as often as expected than by chance alone. An elevated EB05 value does not imply a causal relationship but can be used as a threshold for further assessment of an event.

Because VAERS is a routine surveillance program designed to improve an immunization program, analysis of VAERS data was confirmed by CDC review to be nonresearch under the Common Rule in accordance with institutional procedures; therefore, this work was not subject to Institutional Review Board evaluation and informed consent requirements.

RESULTS

Descriptive Analysis

There were 132 763 998 VAR doses distributed in the United States during 2006–2020, with 40 684 AE reports received in VAERS (30.6/100 000 doses distributed) (Figure 1). Of all VAR reports, 1664 (4.1%) were classified as serious (1.3/100 000 doses distributed). There were 35 460 647 MMRV doses distributed during 2006–2020; 13 325 AE reports (37.6/100 000 doses distributed), including 445 (3.3%) SAE reports (1.3/100 000 doses distributed), were received in VAERS.

Among reports with age information (88% for VAR and 80% for MMRV), most were in children aged 1–3 years (11 443; 32.1%) for VAR and 4–6 years (6391; 60.1%) for MMRV; 14.8% (5260) of reports after VAR administration were in adults aged ≥18 years (Table 1). A small percentage of reports involved ages outside the licensed indications: 1.0% in children aged <12 months for each VAR and MMRV and 6.6% in persons aged ≥13 years for MMRV. Most reports involved concomitant administration with other vaccines, 65% and 61% for VAR and MMRV, respectively.

The most commonly reported AEs were injection site reactions (31%), rash (28%), vaccination errors (23%), fever (12%), and pruritus/urticaria (9%) after VAR and vaccination errors (41%), injection site reactions (27%), rash (20%), fever (14%), and pruritus/urticaria (7%) after MMRV (Table 2). Most (≥95%) reports for these common AEs were nonserious, except fever, for which 14% (708) of VAR and 12% (217) of MMRV reports were serious. However, in 99.7% and 100% of VAR and MMRV reports, respectively, fever was accompanied by at least 1 other sign or symptom. While vaccination error was the third most common AE reported after VAR at 23% (9482), it was the most common AE reported after MMRV at 41% (5470). The most common vaccination errors for VAR were incorrect storage of vaccine (5687; 59.9%), wrong vaccine administered (1127; 11.9%), and expired vaccine administered (772; 8.1%); and incorrect storage (3040; 55.6%), extra dose administered (651; 11.9%), and wrong vaccine administered (518; 9.5%) for MMRV. Over 95% of vaccination error reports did not describe an adverse health event. Most of the few adverse health events among vaccination errors were fever and nonspecific systemic reactions (Supplementary Table 1). For AESI, the reporting rate varied from 0.02/100 000 doses for meningitis to 0.34/100 000 doses for HZ; for anaphylaxis it was 0.15/100 000 doses and 0.18/100 000 doses after VAR and MMRV, respectively.

Clinical Review of AESI

Deaths—During 2006–2020, 78 deaths were reported after VAR administration. The median interval between vaccination and death was 4 days (range, <1 day–9.7 years). The most common fatal events reported were sudden infant death syndrome (SIDS) (n = 16), and neurologic (n = 14) and respiratory (n = 13) conditions (Table 3).

Complications due to vVZV were considered the cause of death in 6 reports, all previously published [9, 19–23]; 3 were in children (aged 13 months, 15 months, and 15 years) and 3 in adults (aged 36, 47, and 67 years). Five received 1 dose of VAR, and median time from vaccination to illness onset was 20 days (range, 16–61 days). A sixth decedent

reportedly had received 2 doses of VAR; illness onset was estimated at least 6 months after the second dose. Five decedents had immunocompromising medical conditions and/or were taking immunosuppressive medications (non-Hodgkin lymphoma, chronic leukopenia, and chemotherapy; end-stage renal disease and lupus; hypomorphic RAG2 deficiency and high-dose corticosteroids; focal segmental glomerulosclerosis and immunosuppressive therapy; HIV with severe immunocompromise). The sixth decedent (age 15 months) did not have a diagnosis of primary immune deficiency, but her history of failure to thrive and repeated prior hospitalizations were suggestive of a primary or acquired immune deficiency [19]. Causes of death included multiorgan system failure (4, 1 had HZ [20]), autoimmune hemolytic anemia (1), and disseminated varicella (1, likely HZ). An additional report of a 13-month-old child diagnosed with severe combined immunodeficiency and adenosine deaminase deficiency indicated bronchial lavage fluid containing vVZV, measles, mumps, and rubella vaccine viruses; the cause of death was left intracerebral hemorrhage and cerebellar herniation [24].

