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RESEARCH PAPER

Post-licensure safety surveillance of zoster vaccine live (Zostavax®) in the United States, Vaccine Adverse Event Reporting System (VAERS), 2006–2015

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ABSTRACT

Background: Herpes zoster (HZ), or shingles, is caused by reactivation of varicella-zoster virus in latently infected individuals. Live-attenuated HZ vaccine (zoster vaccine live, ZVL) is approved in the United States for persons aged ≥50 years and recommended by the CDC for persons ≥60 years. **Methods**: We analyzed U.S. reports of adverse events (AEs) following ZVL submitted to the Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting system to monitor vaccine safety, for persons vaccinated May 1, 2006, through January 31, 2015. We conducted descriptive analysis, clinical reviews of reports with selected pre-specified conditions, and empirical Bayesian data mining. **Results**: VAERS received 23,092 reports following ZVL, of which 22,120 (96%) were classified as non-serious. Of reports where age was documented (n = 18,817), 83% were in persons aged ≥60 years. Reporting rates of AEs were 106 and 4.4 per 100,000 ZVL doses distributed for all reports and serious reports, respectively. When ZVL was administered alone among persons aged ≥50 years, injection site erythema (27%), HZ (17%), injection site swelling (17%), and rash (14%) were the most commonly reported symptoms among non-serious reports; HZ (29%), pain (18%), and rash (16%) were the most commonly reported symptoms among serious reports. Six reports included laboratory evidence of vaccine-strain varicella-zoster virus (Oka/Merck strain) infection; AEs included HZ, HZ- or varicella-like illness, and local reaction with vesicles. In our review of reports of death with sufficient information to determine cause (n = 46, median age 75 years), the most common causes were heart disease (n = 28), sepsis (n = 4), and stroke (n = 3). Empirical Bayesian data mining did not detect new or unexpected safety signals. **Conclusions:** Findings from our safety review of ZVL are consistent with those from pre-licensure clinical trials and other post-licensure assessments. Transient injection-site reactions, HZ, and rashes were most frequently reported to VAERS following ZVL. Overall, our results are reassuring regarding the safety of ZVL.

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Introduction

Herpes zoster (HZ), or shingles, is caused by reactivation of varicella-zoster virus (VZV) years to decades after initial infection.[1] Varicella incidence has declined in the United States since the introduction of varicella vaccine (Varivax®, Merck & Co.) in 1996.[2] However, in 2017, almost all adults aged 65 or older remain latently infected with wild-type VZV (w-VZV).[3] An estimated 1 million cases of HZ occur each year in the United States, often resulting in lasting and debilitating pain.[1,4,5] Increasing age and immunosuppression are primary risk factors.[1,5] Symptoms are difficult to control, particularly among the elderly, who are often unable to tolerate analgesics and psychoactive medications.[6]

Live-attenuated HZ vaccine (zoster vaccine live, ZVL) (Zostavax®, Merck & Co.), which prevents development of HZ, contains the same Oka/Merck vaccine-strain VZV (v-VZV) used in Varivax®, but with ≥19,400 plaque-forming units per dose compared to ≥1,350 for Varivax®.[7-10] In clinical trials, ZVL was 51.3% (adults aged ≥60 years)[11] and 69.8% (adults aged 50–59 years)[12] efficacious in preventing HZ. Injection-site reactions and headaches were common following ZVL[11,12]; serious adverse events (AEs) within the first 42 days after vaccination occurred in 1.4 % of persons aged ≥60 years[11,13] and in 0.6% among persons aged 50–59 years.[12] In 2006, the U.S. Food and Drug Administration (FDA) approved ZVL for adults aged ≥60 years.[7,8] Approval was expanded to include adults aged 50–59 years in 2011.[14] The Advisory Committee on Immunization Practices (ACIP) recommends ZVL for persons aged ≥60 years.[5,14] It is the first live-attenuated vaccine routinely recommended for older adults. Results from a post-licensure safety study in the early years following licensure were consistent with findings from pre-licensure clinical trials.[15] However, routine safety surveillance of ZVL is confounded by age-related illnesses that are common in in the elderly population recommended for vaccination with ZVL. To further assess the safety of ZVL, we reviewed AE reports to the U.S. Vaccine Adverse Event Reporting System (VAERS).

