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MAJOR ARTICLE

Varicella Virus Vaccine Live: A 22-Year Review of Postmarketing Safety Data

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Background. Varicella, a contagious infectious disease caused by varicella zoster virus (VZV), can result in hospitalization and, occasionally, death. Varicella virus vaccine live (VVVL [VARIVAX]) was introduced in the United States in 1995.

Methods. This comprehensive review of the VVVL safety profile is based on 22 years of postmarketing adverse event (AE) data received through spontaneous and noninterventional study reports submitted by health care providers and on a review of the published literature (cumulatively from March 17, 1995, through March 16, 2017, during which period >212 million doses were distributed globally).

Results. The VVVL safety profile was consistent with previous publications, with common AEs including varicella, rash, and pyrexia. AE reports have decreased over time, from ~500 per million doses in 1995 to ~40 per million doses in 2016; serious AEs comprise 0.8 reports per million doses. Secondary transmission was rare (8 confirmed cases); polymerase chain reaction analysis indicated that 38 of the 66 reported potential secondary transmission cases of varicella were attributable to wild-type VZV. The prevalence of major birth defects in the Pregnancy Registry was similar to that in the general US population. In total, 86 cases of death were reported after vaccination with VVVL; immunocompromised individuals appeared to be most at risk for a fatal varicella- or herpes zoster–related outcome.

Conclusions. This comprehensive 22-year review confirms the overall safety profile for VVVL, with no new safety concerns identified. Since VVVL's introduction in 1995, notable declines in varicella cases and in varicella-related deaths have occurred compared with the prevaccination period.

Keywords. postmarketing; safety; varicella; varicella vaccine; varicella zoster vaccine.

Varicella (chickenpox), an acute infectious disease caused by varicella zoster virus (VZV), is extremely contagious, with secondary attack rates of up to 90% among household contacts of infected persons [1]. VZV persists as a latent infection in the sensory nerve ganglia, with reactivation causing the recurrent infection of shingles (herpes zoster [HZ]) [1]. Before vaccine introduction, the average US incidence of varicella was ~4 million cases per year, with >10 000 hospitalizations and ~145 deaths per year attributable to varicella [1–4]. Recent data indicate that >90% of US children are vaccinated against varicella (Figure 1) [5], and varicella annual incidence has declined to <350 000 cases, with <1700 hospitalizations and <20 deaths per year [3, 6].

Varicella virus vaccine live (VVVL; VARIVAX [Oka/Merck]; Merck & Co., Inc., Kenilworth, NJ) was licensed in the United States in May 1995 [7, 8]. In 1996, a single dose of varicella vaccine for children aged 12–18 months was recommended [2], but despite vaccine effectiveness of 81%, outbreaks continued to occur in populations with high coverage rates [9]. In June 2006, the recommendation was changed to a 2-dose regimen (first dose: age 12–15 months; second dose: age 4–6 years) [2]. VVVL is currently indicated for active immunization for the prevention of varicella in individuals aged ≥12 months [7]. In common with other live, attenuated viral vaccines, use in individuals with primary or acquired immunodeficiency states, any febrile illness or active infection, or pregnancy is contraindicated [7].

The efficacy of VVVL was established in clinical trials, and its effectiveness has been based on comparisons with historical data [7]. In a study of healthy children who received 1 or 2 doses of VVVL, vaccine efficacy for the 10-year observation period was 94% for 1 dose and 98% for 2 doses ($P < .001$). Compared with historical data for wild-type VZV (WTV), there was an 80% decrease in the expected number of cases after the 2-dose vaccination [7].

A 10-year postmarketing safety review showed that VVVL was generally safe and well tolerated [8]. This report reviews 22 years of postmarketing safety data received by Merck, Sharp & Dohme (MSD).

METHODS

Resources

MSD Postmarketing Database for VVVL

MSD maintains an active database of postmarketing adverse events (AEs), with most data received through spontaneous

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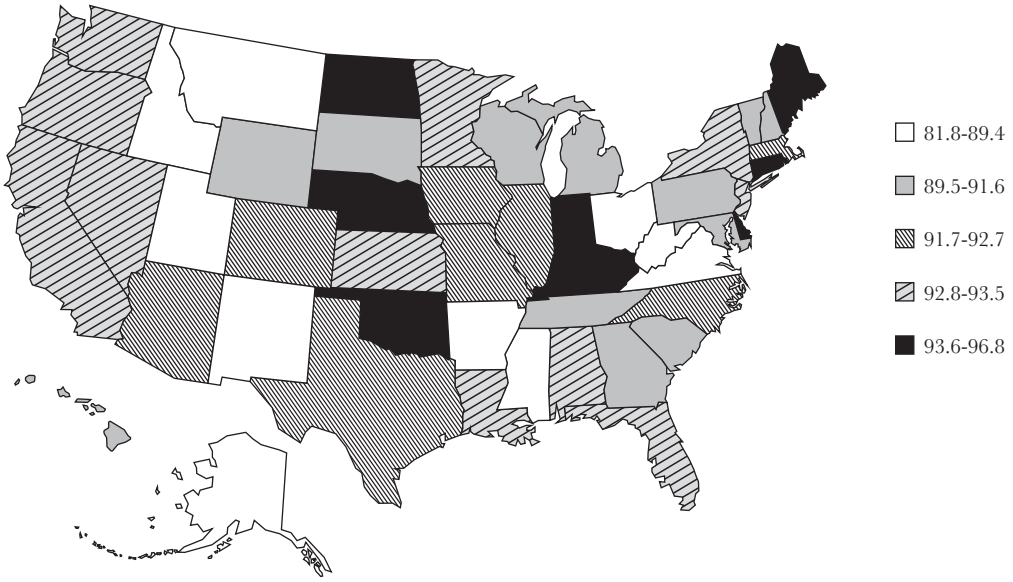

State	Coverage, %	State	Coverage, %	State	Coverage, %	State	Coverage, %
AL	92.9	IL	91.7	NC	92.7	SC	91.0
AK	81.8	IN	94.1	ND	95.3	SD	90.3
AR	89.1	KS	92.8	NE	94.4	TN	89.7
AZ	92.7	KY	95.7	NH	89.6	TX	92.3
CA	93.4	LA	93.4	NJ	93.0	UT	88.8
CO	92.5	MA	92.0	NM	86.4	VA	84.2
CT	96.8	MD	91.5	NV	92.9	VT	91.5
DE	95.8	ME	93.8	NY	93.4	WA	92.9
FL	93.0	MI	89.5	OH	86.2	WI	90.3
GA	89.5	MN	93.4	OK	93.6	WV	85.9
HI	91.6	MO	92.4	OR	93.0	WY	91.2
IA	92.1	MS	89.2	PA	90.4		
ID	88.5	MT	89.1	RI	95.1		

Figure 1. Varicella vaccination coverage among children aged 19–35 months by US state (2015). Modified from the Centers for Disease Control and Prevention's "2015 Childhood Varicella Vaccination Coverage Report" [5].

reports from health care providers and consumers. Although ideally all AEs should be reported, this is a voluntary process, with the level of detail dependent upon the individual who submits the report. Despite efforts to solicit additional facts, demographic, medical/clinical, and laboratory information may vary in completeness and accuracy. The database also includes AEs from noninterventional studies and the published literature. The National Childhood Vaccine Injury Act of 1986 [10] requires that certain AEs occurring postvaccination in the United States be reported to the Vaccine Adverse Event Reporting System.

