Herpes Zoster Vaccination: Update

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Outline

- GSK postmarketing commitments for Recombinant Zoster Vaccine (RZV)
- CDC postmarketing monitoring
  - RZV Safety
  - RZV Effectiveness
  - Zoster Vaccine Coverage
  - RZV Supply

GSK Postmarketing Committments for RZV

- To assess the safety, reactogenicity and immunogenicity of RZV in adults ≥50 years of age with a prior episode of Herpes Zoster
  (*Protocol submission: Q2, 2018 | Study complete:Q4, 2020*)

- A targeted safety study to evaluate the safety of RZV in adults ≥50 years
  (*Protocol submission: Q4, 2020 | Study complete:Q2, 2024)*

- A study to assess the long-term efficacy, immunogenicity and safety of RZV in adults ≥50 years of age
  (*Protocol submission: Q4, 2021 | Study complete: Q3, 2023)*

https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM581750.pdf

RZV Safety

Vaccine Adverse Event Reporting System (VAERS)[1]

Strengths

- National data
- Accepts reports from anyone
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess causality

As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems

[1] Co-managed by CDC and FDA (http://vaers.hhs.gov)

Reports to VAERS following RZV

- From Oct 20, 2017–Apr 27, 2018, n= **680 reports**
- No unusual patterns or unexpected adverse events
- 48 (7%) involved co-administration with ≥1 additional vaccines:
  - Pneumococcal polysaccharide (14)
  - Pneumococcal conjugate (12)
  - Quadrivalent inactivated influenza (7)
  - Tdap (tetanus, diphtheria, acellular pertussis) (6)
  - Adjuvanted inactivated influenza (1)

Reports to VAERS following RZV	
Total reports[1]	**680**
Female	430 (63%)
Non-serious[2]	649 (95%)
Death	5 (1%)
Age group	
50–59 years	145 (21%)
60–69 years	278 (41%)
70–79 years	143 (21%)
80+ years	35 (5%)
Unknown	79 (12%)
Reporter type	
Patient or caregiver	129 (19%)
Health care professional	296 (45%)
Vaccine manufacturer	228 (34%)
Other	27 (4%)

[1] Total reports received 1,963 (lag time involves processing, MedDRA coding, data entry, and quality control)

[2] Serious reports are based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability

Most common symptoms in reports to VAERS following RZV, Oct 20, 2017–Apr 27, 2018

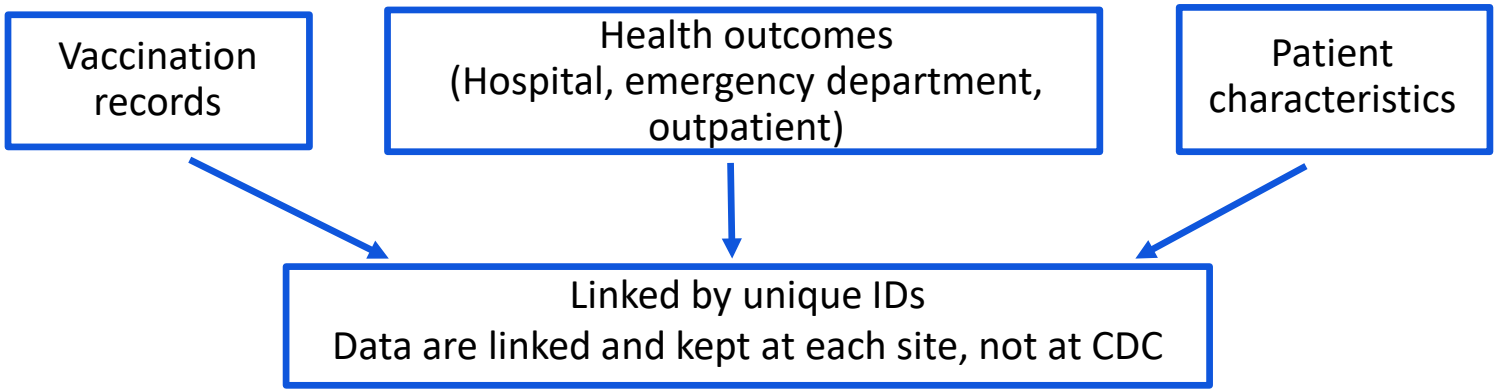
MedDRA[1] Preferred Term[2] (symptom)
Injection site pain (25% of reports)
Pyrexia (22%)
Injection site erythema (21%)
Chills (19%)
Pain (17%)
Headache (16%)
Pain in extremity (15%)
Injection site swelling (14%)
Erythema (10%)
Myalgia (10%)
Rash (10%)
Injection site warmth (9%)
Nausea (8%)
Herpes zoster (7%)
Rash, erythematous (6%)