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Methods

Overview and data source

VAERS is a national spontaneous reporting system, co-managed by the Centers for Disease Control and Prevention (CDC) and the FDA, that monitors the safety of U.S.-licensed vaccines.[16] VAERS receives reports of AEs following vaccination from healthcare providers, vaccine manufacturers, patients, parents, and others. Signs and symptoms of reported AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA), an internationally standardized terminology.[17] Reports are assigned 1 or more MedDRA preferred terms (PT); MedDRA PTs are not necessarily medically confirmed diagnoses. VAERS may also receive reports of administration errors (i.e., wrong vaccine administered, wrong age) regardless of outcome.

Reports describing death, life-threatening illness (as defined by the reporter), hospitalization (or its prolongation), or permanent disability are classified as serious according to the Code of Federal Regulations.[18] For serious reports submitted by anyone other than vaccine manufacturers, medical records are routinely requested and made available to VAERS personnel; for reports of deaths, efforts are made to obtain autopsy reports or death certificates. Vaccine manufacturers are required to submit reports to VAERS of AEs that come to their attention and are responsible for conducting appropriate follow-up on these reports.

We conducted 3 categories of analyses: automated descriptive analysis of reports, clinical reviews of reports of pre-specified conditions, and empirical Bayesian (EB) data mining.

Automated analysis

We searched the VAERS database for U.S. reports received from May 1, 2006, through February 28, 2015, with a ZVL vaccination date from May 1, 2006, through January 31, 2015. We conducted descriptive analyses of reports by age, sex, serious and non-serious status, reporter type, and the most commonly reported MedDRA PTs. We calculated crude AE reporting rates for all reports, serious reports and anaphylaxis reports, dividing reports by the number of ZVL doses distributed in the U.S. market for years 2006 through 2014.

Clinical review of reports

We reviewed reports of the following pre-specified conditions (see Appendix 1 for search strategy): serious reports of cellulitis at (or around) the ZVL injection site within 7 days of vaccination, anaphylaxis, serious reports of ophthalmic herpes zoster, rash in a contact of a vaccinated patient, vaccination error reports involving administration of a wrong vaccine, reports with laboratory evidence of v-VZV infection, reports of ZVL administration during pregnancy, and deaths. We chose these conditions because they represent serious or medically important AEs of concern for post-licensure vaccine safety surveillance (cellulitis, anaphylaxis, ophthalmic herpes zoster, and deaths, rash in a contact of a vaccinated patient, and reports with laboratory evidence of v-VZV infection), or represent common, preventable vaccination errors (a wrong vaccine given and ZVL administration during pregnancy). For reports of death, a board certified pathologist reviewed medical records, autopsy reports, death certificates, and other available documentation obtained on follow-up to determine cause of death.

Empirical Bayesian (EB) data mining

We conducted EB data mining[19] to identify AEs reported more frequently than expected following ZVL compared to all other U.S.-licensed vaccines. We used published criteria[20] and adjusted for sex, age and year to identify ZVL-AE pairs reported at least twice as frequently as expected (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05 >2]).

Results

Descriptive analysis

VAERS received 23,092 U.S. reports following ZVL during the analytic period (Table 1); 972 (4%) were classified as serious, including 74 deaths. Among reports that included patient age (n = 18,817), median age was 65 years (range 7 months-101 years), with the majority aged ≥60 years (Table 1). In 20,884 (90% of total reports), ZVL was given alone. Among persons aged ≥50 years who received ZVL alone, injection-site reactions, HZ and rash were the most commonly reported non-serious AEs; while HZ, pain, rash, dyspnea and pyrexia were the most commonly reported serious AEs (Table 2).

Based on 21,846,030 doses of ZVL distributed in the United States from licensure in 2006 through 2014 (personal communication, Merck & Co.), crude AE reporting rates were 106 per 100,000 doses distributed for all reports and 4.4 per 100,000 for serious reports.