Once received by MSD, AEs are coded using preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) [11].

This analysis includes all spontaneous postmarketing and noninterventional study reports submitted by health care providers or reported in the published literature received worldwide during the 22-year period following licensure of VVVL, from March 17, 1995, through March 16, 2017 (reports received from consumers present in the database were not included in this analysis). The available data are inadequate to reliably estimate the number of exposed individuals; therefore, reporting rates are calculated based on total doses distributed, with the assumption that each patient received 1 dose. Time to AE onset was calculated from the date of vaccination (day 1) to the date of onset of the first reported AE. AE outcome was defined as the outcome provided at the time of the report. Reports of rash (including HZ, HZ-like, varicella, and varicella-like rash) were evaluated between 1 and 42 days postvaccination. The 42-day time frame, based on twice the VZV incubation period of 21 days, represents the upper limit of time during which a vaccinee would be expected to mount an immune response.

MSD Pregnancy Registry

VVVL is contraindicated during pregnancy. The company recommends that women avoid pregnancy for 3 months after vaccination; however, the Advisory Committee on Immunization Practices (ACIP) recommendation for live varicella vaccine administration advises that pregnancy be avoided for 1 month following each dose of VVVL [2]. However, it is recognized that, despite these contraindications and precautions [7], vaccination of pregnant women may occur inadvertently. A Pregnancy Registry was established (March 1995) to collect reports of and evaluate the safety and outcomes of women reported to have received VVVL within 3 months before conception or during pregnancy. On October 16, 2013, the Registry was closed to new enrollment [12]; individuals enrolled before closure were followed until after their estimated delivery date.

Definitions

The MedDRA preferred terms are listed in Supplementary Appendix 1. A report may contain ≥1 AE and includes all AEs reported by that individual. Serious AEs (SAEs) were defined per the International Conference on Harmonisation guidelines [13, 14]. Secondary transmission was defined as the documented presence of Oka/Merck vaccine strain VZV in a nonvaccinated contact of an individual vaccinated with VVVL. Based on European Medicines Agency (EMA) guidelines [15], potentially immunocompromised patients were identified based on medical histories, concurrent conditions, and concomitant therapies. Samples were analyzed using polymerase chain reaction (PCR) methodology to confirm the presence and type (vaccine strain or wild-type virus [WTV]) of VZV [16].

RESULTS

Postmarketing Surveillance Data: Overview

During the 22-year evaluation period, >212 million doses of VVVL were distributed worldwide, and 46 855 AE reports were received. Rates of the most commonly reported AEs are presented in Figure 2. From 1995 to 2000, the most common AE was varicella (peaking at 183 reports per 10^6 doses in 1997). In 2006, reports of varicella trended upward again, with 170 reports per 10^6 doses, but have subsequently decreased, with 4–5 reports per 10^6 doses in 2015 and 2016. Reports of rash also decreased, from 165 per 10^6 doses in 1995 to 10 per 10^6 in 2016.

Rates of SAEs fluctuated over time (Figure 3). Central nervous system (CNS) SAEs declined by approximately two-thirds during the review period, whereas the incidence of varicella SAEs remained relatively stable during that time.

Reports of AEs of interest, with PCR analysis from all laboratories, are presented in Table 1. Table 2 presents AEs reported in immunocompromised patients in whom vaccine strain VZV was identified.

Varicella After Vaccination

There were 10 677 reports of 11 095 varicella events (10 751 AEs, 344 SAEs). Time to onset was available for 6692 reports, of which 22% (1471/6692) occurred within 42 days postvaccination. Of the 56% (5927/10 677) of cases with

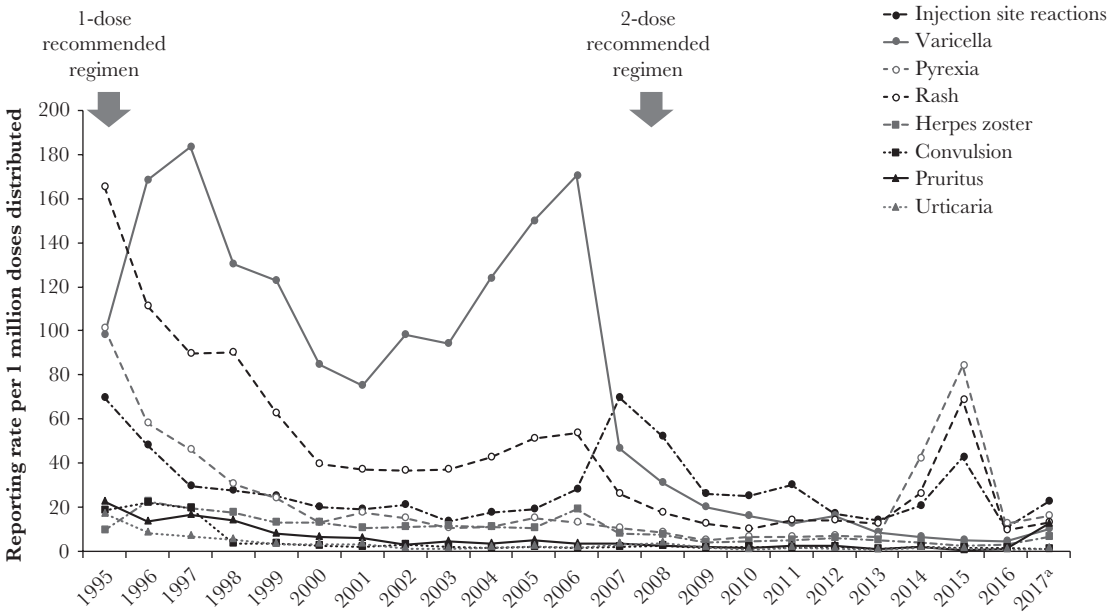

Figure 2. VVVL global adverse event (AE) reports for the most common AEs, March 1995 to March 2017. Reported as AEs per 1 million doses distributed. See Supplementary Appendix 1 for a full breakdown of MedDRA preferred terms. [a]Includes January 1, 2017, to March 16, 2017. Abbreviation: VVVL, varicella virus vaccine live (VARIVAX [Oka/Merck]; Merck & Co., Inc., Kenilworth, NJ, USA).