Five additional death reports after VAR administration (4 in children aged 4–17 years, 1 in an adult aged 42 years) indicated positive VZV PCR without strain information with a median interval between vaccination and illness onset of 277 days (range, 60 days to 10 years); all decedents also were immunocompromised (acute lymphocytic leukemia; juvenile idiopathic arthritis on prednisolone; systemic lupus with nephritis and end-stage renal disease on chronic immunosuppressive medication; IgA nephropathy on immunosuppressive medication; and Hodgkin lymphoma). Lastly, 1 report in an adult aged 41 years with lupus and immunosuppressive treatment indicated disseminated varicella and pneumonia 20 days after the first dose; no VZV testing was reported.

There were 18 death reports after MMRV administration, all in children aged 1–6 years. The median interval between vaccination and death was 4 days (range, <1–100 days). The most common causes of death were neurologic conditions (4) and SIDS and cardiac conditions (3 each) (Table 3). No reports identified the presence of VZV or measles, mumps, or rubella vaccine viruses.

Meningitis—Twenty-eight reports after VAR administration had meningitis PT. The median age of patients was 11 years (range, 1–48 years) and median time from vaccination to symptom onset was 7 days (range, <1 day to 12.6 years). Among the 28 patients, 17 had a diagnosis of aseptic or viral meningitis, 6 meningoencephalitis, and the rest were status epilepticus, acute demyelinating encephalomyelitis (ADEM), transverse myelitis, acute cerebellar ataxia, and viral versus bacterial meningitis. In a report of acute meningitis, death occurred due to myxoid degeneration of the mitral valve (Table 3).

vVZV was detected in cerebrospinal fluid (CSF) in 4 patients; 3 were immunocompetent children with symptom onset years after vaccination: an 11 year old with meningitis 6.5 years after the second dose (no skin rash), an 11 year old with meningitis 8 years after the second dose (no rash reported, aphthous ulcer in mouth), and a 16 year old with a history of epilepsy who developed HZ of the left leg and meningoencephalitis 10 years after the second dose. The fourth, a 31-year-old HIV-positive patient, developed generalized vesicular rash, meningitis, and necrotizing retinitis 1 month after the first dose.

Additionally, VZV in CSF without strain information was indicated in 2 reports of immunocompetent patients: a 16 year old who developed HZ of the leg with meningitis 11 years after the second dose, and a 19 year old who developed meningitis, and faint scattered vesicles on the trunk and extremities 3 weeks after VAR. Providers attributed these rashes to vVZV based on the absence of a varicella history.

Two additional meningoencephalitis cases after VAR that did not have meningitis or encephalitis PTs were identified during the review of HZ reports: a 12-year-old immunocompetent patient with vVZV detected in CSF, and a 15 year old with lupus nephritis and end-stage renal disease with VZV (not strain-typed) detected in CSF who died of meningoencephalitis (Table 3).

Seven reports coded as meningitis after MMRV were received, 5 in children aged 1–4 years and the other 2 in an 11 and a 34 year old. Symptom onset ranged from 1 to 19 days postvaccination. Four had a diagnosis of meningitis (aseptic meningitis, “meningitis-like symptoms,” “signs of meningitis with altered neurologic status”), in 2 reports the diagnoses were transverse myelitis and complex febrile seizures; 1 report did not have a diagnosis listed.