Table 1. Characteristics of zoster vaccine live (ZVL) reports submitted to VAERS, May 2006–January 2015.

Report characteristics	N (%)
Total reports	23,092
Serious[1]	972 (4)
Female	15,469 (67)
ZVL given alone[2]	20,884 (90)
Type of reporter	
Manufacturer	11,390 (49)
Healthcare provider	6,408 (28)
Other	3,463 (15)
Patient/parent	1,831 (8)
Age groups (years)	
<50[3]	877 (4)
50–59	2,257 (10)
≥60[4]	15,683 (68)
Missing or unknown age	4,275 (19)

[1]Includes death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.
[2]Among persons aged ≥50 years, when ZVL was given concomitantly with other vaccines, the most common vaccines included: inactivated influenza (53%), 23-valent pneumococcal polysaccharide (29%), and tetanus, diphtheria, pertussis (Tdap) (18%).
[3]ZVL is not FDA approved for this age group.
[4]When restricting analysis to reports where age was documented (n = 18,817), 83% were in persons aged ≥60 years.

Table 2. Most commonly reported adverse events among persons aged ≥50 years following zoster vaccine live (ZVL) in VAERS, May 2006–January 2015[1], based on automated analysis.

Non-serious reports		
MedDRA Preferred Term[2]	Total[3] N = 17,089	ZVL alone N = 15,397
	n (%)	n (%)
Injection site erythema	4,661 (27)	4,193 (27)
Injection site swelling	2,854 (17)	2,555 (17)
Herpes zoster	2,781 (16)	2,644 (17)
Rash	2,283 (13)	2,094 (14)
Erythema	2,215 (13)	1,943 (13)
Injection site pain	1,993 (12)	1,743 (11)
Pruritus	1,947 (11)	1,768 (11)
Pain	1,811 (11)	1,605 (10)
Injection site warmth	1,791 (10)	1,625 (11)
Injection site pruritus	1,714 (10)	1,575 (10)
Serious reports[1]		
MedDRA Preferred Term[2]	Total[3] N = 851	ZVL alone N = 753
	n (%)	n (%)
Herpes zoster	228 (27)	221 (29)
Pain	154 (18)	133 (18)
Rash	131 (15)	123 (16)
Pyrexia	118 (14)	90 (12)
Dyspnea	114 (13)	94 (12)
Asthenia	104 (12)	78 (10)
Headache	97 (11)	81 (11)
White blood cell count increased	96 (11)	75 (10)
Nausea	91 (11)	75 (10)
Dizziness	81 (10)	63 (8)

[1]Vaccinated May 1, 2006 to January 31, 2015; reports received through February 28, 2015.
[2]A single report may contain more than 1 adverse event (i.e., not mutually exclusive).
[3]Total includes reports with ZVL +/− any other concomitant vaccines given at the same visit.
[4]Includes death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.

Clinical review of reports of pre-specified conditions (as defined in Appendix 1)

Serious reports of cellulitis at (or around) the ZVL injection site within 7 days of vaccination

We identified 41 reports of cellulitis at (or around) the ZVL injection site that occurred within 7 days of vaccination and were classified as serious; 31 when ZVL was the only vaccine administered in the arm with cellulitis. Nineteen reports described hospitalization specifically for the cellulitis and treatment with intravenous antibiotics, 15 of which documented administration of ZVL only.

Anaphylaxis

We identified 36 reports of anaphylaxis following ZVL, a reporting rate of 1.6 reports per million doses distributed. Median age was 66 years (range 50–79 years). Medical records were available for 13 reports; onset ranged from 10 minutes to less than 3 days. A diagnosis of anaphylaxis was supported in 11 of the 13 reports, based on either Brighton Collaboration criteria[21] (n = 4 at Level 1 – the highest level of diagnostic certainty, and n = 4 at Level 2) or documented physician diagnosis (n = 3). When restricted to these 11 cases, the reporting rate for anaphylaxis was 0.5 reports per million doses distributed. Among the 11 cases, 7 received ZVL only. Eight reports documented hospitalization. Six of these 11 reports documented a history of allergies as follows: 1) iodine, erythromycin 2) dust mites, food additives (including monosodium glutamate which is contained in the vaccine) 3) shellfish, bee stings, contrast dye used in intravenous pyelogram, codeine 4) clindamycin, erythromycin, penicillin, raloxifene, 5) Nonsteroidal anti-inflammatory drugs, barbiturates 6) beef and pork (their by-products are contained in the vaccine) and dairy. There were no deaths among the anaphylaxis reports.