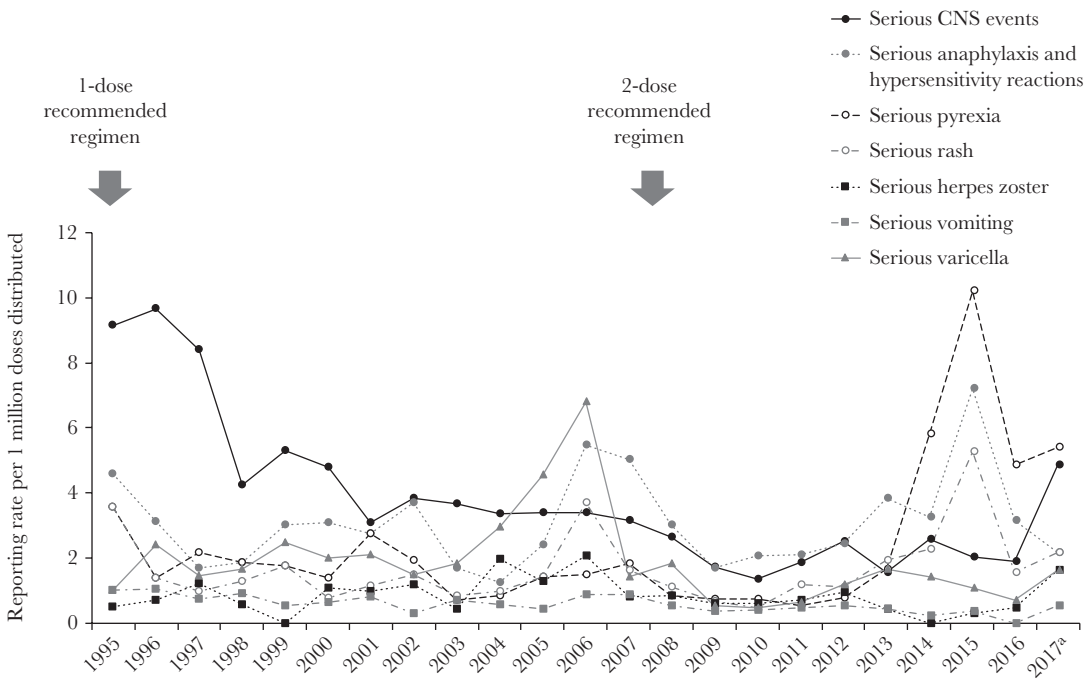

Figure 3. VVVL global SAE reports for the most common SAEs, March 1995 to March 2017. Reported as SAEs per 1 million doses distributed. See Supplementary Appendix 1 for a full breakdown of MedDRA preferred terms. [a]Includes January 1, 2017, to March 16, 2017. Abbreviations: CNS, central nervous system; SAE, serious adverse event; VVVL, varicella virus vaccine live (VARIVAX [Oka/Merck]; Merck & Co., Inc., Kenilworth, NJ).

a reported outcome, 93% (5519/5927) were recovered/recovering and 7% (403/5927) had not recovered at the time of reporting; 9 cases resulted in a fatal outcome (Supplementary Appendix 2). Most fatal outcomes occurred in immunocompromised patients, in whom VVVL is contraindicated (see below). Lesion samples (n = 204; more than 1 sample may have been submitted per patient) submitted for PCR testing included 49 from immunocompromised patients (32 vaccine strain VZV, 9 WTV, 4 untypable/no strain identified, and 4 inadequate samples).

Herpes Zoster

Over the evaluation period, 1602 reports of 1803 HZ events were submitted (1646 AEs, 157 SAEs). Of the 1602 reports with

Table 1. PCR Results From All Laboratories by AE of Interest[a]

AE,[b] No.	Oka/Merck Vaccine Strain VZV	Wild-Type VZV	VZV-Negative	VZV-Positive Untypable/No Strain[c]	Inadequate Sample	Total
Varicella	67	97	12	9	19	204
Herpes zoster	117	57	27	9	51	261
Rash events	25	39	33	4	27	128
Secondary transmission[d]	8	38	14	0	8	68
CNS events[e]	17[f]	7	40	11	3	78
Other AEs[g]	17	2	13	5	2	39
Total No. of samples	251	240	139	37	110	778

Abbreviations: AE, adverse event; CNS, central nervous system; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; VZV, varicella zoster virus.

[a]The table includes all PCR samples received by MSD from all laboratories through March 16, 2017; 1 individual may have had more than 1 type of sample (ie, rash/lesion sample and sputum sample).

[b]See Supplementary Appendix 1 for a full breakdown of MedDRA preferred terms.

[c]Results include samples that were VZV-positive; however, strain identification was not able to identify either the wild-type virus or vaccine strain virus. Reports in which samples were found to be VZV-positive without strain identification testing are presented in this table.

[d]All samples presented were lesion samples, with the exception of 3 samples: 1 patient had 2 samples submitted for analysis (1 CSF and 1 throat swab); both were found to be negative. Another patient (a 30-year-old pregnant woman) had a lesion sample identified as vaccine strain; she elected to have a therapeutic abortion, and the products of conception were negative for VZV.

[e]Samples included cerebrospinal fluid and brain tissue.

[f]Per review of 1 disseminated varicella, CSF was identified to be VZV-positive untyped and interpreted to be vaccine strain based on Oka identified in the lesion, urine, serum, nasopharyngeal swab, and oropharyngeal swab.

[g]Samples included autopsy tissue samples, bronchoalveolar lavage, blood, esophagus tissue, gastric biopsy tissue, liver biopsy tissue, lung biopsy tissue, lymph nodes, mouth swab, nasopharyngeal swab, plasma, products of conception, saliva, serum, throat samples, and urine.

Table 2. Summary of AE Reports in Immunocompromised Patients With Oka/Merck VZV Postvaccination

Age, Sex	Reported AEs[a]	TTO PV for Vaccination-Associated AE	Medically Significant Case Information	IS Concomitant Therapies	PCR Analysis for VZV	AE Recovery Status at Time of Report
12 mo, male	Disseminated varicella (as reported)	NR	"Severe immunodeficiency"	NR	Oka/Merck vaccine strain VZV identified in lesion sample	NR
13 mo, male	Pulmonary hemorrhage; Cardiac failure congestive; Hematemesis; Hypophagia; Lethargy; Retching; Respiratory distress; Pneumonitis; Rash papular; Hemolytic anemia; Rash vesicular; Candida pneumonia; Hepatomegaly; Varicella zoster virus infection; Lung disorder; Lymphadenopathy	27 d	DiGeorge's syndrome (central shunt); Cardiac failure; Congestive and complex congenital heart disease; History of Fallot's tetralogy, Rastelli repair; Oral candidiasis recurrent; Immunosuppression; Concomitant vaccination with MMR on same day, CDC reported that the tracheal aspirate was positive for measles virus	None	Oka/Merck vaccine strain VZV identified in bronchial washings and lesion samples	Varicella cleared; Patient subsequently died of pulmonary hemorrhage after prolonged intubation for chronic lung disease
13 mo, male	Subacute sclerosing panencephalitis; Immunodeficiency; Varicella; Diarrhea; Malnutrition; Hypogammaglobulinemia; Leukopenia; Vasculitis cerebral	21 d	Primary immune deficiency; Clinically defective antiviral T-cell function	None	Oka/Merck vaccine strain VZV identified in lesion samples	Varicella cleared; Patient subsequently died of measles inclusion body encephalitis
13 mo, male	Pneumonia viral; Vomiting; Croup infectious; Varicella; Dermatitis bullous; Lumbar radiculopathy; Antibody test negative	14 d	History of failure to thrive and oral candidiasis; Subsequently diagnosed with HIV	None	Oka/Merck vaccine strain VZV identified in BAL and lung biopsy material	Recovered; No recurrence of varicella
13 mo, male	Combined immunodeficiency; Drug administration error; Diarrhea; Pyrexia; Pneumonia; Hepatitis; Malaise; Enterovirus infection; Hepatic function abnormal; Ascites; Hepatomegaly; Leukocytosis; Respiratory distress; Nasopharyngitis; Necrosis; Influenza; Coagulopathy; Colitis; Feeling abnormal; Dehydration; Amebiasis; Varicella; Neutropenia; Lymphopenia; Viral infection; Bronchiolitis	15 d PV hospitalized and 28 d varicella rash	Adenosine deaminase deficiency; Bronchiolitis; Reactive airway disease; Recurrent oral candidiasis	None	Oka/Merck vaccine strain VZV identified from liver biopsy and lesion sample	Recovered
13 mo, female	Hemorrhage intracranial; Combined immunodeficiency; Mumps; Lung disorder; Leukopenia; Drug tolerance; Hepatitis; Disseminated intravascular coagulation; Hemolysis; Pseudomonas infection; Rubella; Adenovirus infection; Renal failure; Acidosis; Hyperammonemia; Pancreatitis; Amylase increased; Carbon dioxide increased; Acute respiratory distress syndrome; Measles; Respiratory failure; Cough; Diarrhea; Rash vesicular; Varicella; Pyrexia	25 d	Adenosine deaminase deficiency; History of recurrent sinopulmonary infections; Refractory oral candidiasis; Poor weight gain	Inhaled corticosteroid	Oka/Merck vaccine strain VZV identified in BAL and lesion samples; Samples also noted to be positive for measles, mumps, and rubella vaccine strains	Varicella cleared; Patient subsequently died of intracranial hemorrhage while on ECMO
13 mo, female	Autoimmune hemolytic anemia; Renal failure; Hepatic failure; Disseminated intravascular coagulation; Disseminated varicella zoster vaccine virus infection; Lymphopenia; Mumps; Rubivirus test positive	21 d	Primary immunodeficiency due to heterozygous missense mutation in recombination activating gene 2 diagnosed PV	None	Oka/Merck vaccine strain VZV identified in CSF, skin, and esophagus VZV was identified in autopsy tissues in lungs and liver; Corneal dendrites with typical features of VZV	Patient died due to multi-organ failure associated with disseminated varicella
13 mo, female	Herpes zoster disseminated; Herpes zoster	35 d to disseminated HZ occurrence; 61 d to possible: recurrent episode of HZ	Congenital dyskeratosis	NR	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered from first occurrence; Not recovered from the "possible" recurrence of HZ at the time of the report
13 mo, female	Meningoencephalitis viral; Varicella zoster; Rubella viral infection	3 wk	Severe combined immune deficiency; Neutropenia	Myeloablation and hematopoietic stem cell transplantation	Oka/Merck vaccine strain VZV identified in serum, lesion, urine, nasopharyngeal swab, and oropharyngeal swab, and VZV (untyped) identified in the CSF	Recovered
14 mo, male	Aspartate aminotransferase increased; Varicella; ALT increased; Febrile reaction; Cough; Upper respiratory tract congestion	18 d	Asthma; "Serious immunodeficiency" not further specified	None	Oka/Merck vaccine strain VZV identified in lesion sample	Patient has progressive varicella with workup ongoing