[1] Medical Dictionary for Regulatory Activities (https://www.meddra.org/)

[2] More than one MedDRA Preferred Term (symptom) may be assigned to a VAERS report (i.e., not mutually exclusive)

Vaccine Safety Datalink (VSD)

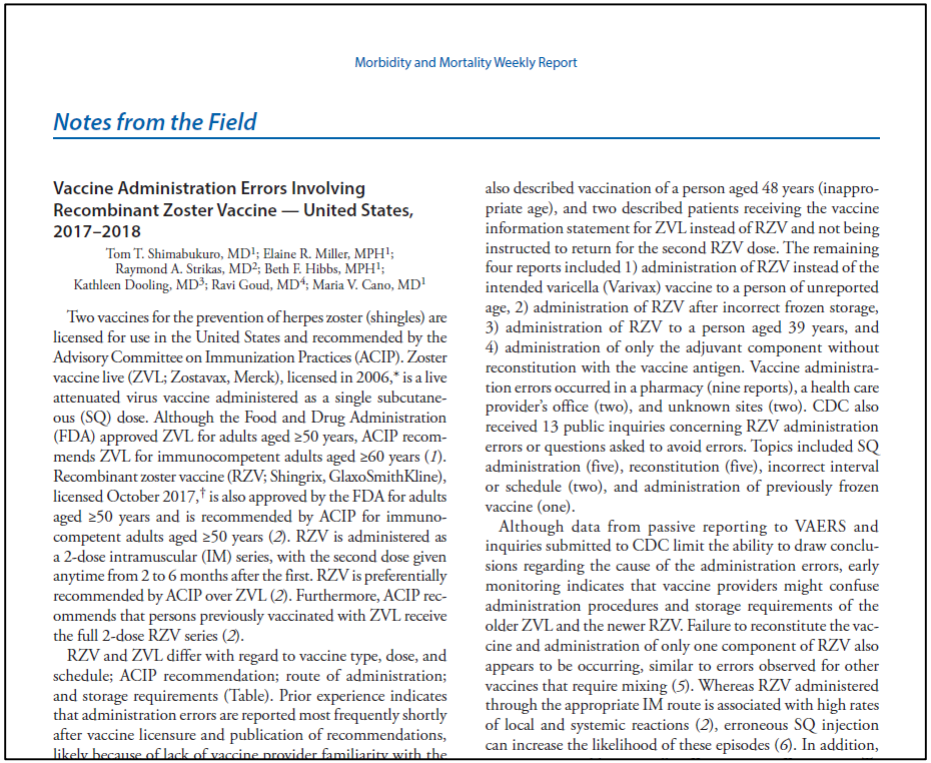
- Established in 1990
- Collaboration between the CDC and several integrated healthcare plans
- Data on over 10 million persons per year (~3% of U.S. population)
- Links vaccination data to health outcome data



Vaccine Safety Datalink (VSD) monitoring for RZV

- As of May 31, 2018, 37,303 total doses of RZV administered at the 6 VSD sites that are participating in safety monitoring
  - 35,431 first doses, 1,872 second doses
- VSD Rapid Cycle Analysis (RCA) protocol under review at VSD sites
  - First data extraction anticipated in early August 2018 with a 3 month lag for risk windows (i.e., doses administered up to April 2018)
- VSD monitoring for RZV includes:
  - High priority short-term RCA outcomes (e.g., Guillain-Barré syndrome, anaphylaxis, acute myocardial infarction)
  - Lower priority short-term outcomes for descriptive analysis (e.g., gout, local and systemic reactions)
  - Longer term outcomes (e.g., potential immune-mediated diseases)

Vaccine administration errors involving RZV[1]



Morbidity and Mortality Weekly Report

Notes from the Field

Vaccine Administration Errors Involving Recombinant Zoster Vaccine — United States, 2017–2018

Tom T. Shimabukuro, MD[1]; Elaine R. Miller, MPH[1]; Raymond A. Strikas, MD[2]; Beth F. Hibbs, MPH[1]; Kathleen Dooling, MD[3]; Ravi Goud, MD[4]; Maria V. Cano, MD[1]

Two vaccines for the prevention of herpes zoster (shingles) are licensed for use in the United States and recommended by the Advisory Committee on Immunization Practices (ACIP). Zoster vaccine live (ZVL; Zostavax, Merck), licensed in 2006,* is a live attenuated virus vaccine administered as a single subcutaneous (SQ) dose. Although the Food and Drug Administration (FDA) approved ZVL for adults aged ≥50 years, ACIP recommends ZVL for immunocompetent adults aged ≥60 years (*1*). Recombinant zoster vaccine (RZV; Shingrix, GlaxoSmithKline), licensed October 2017,† is also approved by the FDA for adults aged ≥50 years and is recommended by ACIP for immunocompetent adults aged ≥50 years (*2*). RZV is administered as a 2-dose intramuscular (IM) series, with the second dose given anytime from 2 to 6 months after the first. RZV is preferentially recommended by ACIP over ZVL (*2*). Furthermore, ACIP recommends that persons previously vaccinated with ZVL receive the full 2-dose RZV series (*2*).