Serious reports of ophthalmic herpes zoster

Of 106 reports with a MedDRA PT of ophthalmic herpes zoster, 15 met the regulatory definition of serious. Seven reports stated that ophthalmic herpes zoster occurred several months or years after ZVL vaccination. In 3 reports, the onset interval of ophthalmic signs or symptoms was not provided. Two cases were not zoster; 1 person developed herpes simplex iridocyclitis, and another developed uveitis but it was unclear whether the uveitis case had ever received ZVL. Of the remaining 3, ophthalmic complications began within 15 days after vaccination: ophthalmic shingles and herpetic keratitis with corneal involvement, both in ZVL recipients, and herpes zoster of the right eye of a family member of someone who had received ZVL 7 days earlier.

Rash in a contact of a vaccinated patient

We identified 98 reports of rashes occurring in contacts of vaccinated patients; 12 were serious, with concurrent AEs including pneumonia and confusion, and HZ- and varicella-like illnesses. Among 55 reports documenting age of the contact, ages ranged from 6 weeks to 90 years (median 58 years). Among 59 reports documenting onset, median time to rash was 10 days following ZVL vaccination of the primary patient (range 0 days-2 years). Of the 98 reports of rashes occurring in contacts of vaccinated patients, in 71, it was unknown from the report if the primary vaccinated patient had a rash. Among the remaining 27 reports, 5 primary vaccinated patients had various rashes preceding the rash in the contact and 22 did not have any rash. Laboratory test results were documented for 5 contacts with a rash; 2 tested positive for w-VZV and the remainder were negative for any VZV. Of these 5 contacts with laboratory testing, in 3, the primary vaccinated patient did not have a rash and in 2 it was unknown if the if the primary vaccinated patient had a rash. No laboratory tests were documented on contacts of primary vaccinated patients who had rashes.

Vaccination error reports involving a wrong vaccine given

We identified 744 reports of ZVL vaccination errors involving administration of a wrong vaccine; 183 of these errors were reported in 2007, the first full year of ZVL use, and the number fell to 76 by 2014. Of 686 reports with adequate documentation to assess circumstances surrounding the error, 570 (83%) were a mix-up involving administration of ZVL or varicella vaccine (Varivax®) when the intent was to give the other. The remaining errors involved several other vaccines. Among 510 reports

of ZVL being given in error instead of varicella vaccine, the median patient age was 8 years (range 1–74 years).

Reports with laboratory evidence of v-VZV infection

We identified 6 reports of AEs following ZVL with evidence of v-VZV infection on laboratory testing. These reports are described in Table 3.

Reports of ZVL administration during pregnancy

We identified 9 reports documenting ZVL administration during pregnancy (a contraindication[7,8]). Median age was 35 years (range 30–50 years), based on 8 reports with information on age. Among 7 reports with information on timing of vaccination, 6 women were vaccinated during first trimester and 1 was vaccinated during third trimester. In 5 reports, an AE was documented, including: uncontrolled hyperglycemia (diabetic patient), infant born with cleft lip, 2 spontaneous abortions, and injection site erythema. Four reports did not document an AE.

Table 3. Reports of adverse events following zoster vaccine live (ZVL) with laboratory evidence of vaccine-strain varicella-zoster virus (Oka/Merck strain) infection in VAERS, May 2006–January 2015.