Table 2. Continued

Age, Sex	Reported AEs[a]	TTO PV for Vaccination-Associated AE	Medically Significant Case Information	IS Concomitant Therapies	PCR Analysis for VZV	AE Recovery Status at Time of Report
15 mo, male	Renal function disorder; Herpes zoster; Hypertension; Pyrexia; Neutropenia; Encephalopathy	~ 3 mo	Neuroblastoma; Bone marrow transplantation	Chemotherapy	Oka/Merck vaccine strain VZV identified in lesion and CSF samples	Recurrent episodes of HZ over several wk, but patient recovered and was discharged
15 mo, female	Multi-organ failure; Respiratory distress; Sepsis; Varicella; Varicella Zoster pneumonia; Pneumothorax; Respiratory distress; Acute respiratory failure; Contraindication to vaccination	20 d	Unconfirmed underlying immunodeficiency; Developmental delay; Failure to thrive; Muscular dystrophy; Hypotonia	Budesonide; Methylprednisolone; Prednisone	Oka/Merck vaccine strain VZV identified in lesion and BAL samples	Patient died of respiratory/multi-organ failure associated with disseminated varicella
17 mo, female	Varicella zoster virus infection	>4 mo	Immunodeficiency; Hurler syndrome; HLA matched cord blood transplant	None	Oka/Merck vaccine strain VZV identified in lesion sample	Lesions crusted over
17 mo, male	Varicella	16 d	Failure to thrive; Abnormal IgG levels (unknown at time of vaccination); T-lymphocyte count abnormal; Intestinal dysmotility	NR	Oka/Merck vaccine strain VZV identified in lesion sample	NR
17 mo, female	Varicella zoster virus infection; Anemia macrocytic; Pancytopenia; Lymphadenopathy; Rash vesicular; Aplastic anemia	23 d	Macrocytic-normochromic-hyporegenerative anemia	NR	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
18 mo, male	Herpes zoster (reported as mild); asthma	122 d	Asthma exacerbation requiring corticosteroid use	Corticosteroid	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
18 mo, female	Respiratory failure; Varicella; *Staphylococcus aureus* bacteremia; Systemic candida; Methicillin-resistant *S. aureus* infection	4 wk	Deficits in cellular immunity; Severe humoral dysregulation	None	Oka/Merck vaccine strain VZV identified in lesion sample	Varicella cleared; Patient subsequently died of respiratory failure at 2 y 2 mo of age
20 mo, male	Herpes zoster	214 d	S/p "recent" liver transplant	Tacrolimus	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
21 mo, female	Neuroblastoma recurrent; Respiratory arrest; Acute renal injury; Mentally late developer; Leukocytosis; Proteinuria; Varicella; Meningitis	35 d	Stage IV neuroblastoma diagnosed 1-wk PV	Chemotherapy (4 courses of cyclophosphamide, adriamycin, and vincristine, and 2 courses of cisplatin and etoposide), followed by autologous stem cell transplant	Oka/Merck vaccine strain VZV identified in lesion sample	Varicella cleared; Patient subsequently died of complications of neuroblastoma
22 mo, female	Herpes zoster; Immunoglobulins increased; Cellulitis; Otorrhea	10 mo	Diagnosed with Job-Buckley syndrome after vaccination (date not reported)	NR	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
2 y, male	Skin lesion; Leukemia	37 d	Diagnosed with leukemia after vaccination	NR	Oka/Merck vaccine strain VZV identified in lesion	Recovering
25 mo, male	Acute lymphocytic leukemia; Herpes zoster	22 d	Diagnosed with acute lymphocytic leukemia 10 d PV	Chemotherapy	Oka/Merck vaccine strain VZV identified in lesion sample	3 episodes of HZ over several wk, but ultimately recovered
25 mo, male	Herpes zoster; Asthenia; Decreased appetite; Pain in extremity; Somnolence; Astrocytoma	8 mo	Diencephalic syndrome, "suboptimal" growth, developmental delays	Started on chemotherapy for newly diagnosed astrocytoma 2 mo before developing HZ (carboplatin and vincristine)	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered from HZ event
3 y, male	Varicella; Hepatic function abnormal	19 d	History of severe combined immunodeficiency, s/p unrelated bone marrow transplantation	NR	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
4 y, NR	Herpes zoster; Meningitis; Acute lymphocytic leukemia	19 mo	Diagnosed with acute lymphocytic leukemia >1-y PV	Chemotherapy	Oka/Merck vaccine strain VZV identified from CSF and lesion sample	Recovered
4 y, female	Herpes zoster	21 mo	Dermatomyositis	Prednisone; Methotrexate	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
5 y, female	Varicella; Medication error; Pneumonia; Pyrexia; HIV test positive	36 d	HIV-positive	Antiviral (unspecified); Lopinavir (+) ritonavir	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
5 y, male	Herpes zoster	453 d	Neutropenia	None	Oka/Merck vaccine strain VZV identified in lesion sample	Recovering