Encephalitis—Eighty reports after VAR administration had encephalitis PT. The median age of patients was 1 year (range, 1–79 years) and median time from vaccination to symptom onset was 9 days (range, <1 day–10.6 years). Among the 80 reports, 5 deaths were reported (Table 3), all in persons with underlying conditions (congenital, immunocompromising). Causes of death included cerebral edema; sepsis and peritonitis secondary to disseminated vVZV infection; septic shock due to gram-positive bacteria; autoimmune hemolytic anemia [21]; and influenza B sepsis and encephalitis. Diagnoses in the remaining 75 reports were diverse (eg, encephalitis, meningoencephalitis, including 1 with vVZV [described under “Meningitis”], ataxia, ADEM, encephalopathy, encephalomyelitis, status postseizure, autistic disorder).

vVZV was detected in 1 patient, a 15-month-old child with hypogammaglobulinemia and T-cell deficiency who developed a maculopapular rash 2 weeks after vaccination, followed by 8 vesicular lesions 3 weeks after vaccination. VZV without strain information was detected in CSF in 1 patient, a 16 month old with a history of failure to thrive who had seizures 2 and 5 days after vaccination; the patient did not develop rash but progressed to encephalopathy after the last seizure which prompted a lumbar puncture.

Twenty-two reports with encephalitis PT were received after MMRV administration, all in children aged 1–7 years. The median interval from vaccination to onset was 8 days (range, <1–100 days, and 6 years in 1 report). Three reports indicated deaths, all neurologic: in 1 the cause of death was anoxic brain injury due to acute cerebellitis (laboratory studies did not find evidence of acute infection, including viral encephalitis, or autoimmune disease); the other 2 causes of death were ischemic encephalopathy and cerebral edema following multifocal brain herniation (Table 3). A 7 year old developed vesicular rash in a V1 dermatomal distribution (consistent with HZ) and meningoencephalitis 6 years after MMRV receipt; VZV, not strain-typed, was detected from a skin lesion. Diagnoses in the other

patients included ADEM, encephalitis (1 autoimmune), encephalopathy, cerebellitis with ataxia, viral infection, autism, and others.

Herpes Zoster—Of 456 reports of HZ after VAR, 39 (8.6%) were serious, of which 26 (66.7%) were in children and adolescents aged 1–17 years (median, 12 years; range, 1–80 years). Two serious reports were laboratory confirmed as wild-type VZV, 13 as vVZV, and 5 as VZV (strain unknown). Four deaths with vVZV and 1 PCR positive in CSF for VZV had HZ codes (described under "Deaths"). Upon review of records and published reports, 2 were reclassified as varicella deaths [9, 22].

Among the HZ serious reports after VAR, there were 5 reports with meningitis or meningoencephalitis (described above); 1 was reclassified as varicella according to the published report [25]. For the 4 remaining reports, HZ rash onset occurred 7–12 years after vaccination. vVZV was reported in 2 reports and VZV (not strain-typed) in 2 reports; 2 patients were immunocompetent and 2 immunocompromised.

Of 72 reports of HZ after MMRV, 5 (6.9%) were serious. The patients were aged 1, 1, 3, 9, and 41 years. One report was confirmed as vVZV and 2 as VZV (not strain-typed); of the 2 with laboratory resuts unavailable, 1 report (of a 1 year old) was unlikely to represent HZ given the early onset of symptoms (6 days postvaccination).

Anaphylaxis—Two-hundred reports after VAR were coded as anaphylaxis. The interval between vaccination and onset was <24 hours for 191 (96%) reports; of them, most (176, 92%) were in children and adolescents aged 1–17 years (median, 4 years). VAR was administered alone in 36 (19%) reports. Among 179 reports with recovery status information, in 172 (96%) the report indicated that the patient recovered from the adverse event. Brighton criteria [26] were not assessed except for the 1 death reported, previously published, which occurred in a 2-year-old male (born premature with hypoplastic left heart syndrome) 20 minutes after receipt of MMR, VAR, and influenza vaccines (Brighton level 2) [27]. The autopsy report indicated the cause of death as anaphylactic reaction following these vaccines.