A 64-year-old male with a history of varicella in childhood and Hashimoto's hypothyroidism received ZVL while on chronic immunosuppression therapy with prednisone and methotrexate for Sjogren's syndrome and leukocytoclastic vasculitis. He developed disseminated herpes zoster- or varicella-like rash approximately 55 days after ZVL vaccination. He was hospitalized for 2 days and improved with treatment of antivirals. (In the month prior to rash development, he had been hospitalized for community-acquired pneumonia). A specimen submitted for testing to the vaccine manufacturer by polymerase chain reaction (PCR) confirmed vaccine strain varicella-zoster virus.
A 68-year-old female with essential hypertension, hypertensive renal disease, stage 3 chronic kidney disease, hypothyroidism, hypertriglyceridemia, osteoporosis, prediabetes, gout, and allergy to penicillin received ZVL and developed herpes zoster approximately 264 days later. She was treated as an outpatient with antivirals and recovered. A specimen from the patient submitted for testing to the CDC National Varicella Zoster Virus (VZV) Laboratory by PCR confirmed vaccine strain varicella-zoster virus.
A 51-year-old male with a history of seronegative spondyloarthritis had underlying immunosuppression from taking methotrexate when he received ZVL. About 6 days later he developed disseminated herpes zoster- or varicella-like illness. He was treated as an outpatient and recovered. Neither the patient nor his mother had any memory of the patient having had prior varicella illness or varicella vaccination. A specimen from the patient submitted for testing to the CDC National VZV Laboratory by PCR confirmed vaccine strain varicella-zoster virus.
A 73-year-old female with rheumatoid arthritis was treated intermittently with steroids. She received ZVL and approximately 18 days later developed herpes zoster for which she was treated as an outpatient. She stated from memory that she had a prior history of varicella. Prior varicella vaccination status is unknown. A specimen from the patient submitted for testing to the vaccine manufacturer by PCR confirmed vaccine strain varicella-zoster virus.
A healthy 60-year-old female with a history of varicella received ZVL. Approximately 48 hours later, she had developed vesicles at the site of injection, flulike symptoms, and achiness. She was treated as an outpatient. A specimen submitted for testing to the vaccine manufacturer by PCR confirmed vaccine strain varicella-zoster virus.
A 62-year-old male with history of obesity and obstructive sleep apnea received ZVL and 19 days later developed disseminated herpes zoster- or varicella-like rash with slight fever and fatigue. He was treated as an outpatient and recovered. A specimen from the patient submitted for testing to the CDC National VZV Laboratory by PCR confirmed vaccine strain varicella-zoster virus.

Deaths

We identified 74 reports of death following ZVL. Among reports with a death certificate, autopsy report, or medical records available (n = 46) to confirm a death occurred, median age was 75 years (range 56–94 years) and median time from vaccination to death was 20 days (range 0–285 days). Causes of death are listed in Table 4.

Empirical Bayesian (EB) data mining

EB data mining for ZVL revealed EB05 > 2 for the following MedDRA PTs: *Herpes zoster, Injection-site reactions, Administration errors,* and *Secondary transmission.*

Discussion

Our review, spanning a nearly 9-year analytic period during which time close to 22 million ZVL doses were distributed, represents the first comprehensive safety evaluation of ZVL in VAERS since its licensure in 2006. Overall, our findings are consistent with those from pre-licensure clinical trials and other post-licensure assessments.[11,13,15,22] Injection site reactions were most commonly reported. Forty-one reports of cellulitis occurring within 7 days of vaccination were classified as serious, nearly half (n = 19) of which described hospitalization and treatment with intravenous antibiotics; however, it is unclear if some of these cases were true bacterial cellulitis or cellulitis-like injection site reactions, which can occur after ZVL and other vaccines.[23] The types, frequencies, and proportions of serious and non-serious AEs are generally comparable with other vaccines given to individuals in similar age groups.[24,25] Exceptions include AEs unique to or more likely to be reported in association with a live herpes zoster vaccine, such as HZ- and varicella-like illnesses (which also accounts for reports of rash), ophthalmic herpes zoster, rash in a contact of a vaccinated patient, and reports with laboratory evidence of v-VZV infection. However, these events have been observed in pre-licensure clinical trials

Table 4. Causes of death for reports of death following zoster vaccine live (VZL) in VAERS, May 2006–January 2015.[1,2]