Table 2. Continued

Age, Sex	Reported AEs[a]	TTO PV for Vaccination-Associated AE	Medically Significant Case Information	IS Concomitant Therapies	PCR Analysis for VZV	AE Recovery Status at Time of Report
5 y, male	Varicella; Neutropenia, Product use issue	NR	Immunocompromised (not further specified)	NR	Oka/Merck vaccine strain VZV identified in lesion sample	NR
5 y, male	Pneumonia; Rash	10 d	Reactive airway disease; Cerebral palsy	Steroids (1–2 mg/kg/d prednisolone sodium phosphate)	Oka/Merck vaccine strain VZV identified in endotracheal secretions	Recovered
5 y, male	Herpes zoster; Lung infection; Chronic granulomatous disease	11 mo	X-linked chronic granulomatous disease; Chronic renal failure; Hypertension; Chronic diarrhea	Cord blood transplant; Long-term prednisolone (5 mg/d)	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
5 y, female	Histiocytosis hematophagic; Pancytopenia; Hepatitis; Varicella zoster virus infection; Rash vesicular	14 d after second dose	Immunodeficiency	Corticosteroids	Oka/Merck vaccine strain VZV identified in lesion sample	Resolving
6 y, male	Varicella; varicella zoster pneumonia	23 d	Cerebral palsy; Spastic quadriplegia; Seizures, recurrent otitis media; Selective reduction of iNKT cells combined with deficient expression of CD1d; Possible subclinical functional impairment of conventional T cells	NR	Oka/Merck vaccine strain VZV identified in lesion sample	NR
6 y, female	Varicella	17 d	Rheumatoid arthritis	Prednisone; Methotrexate	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
8 y, female	Rash vesicular; Rash popular; Pyrexia; Localized infection	23 d	Perinatally infected with HIV	None	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
9 y, male	Varicella; Accidental exposure to product; *Molluscum contagiosum*; Staphylococcal infection	18 d	S/p renal transplant secondary to end-stage renal disease	Mycophenolate mofetil; Tacrolimus; Prednisone	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
9 y, male	Varicella; Blood creatinine increased; Nephrotic syndrome	20 d	Systemic lupus erythematosus	Pulse steroids	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
11 y, male	Varicella; Headache; Meningitis; *Mycobacterium avium* complex infection; Depression; Malnutrition; Protein-losing gastroenteropathy; Cytomegalovirus viremia: Pyrexia; AIDS-related complications; Ear infection	~1 y from second dose, fifth episode of recurrent varicella	Congenital AIDS	None	Oka/Merck vaccine strain VZV identified in lesion sample CSF was VZV-negative with second episode of disseminated VZV ~4 mo PV	Patient with 5 episodes of recurrent varicella. The patient recovered from varicella; Death occurred approximately 1 y 3 mo postvaccination from AIDS complications
11 y, female	Pneumonitis; Dermatitis bullous; Cystic fibrosis; Cell-mediated immune deficiency; Embolism	5 wk	Congenital CMV; Recurrent respiratory infections; Immune deficiency; Cystic fibrosis	None	Oka/Merck vaccine strain VZV identified in BAL and endotracheal secretion sample	Recovered and discharged; patient died 10 mo PV due to embolic complications related to a femur fracture
12 y, male	Renal transplant; Varicella; ANCA; Vasculitis; AST increased; ALT increased; Medication error; Drug administration error; Inappropriate schedule of drug administration	28 d from second dose	Renal transplant; Trisomy 21	Mycophenolate; Tacrolimus	Oka/Merck vaccine strain VZV identified in lesion sample	Resolving
12 y, female	Varicella zoster virus infection; Gait inability; Back pain; Pain in extremity; Arthralgia	~1 wk	Acute myeloid leukemia; Chronic graft-vs-host disease; S/p bone marrow transplant	Betamethasone	Oka/Merck vaccine strain VZV identified in lesion sample	NR
14 y, male	Bone marrow transplant; Meningitis; Disseminated varicella zoster vaccine virus infection; Cord blood transplant therapy; Medication error	>10 y	Precursor B-cell acute lymphocytic leukemia; Bone marrow transplant; Cord blood stem cell transplant; Graft-vs-host disease	Sirolimus; Tacrolimus; Budesonide	Oka/Merck vaccine strain VZV identified in CSF	Recovering
15 y, female	Death; Dermatitis acneiform; Neurological symptom; CD4 lymphocytes decreased; Medication error; Progressive multifocal leukoencephalopathy; Cerebellar syndrome; CNS lymphoma; CNS lesion	NR	Congenital HIV; Progressive multifocal leukoencephalopathy; HIV cerebellar syndrome; Possible CNS lymphoma	None	Oka/Merck vaccine strain VZV identified in CSF	Patient died of complications associated with HIV

Table 2. Continued

Age, Sex	Reported AEs[a]	TTO PV for Vaccination-Associated AE	Medically Significant Case Information	IS Concomitant Therapies	PCR Analysis for VZV	AE Recovery Status at Time of Report
19 y, male	Pneumothorax; Bilateral pneumonia; Rash generalized; Medication error; Varicella; Intubation; Mechanical ventilation; Back pain; Dialysis; Renal impairment; Tracheostomy; Malaise; Adverse drug reaction	3 wk	Transplant; Allergies; History of IgA nephropathy; Immunosuppression	Prednisone; Mycophenolate mofetil	Oka/Merck vaccine strain VZV identified in lesion and saliva samples	Patient slowly stabilizing but remained hospitalized in the ICU
19 y, male	Varicella; Pyrexia; Decreased appetite; Asthenia; Myalgia; Cough	~22 d	Chronic hepatitis; Lymphopenia; "Immune system disorder"; Primary sclerosing cholangitis	NR	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
20 y, male	Necrotising retinitis	~1 wk	Inflammatory bowel disease; Protein-losing enteropathy; Hypogammaglobulinemia; Glucose-6-phosphate dehydrogenase deficiency	Multiple IS therapy	Oka/Merck vaccine strain VZV identified in vitreous aspirate	Lost to follow-up
23 y, male	Varicella	1 mo	HIV	None	Oka/Merck vaccine strain VZV identified in serum sample	Recovered
30 y, female	Necrotising herpetic retinopathy; Varicella	80 d	HIV	None	Oka/Merck vaccine strain VZV identified in ocular fluid	Lesions cleared; Patient discharged from hospital
36 y, male	Varicella; Creatinine high	24 d	Heart transplant 2 y before vaccination	Mycophenolate mofetil; Cyclosporine	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
45 y, female	Respiratory failure; Cholecystitis; Herpes zoster; Infection; Encephalitis; Pneumonia; Medication error	1 mo	End-stage renal disease; Lupus; Failing renal transplant	IS therapy	Oka/Merck vaccine strain VZV identified in lesion sample	Patient died of unspecified infection
48 y, male	Pneumonitis; Varicella; Death; Ascites	19 d	Down syndrome; Drug hypersensitivity; History of dermatitis	None	Oka/Merck vaccine strain VZV identified in lesion and saliva samples	Recovered and discharged; Patient died 6.5 mo PV from pneumonia and ascites, not thought to be related to varicella vaccination
54 y, male	Varicella; Seizure; Confusional state; Medication error; Inappropriate schedule of drug administration; Blood creatinine increased; Platelet count decreased	14 d	Myelofibrosis; Rheumatoid arthritis; Epilepsy	Methotrexate; Ruxolitinib phosphate	Oka/Merck vaccine strain VZV identified in lesion sample	Recovered
67 y, male	Pancytopenia; Herpes zoster; Hepatitis; Bone marrow granuloma; Respiratory distress; Asthenia; Multi-organ dysfunction syndrome; Histiocytosis hematophagic; Varicella; Seborrheic keratosis; Granuloma; Pneumonia; Bacteremia; Herpes zoster disseminated; Leukopenia; Neutropenia; Herpes zoster; Medication error	~8 wk	Non-Hodgkin lymphoma; Chronic leukopenia; Prior chemotherapy and bone marrow transplantation	None	Oka/Merck vaccine strain VZV identified in lesion sample	Recurrent varicella lesions and shingles; Patient died of disseminated varicella (multi-organ failure) 7 mo PV
NR, male	Blindness; Necrotizing herpetic retinopathy	NR	Common variable immunodeficiency	NR	Oka/Merck vaccine strain VZV identified in aqueous fluid	Unknown
Unk/Unk	Varicella; herpes zoster	~30 d (varicella); 49 d to herpes zoster	History of leukemia	NR	Oka/Merck vaccine strain VZV identified in lesion sample	NR