For MMRV, 64 reports of anaphylaxis were identified. Onset was <24 hours after vaccination in 60 (94%); reports were in children aged 1–6 years and a 19-year-old patient. MMRV was given alone in 8 reports; among 53 patients with recovery status information, all were reported recovered from the adverse event.

Data Mining

Using empirical Bayesian methods, no disproportionate reporting was found of any clinically meaningful PT (or AE) that was unexpected. PTs disproportionately reported pertained to AEs that are already listed in the US package inserts for VAR or MMRV (Supplementary Table 2).

DISCUSSION

Our review of AEs reported to VAERS in the last 15 years after VAR and MMRV reinforces the favorable safety profile of vaccines recommended for the prevention of varicella in the United States. With approximately 132.8 million VAR doses and 35.5 million MMRV doses distributed since 2006, >95% of reports were classified as nonserious and no new or unexpected safety findings were identified. Commonly reported AEs (injection site reactions, rash, and fever, which accounted for around two-thirds of all AEs reported) were observed in the prelicensure clinical trials [28, 29] and have been previously described in postlicensure monitoring [4–6, 9]. New since the previous evaluations was the characterization of vaccination errors, in 23% and 41% of the reports received after VAR and MMRV vaccination, respectively; these errors included mainly inappropriate storage and dispensing errors and ≥95% were not accompanied by adverse health events. SAEs continue to be infrequently reported (approximately 1 report/100 000 doses); laboratory-confirmed vVZV meningitis, encephalitis, HZ with meningitis, and 6 deaths due to vVZV-related complications (in immunocompromised persons with contraindications to vaccination), have been previously reported after VAR [5, 9, 19–23].

Meningitis and encephalitis are known complications of infection with wild-type VZV and had been reported rarely from vVZV infection in vaccinated persons following VAR. For MMRV there were no reports confirming isolation of vVZV, or other vaccine-strain viruses. VAERS continued to capture a few reports of HZ with VZV meningitis/meningoencephalitis, 2 identified as vVZV in both immunocompetent and immunocompromised patients, adding to the previously reported vVZV HZ with meningitis [5]. A review of manufacturer's safety data for 1995–2017 also described HZ and meningitis with vVZV identified in CSF among immunocompetent and immunocompromised children and adolescents [9]. Some cases might be reported to both surveillance systems. Underreporting is also likely given the latency and time since vaccination, usually years. Additionally, we identified a first report of HZ and meningoencephalitis after receipt of MMRV; VZV was detected from a skin lesion but was not strain-typed. Health care providers should be aware of vVZV-associated disease of the central nervous system (CNS), with or without HZ, in both immunocompetent and immunocompromised patients, and obtain specimens for viral testing and strain-typing if vVZV is considered a possible causative agent, even years or decades postvaccination. PCR is the method of choice for laboratory confirmation of VZV and samples from skin lesions (vesicular fluid or crusts) are the preferred specimens; also, CSF in case of CNS disease. Specialized laboratories, the National VZV Laboratory at CDC, the American Public Health Laboratory Association Vaccine Preventable Diseases Reference Centers, or Columbia University VZV identification program, have the capacity to distinguish wild type from vVZV [30].

Death reports after vaccination should be interpreted with caution. The most common fatal events after VAR or MMRV were related to SIDS; the Institute of Medicine's Immunization Safety Review Committee has rejected a causal relationship between multiple simultaneous vaccines and SIDS [31]. Other causes of death included infections, congenital anomalies, cardiac disorders, and other conditions that were not vaccine-related. We identified 6 previously published deaths in which complications due to vVZV infection were considered

the cause of death [9, 19–23]. In 5 of these reports the decedents were immunocompromised based on medical conditions and/or medications and a sixth report involved a child with undiagnosed but suspected primary or acquired immune deficiency. In 5 other death reports, all involving immunocompromised patients, a positive VZV PCR was noted without reported strain-typing results. Our findings emphasize the importance of following the Advisory Committee on Immunization Practices (ACIP) recommendations to not administer varicella vaccine to severely immunocompromised patients or those taking or undergoing immunosuppressive medication or procedures [1]. Immunosuppression is also listed as a contraindication in the US package inserts for both vaccines [28, 29].