Cause of death	n (%)
Heart disease[3]	28 (61)
Sepsis (other bacterial diseases)	4 (9)
Stroke (cerebrovascular diseases)	3 (7)
Acute kidney failure and chronic kidney disease	2 (4)
Aortic aneurysm (diseases of arteries, arterioles and capillaries)	2 (4)
Acute pancreatitis	1 (2)
Cancer (female breast inflammatory cancer)	1 (2)
Gastrointestinal hemorrhage	1 (2)
Hypertensive heart disease	1 (2)
Leukocytosis, unspecified	1 (2)
Unspecified viral encephalitis[4]	1 (2)
Urosepsis	1 (2)
Total	46

[1]Of the 74 reports of death following ZVL, sufficient information was available in 46 reports from a death certificate, autopsy report, or medical record to confirm a death and determine cause.
[2]All death reports were reviewed by a board certified pathologist.
[3]Includes acute myocardial infarction, cardiac arrest, cardiorespiratory failure, and coronary artery disease.
[4]No herpes simplex virus or varicella zoster virus isolated from cerebrospinal fluid.

and other post-licensure safety reviews[7,8,11-13,15,22] and are therefore not considered new safety concerns.

In a pivotal clinical trial, ZVL was 51.3% (95% confidence interval 44.2% to 57.6%) efficacious in preventing HZ in adults aged ≥60 years.[11] Later, in a long-term persistence study, vaccine efficacy was observed to decrease substantially over time, with confidence intervals overlapping 0% for incident HZ after 8 years.[26] HZ is relatively common in the United States as individuals age past 60 years[1,4,5] and given ZVL's modest vaccine efficacy and waning immunity over time, a substantial number of vaccinated individuals (coverage around 31% among adults ≥60 years[27]) will be susceptible to wild-type HZ disease. Reports to VAERS of HZ and HZ-like illness following ZVL (10% of which occurred a year or more after vaccination) could represent cases of vaccine failure or waning immunity.

Transmission of v-VZV to a contact of a ZVL vaccinated patient has not been reported,[28] but could potentially pose a safety risk, especially if the contact has not previously been exposed to VZV (i.e., VZV-naïve). VZV from HZ is transmissible from person-to-person during the time rash is present until lesions crust,[5] and given that we identified reports of vaccinated patients with HZ- and varicella-like illness and specimens positive for v-VZV, transmission to a contact is theoretically possible. However, we did not identify any reports with laboratory evidence of transmission of v-VZV to a contact of a vaccinated patient.

Of the 6 reports of vaccine recipients with laboratory evidence of v-VZV infection, 3 were taking, or had a history of taking, immunosuppressing drugs (prednisone, methotrexate). ZVL has been given safely to immunocompromised individuals and may be particularly beneficial to individuals with immunocompromising conditions and those on immunosuppressive therapy.[29,30] Healthcare providers, though, should be aware of contraindications and precautions and proper screening procedures prior to vaccination with live virus vaccines.

ZVL is recommended for adults aged ≥60 years,[5] a group with increasing baseline age-related illnesses and mortality, especially as individuals move into the eighth and ninth decades of life. As a result, deaths following ZVL, some in close temporal association with vaccination, would be expected due to chance alone. Of the 46 reports of death (median age 75 years) where death certificates, autopsy reports, or medical records were available for review, causes were consistent with those commonly observed in individuals aged ≥65 years in the United States,[31] with heart disease and stroke accounting for 67% of reported deaths (Table 4). We did not observe any unusual patterns or clustering of deaths that would suggest a causal association with ZVL.

There were a substantial number of reports (n = 744) of errors involving wrong vaccine administered, and administration errors signaled in empirical Bayesian data mining. Upon review, most wrong vaccine administered reports were mix-ups between ZVL and varicella vaccine. Vaccination errors involving mix-ups between ZVL (Zostavax®) and varicella vaccine (Varivax®) – which contain the same antigen, have similar naming conventions, and use similar looking antigen and diluent vials – are preventable if proper preparation and administration procedures are followed. These procedures include confirming the patient name and age, confirming the vaccine type and brand name, and reviewing prescribing information in the vaccine package insert.[32]

Reported errors decreased over time following licensure, but training and other prevention strategies remain important for healthcare providers involved in vaccine administration.[32] In addition, ZVL was, on rare occasions (n = 9) reported to have been administered during pregnancy, a contraindicating condition.[7,8] This likely represents 2 errors occurring at the same time, wrong vaccine given (women of reproductive age should be getting varicella vaccine, not ZVL, if they need vaccination) and a live vaccine administered to a pregnant women.