Abbreviations: AE, adverse event; ALT, alanine transaminase; ANCA, antineutrophil cytoplasmic antibody; AST, aspartate transaminase; BAL, bronchoalveolar lavage; CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; ECMO, extracorporeal membrane oxygenation; HZ, herpes zoster; IgA, immunoglobulin A; IS, immunosuppressive; MMR, measles, mumps, and rubella vaccine; MSD, Merck Sharp & Dohme; NR, not reported; PCR, polymerase chain reaction; PV, postvaccination; NR, not reported; s/p, status post; TTO, time to onset; Unk, unknown; VZV, varicella zoster virus.

[a]See Supplementary Appendix 1 for a full breakdown of MedDRA preferred terms.

an HZ event, 1342 reports included information about patient age (median age, 4 years; range, 11 months to 84 years). Time to onset was provided in 51% (817/1602) of reports, with 9% (71/817) occurring within 14 days postvaccination and 16% (134/817) occurring within 42 days postvaccination. Of the 63% (1008/1602) of cases with a reported outcome, 91% (914/1008) recovered, whereas 2 reports listed HZ as a cause of death (Supplementary Appendix 2). There were 260 reports with 261 rash/lesion samples submitted for PCR analysis, including 26 from immunocompromised patients (17 vaccine strain VZV, 4 WTV, 2 VZV-negative, 1 untypable/no strain identified, and 2 inadequate samples).

Rash (Nonvaricella, Non-HZ)

There were 6153 reports (6887 AEs, 345 SAEs) of a rash-related AE. Of the 4668 cases of rash with a reported time to onset (range, 1–5291 days), 76% (3527/4668) occurred within 42 days postvaccination (median, 9 days). An outcome was reported in 68% of cases (4078/6153), 90% (3678/4078) of which were recovered/recovering and 10% (410/4078) had not recovered (each case could include more than 1 rash event and, therefore, more than 1 event outcome). No fatal outcomes were reported. There were 127 reports with 128 rash/lesion samples submitted for PCR analysis, including 4 from immunocompromised patients (2 vaccine strain VZV, 1 WTV, and 1 inadequate sample).

Secondary Transmission

During the review period, 357 reports containing the AE "secondary transmission" were received. Outcome was reported in 91 of 357 cases (25%), of which 84 (92%) recovered, 6 (7%) did not recover, and 1 (1%) died (Supplementary Appendix 2). PCR analysis was performed in 66 cases (with 68 samples), including 6 immunocompromised patients (5 WTV and 1 inadequate sample).

CNS Events

There were 781 reports that included CNS events, the majority of which were febrile convulsion (35%), seizure (32%), ataxia (8%), and encephalitis (7%) (Supplementary Table 1). SAEs comprised 73% (571/781) of CNS event reports. The mean time to onset was 57 days postvaccination (median [range], 9 [1–3886] days). Seventy-three cases with 78 samples (samples for PCR analysis included cerebrospinal fluid and brain tissue) submitted for PCR analysis were reported, including 9 from immunocompromised patients (7 vaccine strain VZV, 1 VZV negative, and 1 untypable/no strain identified).

Disseminated Vaccine-Strain VZV

Disseminated disease caused by the Oka/Merck vaccine strain VZV, with or without visceral involvement, was confirmed by PCR analysis in 39 cases. Eleven cases occurred in immunocompetent individuals, and 28 involved patients who had underlying immunosuppressive conditions and/or who reported concomitant use of immunosuppressant therapies (Tables 2 and 3). Among the 11 immunocompetent patients, vaccine strain VZV was identified in cerebrospinal fluid (CSF; n = 10), lesion samples (n = 2), gastric mucosa (n = 1), and saliva (n = 1); among the 28 immunocompromised patients, vaccine strain VZV was identified in lesion samples (n = 18), bronchoalveolar/sputum (n = 8), CSF (n = 6), ocular samples (n = 3), other samples (n = 3), lung biopsy (n = 1), liver biopsy (n = 1), and serum (n = 1).

Pregnancy

All Pregnancy Cases Reported to MSD

Between March 17, 1995, and March 16, 2017, 1216 women were exposed to VVVL during pregnancy and had pregnancy outcomes available for analysis (Table 4). Timing of exposure was available in 1066/1216 reports, including 883 pregnancies that resulted in 895 liveborn infants (1 set of triplets, 10 sets of twins). Of the 883 reports of live births with known timing of exposure, 288 (32.6%) women received VVVL vaccination before their last menstrual period (LMP), 511 (57.8%) were vaccinated in the first trimester and 84 (9.1%) were vaccinated after the first trimester. Of the women exposed to VVVL before or during pregnancy, congenital anomalies were noted in 56 reports (congenital anomalies include major birth defects as defined by the Metropolitan Atlanta Congenital Defects Program [MACDP]—a population-based tracking system for birth defects among children and infants born to mothers living in metropolitan Atlanta—and congenital anomalies that do not meet MACDP classification as major anomalies), with 14 women exposed before their LMP, 33 exposed in the first trimester, and 9 with unknown time of exposure. Utilizing ACIP recommendations to avoid pregnancy for 1 month after vaccination, 180 of the 288 women were vaccinated <30 days before LMP. Of the 14 reports of congenital anomalies in women exposed before LMP, 6 were vaccinated <30 days before LMP.

MSD Pregnancy Registry

Among the 1522 prospectively enrolled women, there were 966 pregnancy outcomes with 809 live births (819 total infants), none of whom had features consistent with congenital varicella syndrome.

Twenty-two reports of major birth defects were submitted. Using the MACDP methodology [17], including pregnancies that progressed >20 weeks post-LMP, 17 defects occurred among 819 live births, giving a birth prevalence of 2.1 per 100 liveborn infants (95% confidence interval [CI], 1.2–3.3) [1]. Pregnancy outcomes in these 17 women included 16 live births and 1 elective termination at 32 weeks' gestation. The MACDP methodology was revised to include elective terminations after prenatal diagnoses of birth defects at any gestational age (minimum and maximum adjusted defect prevalences were calculated by adding definite prenatal defects and definite plus possible prenatal defects to the hospital-based cases) [18], which allowed 4 elective terminations at <20 weeks' gestation with a diagnosis of a fetal abnormality to meet the inclusion criteria; the resulting 21 major defects provided a birth defect prevalence of 2.6 per 100 liveborn infants (95% CI, 1.6–3.9). In the general US population, approximately 3% of all births (live births or stillbirths) are diagnosed with major birth defects [19]. Using either methodology, the prevalence of major birth defects in the Registry is similar to that in the general population.