Anaphylaxis is a serious allergic reaction, which may occur rarely upon receipt of any vaccine [32, 33]. One death report from anaphylaxis occurred in a 2 year old who received several concomitant vaccines [27]. Anaphylaxis after vaccination was assessed in the Vaccine Safety Datalink but estimating the rates of individual vaccines was limited because of the small number of reports; the overall anaphylaxis rate for all vaccines combined was 1.3/million vaccine doses administered [33].

Vaccination errors accounted for a substantial proportion of reports received. Hibbs et al reported increasing numbers of vaccination errors in VAERS since 2007 [16]. VAR was the most common vaccine associated with “wrong vaccine” errors in adults primarily due to mix-ups between varicella and zoster vaccines. The high number of vaccination errors reported for MMRV may have several potential explanations: MMRV was a new vaccine that became available during the study period, requires freezer storage, and is licensed for use among children only. The general increase in vaccination error reports is believed to be multifactorial, including the change to the MedDRA coding system in VAERS in 2007 with an increase in available vaccination errors codes, increases in the size and complexity of the immunization schedule, and increased attention to storage lapses and the need to report errors [16]. Also in 2007, the Institute of Medicine published its report on medication errors [34] which may have raised awareness and stimulated reporting to VAERS. As previously described [16], most vaccination errors have not been associated with adverse health events and we confirmed this in our review of reports after VAR and MMRV administration, which found that <5% described an adverse health event.

Information about whether the vaccine was administered as a first or second dose was often missing: the highest proportion of VAR reports occurred in the age group recommended for the first dose, and for MMRV the highest proportion occurred among children aged 4–6 years recommended for the second dose. A lower number of AEs is expected after a second vaccine dose. Because 2 postlicensure studies of children aged 12–23 months reported an approximately 2-fold increased risk for febrile seizures 5–12 days after the first dose of MMRV compared with the concomitant administration of MMR and VAR [11, 12], recommendations for use of MMRV were revised in 2010 to remove the preference for the use of the combination MMRV over concomitant MMR and VAR for the first dose at ages 12–47 months and to add a personal or family history of seizure as a precaution for use of MMRV [35]. We did not identify disproportionate reporting of febrile seizures after MMRV.

Strengths of VAERS include its broad national scope, timeliness, and usefulness for detecting potential safety signals, which can be further evaluated by more robust surveillance systems using controlled epidemiological methods [14]. As a passive surveillance system, VAERS has inherent limitations requiring careful interpretation of findings based on VAERS data. These include over- or underreporting, biased reporting, and inconsistency in quality and completeness of reports [14]. VAERS generally cannot assess if a vaccine caused an AE. We did not include secondary transmission of vVZV as an AESI; a recent systematic review reported rare transmission to contacts (primarily household contacts) [36].

Our assessment of the safety of VAR and MMRV did not identify any new or unexpected safety findings. The findings are consistent with previous reviews of VAERS and show a reassuring safety profile of both US varicella vaccines when given as recommended. Varicella vaccination carries tremendous public health benefit: it has led to a >90% decline in cases, hospitalizations, and deaths, now preventing >10 500 hospitalizations and 100 deaths each year in the United States [2, 3]. The observation of vaccination errors calls for measures to prevent these errors, such as increased education and awareness of ACIP recommendations, especially regarding contraindications and precautions for immunocompromised individuals, age groups for which these vaccines are recommended, and storage requirements. Although these vaccines have been licensed in the United States for over 20 years, providers should continue to report any potential AEs to VAERS. CDC and FDA will continue to monitor AEs following varicella vaccination reported to VAERS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclaimer.

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.