Limitations

VAERS is national in scope, accepts reports from anyone without judging clinical importance of the AE, and is effective at rapidly detecting safety signals and rare AEs. However, it is subject to the limitations of spontaneous reporting systems, which include underreporting (especially for clinically non-serious AEs or AEs occurring a long time after vaccination, like possible reactivation of v-VZV), reporting biases, problems with data quality and completeness, and lack of an unvaccinated comparison group.[16] Due to these limitations, it is generally not possible to determine if a vaccine caused an AE from VAERS data alone. Exceptions might include HZ- or varicella-like illnesses in a patient with conclusive evidence of laboratory confirmed v-VZV infection (e.g., v-VZV isolated from a vesicle exudate), or anaphylaxis occurring within minutes of ZVL vaccination with no evidence of any other environmental exposure that could reasonably explain an anaphylactic reaction. Estimates of reporting rates using doses of ZVL distributed as a denominator should be interpreted with caution, since the actual number of doses administered is not known, nor is the rate of underreporting. Despite its limitations, VAERS is an important monitoring system to detect potential vaccine safety problems that might require further investigations using controlled studies.

Conclusion

In our review of VAERS reports following ZVL, we did not detect any unusual or unexpected patterns or any previously unidentified safety concerns. Reports of HZ and HZ-like illness following ZVL might indicate vaccine failure or waning immunity, rather than a de novo AE. Overall, the results of our safety review of ZVL are reassuring.

Disclosure of interest

The authors report no conflict of interest.

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 (CDC) or the U.S. Food and Drug Administration (FDA). Mention of a product or company name is for identification purposes only and does not constitute endorsement by the CDC or FDA.

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Appendix 1. Search strategy to identify zoster vaccine live (ZVL) reports of selected pre-specified conditions in VAERS, May 2006–January 2015.[1]

Pre-specified condition	Search strategy to identify pre-specified condition[1]
Serious reports of cellulitis at (or around) the injection site[2]	MedDRA PTs: cellulitis, cellulitis staphylococcal, cellulitis streptococcal, injection site cellulitis, vaccination site cellulitis, post procedural cellulitis (occurring within 7 days of vaccination)
Anaphylaxis	MedDRA PTs: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock
Ophthalmic herpes zoster	MedDRA PTs: herpes zoster ophthalmic, ophthalmic herpes zoster
Rash in a contact of a vaccinated patient	MedDRA PTs: infection transmission via personal contact, secondary transmission, sexual vertical infection transmission, indirect infection transmission
Wrong vaccine given	MedDRA PTs: drug dispensing error, wrong drug administered, drug administration error, medication error, vaccination error
Laboratory evidence of vaccine-strain varicella zoster virus (v-VZV)[3]	Text string search for Box 7 (description of the adverse event) and Box 12 (diagnostic tests/ laboratory data) of the VAERS-1 form: "strain", "pcr", "identification program", "wild type", "wild-type", "specimen", "genotype", "positive", "oka positive", "vaccine type" or "attenuated"
ZVL administration during pregnancy Or MedDRA SOC groupings: pregnancy, puerperium and perinatal conditions, or congenital, familial and genetic disorders Or Text string search for "preg" in the fields for symptoms, pre-existing conditions and medical history	MedDRA PTs: drug exposure during pregnancy, exposure during pregnancy, maternal exposure during pregnancy
Death	MedDRA PT: died; also included reports where the checkbox for "Patient died" was checked in Box 8 (section to determine serious status) of the VAERS-1 form

[1]Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs), System Organ Class (SOC) groupings or text string searches.
[2]Reports were identified using MedDRA PTs and reviewed to exclude cellulitis cases not at (or around) the injection site.
[3]Reports containing the text strings were individually reviewed for laboratory testing and results.