Table 3. Summary of Cases of Disseminated Disease With Confirmed Oka/Merck VZV in Immunocompetent Patients

Age, Sex	Reported AEs[a]	TTO PV for Vaccination-Associated AE	Reported Health Status	Concomitant Therapies	PCR Analysis for VZV	AE Recovery Status at Time of Report
3 y, female	Encephalitis; Vomiting; Pyrexia; Ophthalmic herpes zoster; Meningitis	1.6 y	No history of severe or frequent infections; Considered by physician to have been immunocompetent	NR	Oka/Merck vaccine strain VZV identified in CSF	Recovered
4 y, male	Meningitis aseptic; Herpes zoster; Pain in extremity	2.6 y	No history of disease or immunosuppressive illness	NR	Oka/Merck vaccine strain VZV identified in CSF	NR
7 y, male	Meningitis; Herpes zoster	6 y	Previously healthy	NR	Oka/Merck vaccine strain VZV identified in CSF and skin lesion	Recovered
8 y, male	Herpes zoster; Meningitis	7 y	No significant medical history; No prior atypical infections or recognized exposure to varicella; Received 1 dose of varicella vaccine at age 1 y	NR	Oka/Merck vaccine strain VZV identified in CSF and lesion sample	Recovered
8 y, male	Meningitis; Herpes zoster	3.2 y	Normal healthy child; Negative HIV test	Vaccinated against hepatitis A, MMR, hemophilus B, diphtheria, pertussis, tetanus, polio, pneumococcus, influenza	Oka/Merck vaccine strain VZV identified in CSF	Recovered
9 y, male	Meningitis aseptic; Herpes zoster	8 y	Previously healthy; No history of fever or vomiting; No history of recent contact with anyone with a rash or varicella-like illness; Received 1 dose of VVVL at age 1 y; Never had a chickenpox-like illness	NR	Oka/Merck vaccine strain VZV identified in CSF	Recovered
12 y, female	Meningitis; Herpes zoster	11 y	Previously healthy	NR	Oka/Merck vaccine strain VZV identified in CSF	NR
11 y, male	Varicella virus test–positive; Meningitis aseptic	6.5 y from second dose	Immunocompetent; No chickenpox exposure; No history of breakthrough disease; No shingles or rash	NR	Oka/Merck vaccine strain VZV identified in CSF	Recovered
13 y, male	Rash vesicular; Herpes zoster meningoencephalitis; Lid lag; Enterovirus test–positive	~8 y from second dose	Healthy patient; No chronic conditions, acute infections, or immunosuppressive medications	NR	Oka/Merck vaccine strain VZV identified in CSF	Recovered
16 y, male	Gastric perforation; Gastritis; Hemorrhage; Inappropriate schedule of drug administration; Gastric ulcer	~ 3 y from second dose	Family history of a sibling who died after gastric perforation; Possible inherited immune condition conferring susceptibility to acquiring infection; Additional tests to evaluate immune cell function unsuccessful owing to patient noncompliance	Albuterol; Montelukast sodium	Oka/Merck vaccine strain VZV identified in gastric mucosa from endoscopy biopsy	Recovered
NR, "child"	Herpes zoster; Headache; Photophobia; Vomiting	~4 y	Normal host; No known immunosuppression	NR	Oka/Merck vaccine strain VZV identified in CSF and lesion sample	NR

Abbreviations: AE, adverse event; CSF, cerebrospinal fluid; MMR, measles, mumps, and rubella vaccine; NR, not reported; PCR, polymerase chain reaction; PV, postvaccination; NR, not reported; TTO, time to onset; VVVL, varicella virus vaccine live (VARIVAX [Oka/Merck]; Merck & Co., Inc., Kenilworth, NJ); VZV, varicella zoster virus.

[a]See Supplementary Appendix 1 for a full breakdown of MedDRA preferred terms.

Fatal Outcomes

Fatal outcomes temporally, but not necessarily causally, associated with VVVL were reported in 86 of 46 855 (0.002%) postmarketing reports, including 26 from immunocompromised patients (Figure 4). Twenty-one reports (24%) provided insufficient information for further discussion. Of the remaining 65 cases (24 in immunocompromised individuals), death was associated with the following: preexisting conditions (n = 17), complications of varicella (n = 11), complications of herpes zoster (n = 2), other infections (n = 9), pulmonary

Table 4. Pregnancy Outcomes With VVVL

Pregnancy Outcomes, No. (%)	All Reports Between March 17, 1995, and March 16, 2017 (n = 1216)	
	Prospective	Retrospective
Reports	n = 1092	n = 124
Outcomes	n = 1102[a]	n = 127[b]
Live birth	917 (83.2)	83 (65.4)
Spontaneous abortion	109 (9.9)	31 (24.4)
Elective abortion	74 (6.7)	8 (6.3)
Stillbirth/fetal death	1 (0.1)	5 (3.9)
Ectopic pregnancy	1 (0.1)	0

Pregnancy outcomes comprise all reports worldwide, including reports from health care providers, consumers, and the Pregnancy Registry.

Abbreviation: VVVL, varicella virus vaccine live (VARIVAX [Oka/Merck]; Merck & Co., Inc., Kenilworth, NJ).

[a]Includes 8 sets of twins and 1 set of triplets.

[b]Includes 3 sets of twins.

complications (n = 6), cardiac complications (n = 5), CNS (n = 4), and other causes (n = 11) (Supplementary Appendix 2).

DISCUSSION

Although clinical trials are necessary to determine vaccine safety, immunogenicity, and efficacy, postmarketing surveillance is an essential tool to monitor safety profiles postlicensure [20]. The strength of postmarketing surveillance is that it provides information on real-world use in larger populations than is possible with clinical trials, may include populations not included in clinical trials, and identifies less common and/or rare AEs that may not be observed during clinical trials [21]. These strengths are balanced by the limitations of postmarketing surveillance, which relies heavily on voluntary, passive reporting and is often incomplete. Additionally, the number of exposed (vaccinated) persons is an estimation only [22], and thus calculation of accurate AE incidence rates is limited. Evidence included in AE reports, which includes medical information and diagnostic and laboratory data, is provided by the individual who submits the report, generally without confirmation. The data available in AE reports can be sufficient to provide temporal associations but are generally inadequate to establish causality [23]. In this review, we summarize reports and outcomes collected over >2 decades of postmarketing surveillance of VVVL, with safety surveillance further enhanced by PCR analysis.