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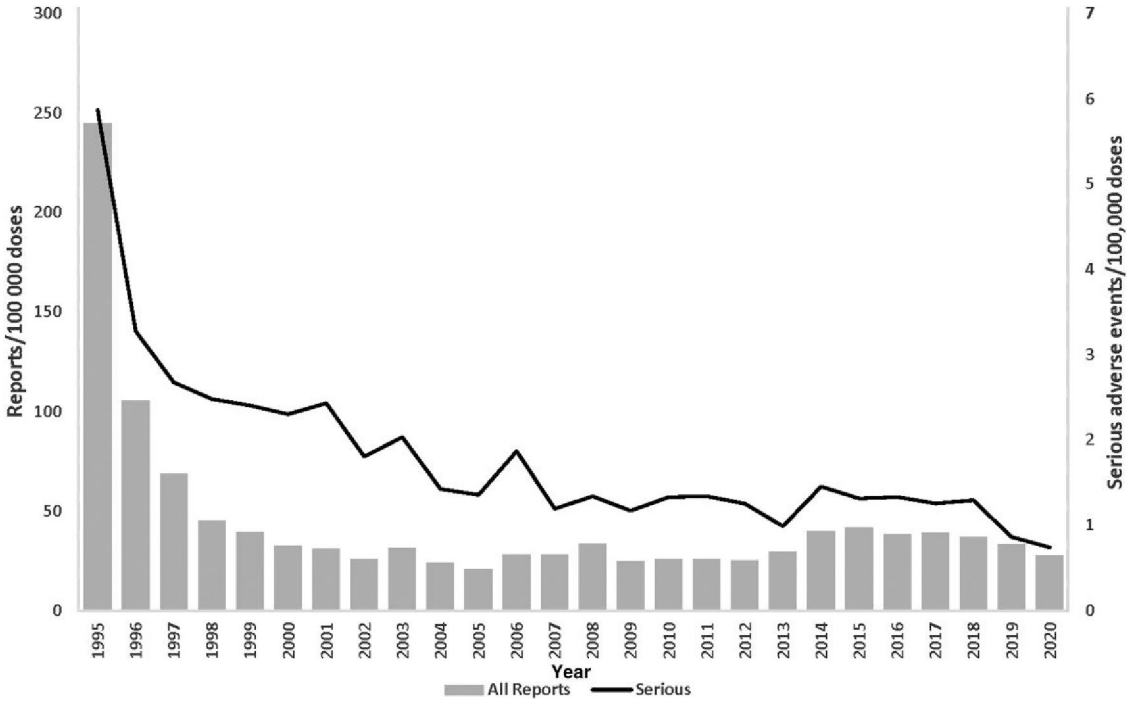

Figure 1.

Adverse event reporting rate per 100 000 doses, all reports (bars) and serious reports (line) after VAR, VAERS, United States, 1995–2020. Abbreviations: VAR, single antigen varicella vaccine; VAERS, Vaccine Adverse Event Reporting System. Data for 1995–2005 are from Chaves et al [5].

Table 1.

Characteristics of Reports After VAR and MMRV, VAERS, United States, 2006–2020

Patient Characteristics	VAR Given Alone		VAR + Other Vaccines[a]		MMRV Given Alone		MMRV + Other Vaccines[a]	
	Adverse Event Reports, No.	Serious No. (%)	Adverse Event Reports, No.	Serious No. (%)	Adverse Event Reports, No.	Serious No. (%)	Adverse Event Reports, No.	Serious No. (%)
Total	14 352	260 (1.8)	26 332	1404 (5.3)	5238	102 (1.9)	8087	343 (4.2)
Sex								
Female	5462	127 (2.3)	13 545	633 (4.7)	1095	42 (3.8)	3642	146 (4.0)
Male	3181	130 (4.1)	11 751	768 (6.5)	1015	58 (5.7)	3864	195 (5.0)
Unknown	5709	3 (0.1)	1036	3 (0.3)	3128	2 (0.1)	581	2 (0.3)
Age groups								
<12 mo	84	2 (2.4)	258	10 (3.9)	54	3 (5.6)	72	6 (8.3)
1–3 y	2065	48 (2.3)	9378	793 (8.5)	853	58 (6.8)	2270	174 (7.7)
4–6 y	1468	42 (2.9)	7391	312 (4.2)	1442	28 (1.9)	4949	158 (3.2)
7–12 y	2198	65 (3.0)	3906	114 (2.9)	103	3 (2.9)	198	1 (0.5)
13–17 y	929	22 (2.4)	2694	103 (3.8)	177	0 (0.0)	111	1 (0.9)
≥18 y	3181	72 (2.3)	2079	67 (3.2)	298	5 (1.7)	114	3 (2.6)
Unknown	4427	9 (0.2)	626	5 (0.8)	2311	5 (0.2)	373	0 (0.0)