During 22 years of routine VVVL use, rates of many AEs and SAEs have noticeably decreased, particularly those of varicella and rash. Concerning reports of varicella, most cases occurred >42 days postvaccination, and PCR data suggest that most cases resulted from infection with WTV. However, reports of pyrexia and serious pyrexia appear to have rebounded in recent

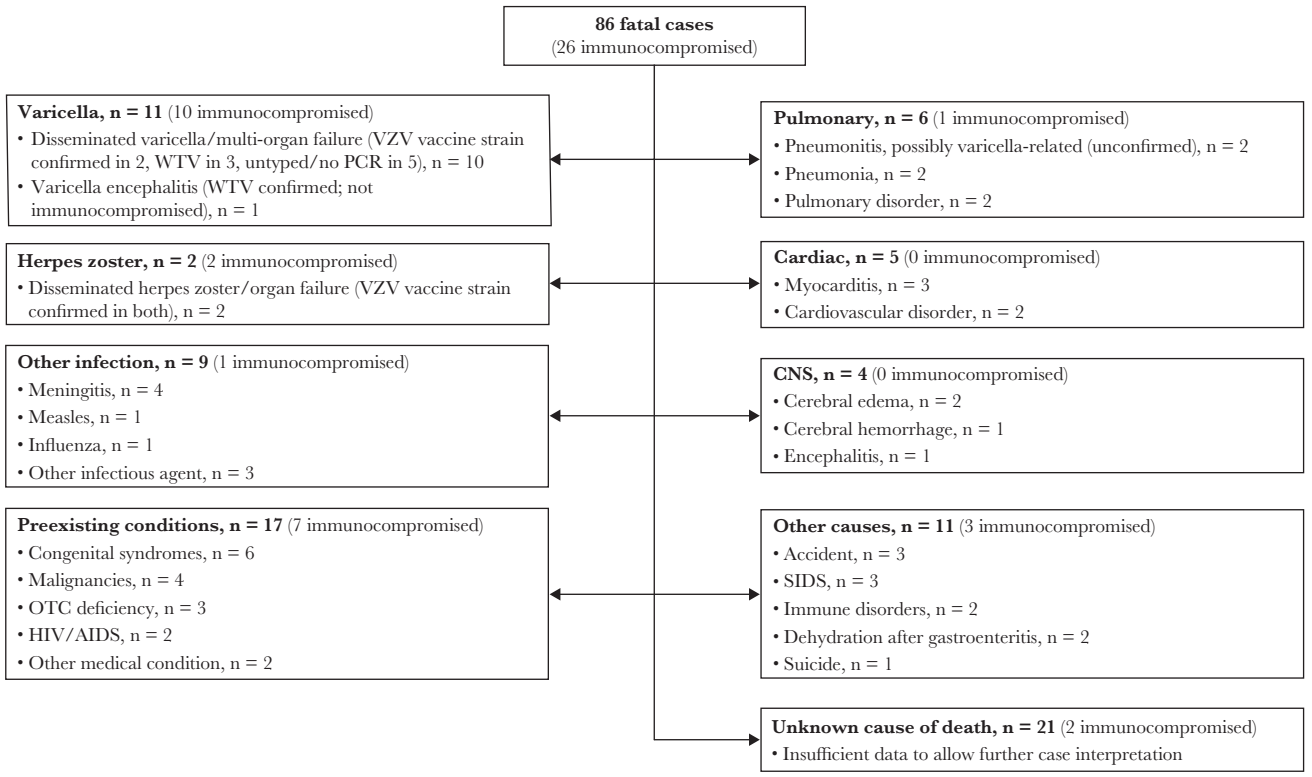

Figure 4. Cases with fatal outcomes. [a]Full details are provided in Supplementary Appendix 2. Abbreviations: CNS, central nervous system; OTC, ornithine transcarbamylase; PCR, polymerase chain reaction; SIDS, sudden infant death syndrome; VZV, varicella zoster virus; WTV, wild-type virus.

years. This increase may be related to the implementation of programs—such as that undertaken in Italy between 2013 and 2014 [24], in which parents of a vaccinated child received preprinted diary cards for specific AEs (eg, injection site reactions, fever, convulsions, headache)—that have correlated with an increase in the reporting of vaccination-associated AEs [25]. Changes in coding also likely contributed to the increase in pyrexia reports. In 2016, MSD adopted the European Medicines Agency list of terms for important medical events [26]; because hyperpyrexia is included in the list, the incidence of pyrexia as an SAE increased almost 3-fold (to 6.14 per million doses between 2015 and 2017), although in the vast majority of reports, medical intervention was not required.

The shift from a 1-dose to a 2-dose vaccination regimen in 2006 was recommended to increase immunity levels, with the second dose added to improve humoral and cellular responses. The introduction of the second dose corresponds with a temporal decrease in the rate of varicella among children and adolescents and a 3.3-fold lower risk of breakthrough disease compared with the prevaccination era [4, 7, 27]. Importantly, overall AE rates did not increase following the introduction of the 2-dose regimen, and no new commonly occurring AEs have been noted in the years since then.

It has been suggested that widespread vaccination may result in decreased maintenance of community immunity, leading to a shift in infections toward older individuals owing to VZV reactivation [2, 28, 29], but to date, studies examining rates of varicella and HZ in adults in the postvaccination era have reported conflicting results [2, 30]. A recent literature review of severe breakthrough cases resulting in disseminated VZV infection suggested that most cases occurred within 5 years of vaccination—that is, in children rather than in adults [31]. Our data would support this, as the immunocompetent patients in whom disseminated disease developed were children (aged 3–16 years) who developed symptoms 2–14 years after vaccination.

Although systemic postvaccination infections are rare in immunocompetent patients, we report 11 cases of Oka/Merck vaccine strain VZV in immunocompetent patients. Secondary transmission is also an uncommon event but has the potential to cause complications in a susceptible contact, such as an immunocompromised or pregnant individual. In prevaccination-era studies, the secondary infection rate of varicella among susceptible children ranged from 61% to 100% [32–34]. In the current analysis, 357 cases (0.0001% of >212 million doses) of potential secondary transmission were recorded, although 38/68 analyzed by PCR proved to be WTV. AEs during pregnancy were uncommon; the prevalence of major birth defects in the Pregnancy Registry was similar to that observed in the general population, and no new safety concerns among susceptible women exposed to the varicella vaccine were identified.

VZV is neurotropic, with recognized presentations including meningoencephalitis, hemiparesis, hemiplegia, myelitis, and peripheral neuritis [35, 36]; however, in general, neurologic complications reported after vaccination were rare. In this analysis, the most commonly reported CNS AEs were seizures/convulsions, which are noted as potential AEs in the VVVL prescribing information [7].

Overall, 86 deaths were reported after VVVL vaccination; however, almost 25% of reports contained insufficient data to identify the cause of death. Immunocompromised individuals are at the highest risk for a fatal varicella-related outcome, and it is important to reiterate that the potential risk of disseminated disease contraindicates VVVL (and other live viral vaccines) in immunosuppressed or immunodeficient individuals, including those on immunosuppressive therapy [7]. Overall, 13 deaths were associated with varicella or HZ, 12 of which occurred among immunocompromised patients. One varicella-associated fatality occurred in an immunocompetent patient and was confirmed by PCR as being due to WTV. Reports of HZ were uncommon (~1 report per 200 000 doses), and although most patients recovered, both cases of HZ with a fatal outcome involved immunocompromised individuals. Oka/Merck vaccine strain VZV was detected from specimens obtained from all 32 immunocompromised patients reporting disseminated disease after receiving VVVL, reinforcing the contraindication for vaccination in these individuals.

CONCLUSIONS

This 22-year analysis, the largest to date, presents the worldwide safety profile as based on spontaneous postmarketing reports for VVVL vaccine after distribution of >212 million doses of vaccine. In addition to VVVL's proven efficacy profile, these data confirm that VVVL is safe and generally well tolerated. Results were consistent with safety trends reported in previous analyses [8, 37], and the overall safety profile of VVVL is consistent with findings from pivotal clinical trials. MSD continues to conduct routine postmarketing surveillance to identify any temporal associations between VVVL vaccine and AEs in order to inform public health practice and ensure the integrity of its product.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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