Abbreviations: MMRV, measles, mumps, rubella, and varicella vaccine; VAERS, Vaccine Adverse Event Reporting System; VAR, single antigen varicella vaccine.

[a]Other vaccines includes any other vaccine(s) included in the immunization schedule that was administered at the same time with VAR or MMRV, respectively.

Table 2.

Most Commonly Reported Adverse Events and Adverse Events of Special Interest Reported After VAR or MMRV, VAERS, United States, 2006–2020[a]

	Adverse Event Reports, No. (%)[b]								
	VAR					MMRV			
Adverse Event	VAR Alone	Serious	Vaccine Recipient <18 y	Total[c]	Reporting Rate[d]	MMRV Alone	Serious	Total[e]	Reporting Rate[d]
Most commonly reported adverse events									
Injection site reaction	3167 (25)	215 (2)	10 561 (84)	12 585 (31)	9.5	424 (12)	61 (2)	3588 (27)	10.1
Rash	2988 (27)	599 (5)	9422 (84)	11 252 (28)	8.5	577 (22)	135 (5)	2670 (20)	7.5
Vaccination error	6740 (71)	32 (0)	4090 (43)	9482 (23)	7.1	3903 (71)	19 (0.3)	5470 (41)	15.4
Fever	825 (16)	708 (14)	4502 (90)	5027 (12)	3.8	415 (23)	217 (12)	1823 (14)	5.1
Pruritus/urticaria	1015 (27)	227 (6)	2982 (81)	3693 (9)	2.8	152 (16)	49 (5)	956 (7)	2.7
Pain	580 (31)	173 (9)	1293 (69)	1881 (5)	1.4	73 (18)	46 (11)	405 (3)	1.1
Skin warm	478 (29)	54 (3)	1330 (80)	1665 (4)	1.3	50 (13)	10 (3)	378 (3)	1.1
Varicella	801 (48)	138 (8)	1382 (83)	1656 (4)	1.3	79 (37)	13 (6)	215 (2)	0.6
Swelling	461 (32)	39 (3)	1121 (78)	1433 (4)	1.1	48 (13)	11 (3)	376 (3)	1.1
Vomiting	179 (14)	365 (28)	1208 (92)	1308 (3)	1.0	65 (15)	90 (21)	421 (3)	1.2
Adverse events of special interest									
Death	9 (12)	78 (100)	71 (91)	78 (0.2)	0.06	1 (6)	18 (100)	18 (0.1)	0.05
Meningitis	6 (21)	26 (93)	22 (79)	28 (0.1)	0.02	2 (29)	5 (71)	7 (0.1)	0.02
Encephalitis	5 (6)	76 (95)	76 (95)	80 (0.2)	0.06	4 (18)	21 (95)	22 (0.2)	0.06
Herpes zoster	230 (50)	39 (9)	368 (81)	456 (1.1)	0.34	32 (44)	5 (7)	72 (0.5)	0.20
Anaphylaxis	39 (20)	138 (69)	184 (92)	200 (0.5)	0.15	10 (16)	30 (47)	64 (0.5)	0.18

Abbreviations: MMRV, measles, mumps, rubella, varicella vaccine; VAERS, Vaccine Adverse Event Reporting System; VAR, single antigen varicella vaccine.

[a] Percentages in the Total columns represent column percentages; all other percentages represent row percentages based on the numbers in the Total columns.

[b] Reported signs and symptoms of adverse events are coded using the Medical Dictionary for Regulatory Activities Preferred Terms. Preferred Terms are not medically confirmed diagnoses and not mutually exclusive.

[c] Percentages are calculated among 40684 VAR reports.

[d] Calculated per 100 000 doses of the respective vaccine distributed in the United States.

[e] Percentages are calculated among 13 325 MMRV reports.

Table 3.

Description of Deaths Reported to VAERS After VAR and MMRV, 2006–2020

Characteristic	VAR (n = 78) No. (%)	MMRV (n = 18) No. (%)
Vaccine given alone	9 (11.5)	1 (5.6)
Female sex	38 (48.7)	7 (38.9)
Age		
12–23 mo	49 (62.8)	13 (72.2)
2–4 y	9 (11.5)	3 (16.7)
5–9 y	4 (5.1)	2 (11.1)
10–17 y	9 (11.5)	0 (0.0)
≥18 y	7 (0.0)	0 (0.0)
Cause of death by body system category/fatal events[a]		
SIDS	16 (20.5)	3 (16.7)
Neurologic	14 (17.9)	4 (22.2)
Seizures/epilepsy	10	...
Meningoencephalitis	1[b]	1[c]
Cerebral hemorrhage[d]	1	...
Meningitis (*Streptococcus pneumoniae*)	1	...
Cerebral edema	1	1
Ischemic encephalopathy		1
Sequelae of brain malformation		1
Respiratory	13 (16.7)	1 (5.6)
Pneumonia/bronchopneumonia[e]	11	...
Other (asthma, hypoxic respiratory failure, pulmonary aplasia)	2	1
Septicemia and multiorgan failure[f]	11 (14.1)	1 (5.6)
Cardiac	7 (9.0)	3 (16.7)
Viral myocarditis	4[g]	2[h]
Other (myxoid degeneration of mitral valve, fibroblastosis, dilated cardiomyopathy, dysrhythmia)	3	1
External causes (accidental suffocation, head trauma, suicide, drowning)	5 (6.4)	1 (5.6)
Gastrointestinal (bowel ischemia, peritonitis)	2 (2.6)	...

Characteristic	VAR (n = 78) No. (%)	MMRV (n = 18) No. (%)
Other infectious (acute febrile illness, *Escherichia coli* Shiga toxin-producing)	2 (2.6)	...
Disseminated varicella (vVZV)	1 (1.3)	...
Autoimmune hemolytic anemia (vVZV)	1 (1.3)	...
Anaphylaxis	1 (1.3)	...
Coagulopathy	1 (1.3)	...
Endocrine diseases (adrenal insufficiency)		1 (5.6)
Undetermined/unknown	4[i] (5.1)	4 (22.2)

Abbreviations: MMRV, measles, mumps, rubella, varicella vaccine; PCR, polymerase chain reaction; SIDS, sudden infant death syndrome; VAERS, Vaccine Adverse Event Reporting System; VAR, single antigen varicella vaccine; vVZV, vaccine strain varicella-zoster virus.

[a] Autopsy or death certificate available in 67 (85.9%) of VAR and 16 (88.9%) of MMRV reports.

[b] Cerebrospinal fluid PCR positive for VZV, genotyping not performed; developed herpes zoster.

[c] Reported as anoxic brain injury due to acute cerebellitis.

[d] vVZV, measles, mumps and rubella detected in bronchiolar lavage by PCR; patient with severe combined immunodeficiency and adenosine deaminase deficiency.

[e] Reported cause: 1 each measles vaccine-strain virus (VZV also detected, not strain-typed), *Klebsiella pneumoniae,* community acquired, human metapneumovirus, aspiration; 1 death for which only death certificate was available indicated disseminated varicella and pneumonia without VZV PCR testing.

[f] vVZV reported for 4 (1 with disseminated herpes zoster), 2 VZV PCR positive (1 with epidemiologic context to support wild-type VZV); 1 report indicated influenza B sepsis and encephalitis.

[g] Parainfluenza reported for 1.

[h] Reported as myocarditis and myocarditis lymphocytic.

[i] One with VZV PCR-positive in saliva collected at the time the patient developed a second episode of prolonged intestinal ileus, 7 months after second dose VAR; cause of death not reported.