RZV and ZVL differ with regard to vaccine type, dose, and schedule; ACIP recommendation; route of administration; and storage requirements (Table). Prior experience indicates that administration errors are reported most frequently shortly after vaccine licensure and publication of recommendations, likely because of lack of vaccine provider familiarity with the

also described vaccination of a person aged 48 years (inappropriate age), and two described patients receiving the vaccine information statement for ZVL instead of RZV and not being instructed to return for the second RZV dose. The remaining four reports included 1) administration of RZV instead of the intended varicella (Varivax) vaccine to a person of unreported age, 2) administration of RZV after incorrect frozen storage, 3) administration of RZV to a person aged 39 years, and 4) administration of only the adjuvant component without reconstitution with the vaccine antigen. Vaccine administration errors occurred in a pharmacy (nine reports), a health care provider's office (two), and unknown sites (two). CDC also received 13 public inquiries concerning RZV administration errors or questions asked to avoid errors. Topics included SQ administration (five), reconstitution (five), incorrect interval or schedule (two), and administration of previously frozen vaccine (one).

Although data from passive reporting to VAERS and inquiries submitted to CDC limit the ability to draw conclusions regarding the cause of the administration errors, early monitoring indicates that vaccine providers might confuse administration procedures and storage requirements of the older ZVL and the newer RZV. Failure to reconstitute the vaccine and administration of only one component of RZV also appears to be occurring, similar to errors observed for other vaccines that require mixing (*5*). Whereas RZV administered through the appropriate IM route is associated with high rates of local and systemic reactions (*2*), erroneous SQ injection can increase the likelihood of these episodes (*6*). In addition,

[1] Shimabukuro TT, Miller ER, Strikas RA, et al. Notes from the Field: Vaccine Administration Errors Involving Recombinant Zoster Vaccine — United States, 2017–2018. MMWR Morb Mortal Wkly Rep 2018;67:585–586. DOI: http://dx.doi.org/10.15585/mmwr.mm6720a4

CDC Communication regarding Administration Errors & RZV Reactogenicity

Provider outreach

- MMWR
- CME-"You call the shots"
- Medscape video
- Web pages
- Webinars and conferences
- Fact sheets

Public outreach

- Vaccine Information sheet (VIS)
- Web pages
- Fact sheet

Fact Sheets for Healthcare Providers

Protect your patients with the new shingles vaccine

CDC recommends new shingles vaccine (Shingrix) for adults 50 and older

patients: 50+ years old

doses: 2-6 months apart

administer: intramuscular in the deltoid

storage: 36°-46° refrigerate

Who should get Shingrix

Give Shingrix to immunocompetent adults **50 years and older**, including those who

- had shingles in the past
- received Zostavax® at least 8 weeks prior
- have health conditions, such as chronic renal failure, diabetes mellitus, rheumatoid arthritis, or chronic pulmonary disease
- are receiving other vaccines, such as influenza and pneumococcal vaccines, at the same visit
- are taking low-dose immunosuppressive therapy

While Shingrix is not contraindicated in immunocompromised people, it is not recommended by the Advisory Committee on Immunization Practices (ACIP) at this time. ACIP will review evidence for Shingrix in immunocompromised people as it becomes available.

Who should not get Shingrix

You should not give Shingrix to a patient who has ever had a severe allergic reaction, such as anaphylaxis, to a component of this vaccine, or after a dose of Shingrix. Consider delaying vaccination if your patient is pregnant, lactating, or experiencing an acute episode of shingles.

Administering and storing Shingrix

- Adults 50 years and older should receive **2 doses** of Shingrix. Give the second dose **2 to 6 months** after the first.
- Administer Shingrix **intramuscularly** in the deltoid region of the upper arm with a 1- to 1.5-inch needle.
- Both vials of Shingrix must be refrigerated at a temperature of 36-46° F. Do not use if exposed to temperatures below 36° F.

Reconstitution

- Prepare Shingrix by reconstituting the antigen component with the adjuvant suspension component.
- Either administer it immediately, or store it in the refrigerator and use it within 6 hours of reconstitution. Otherwise, discard it.

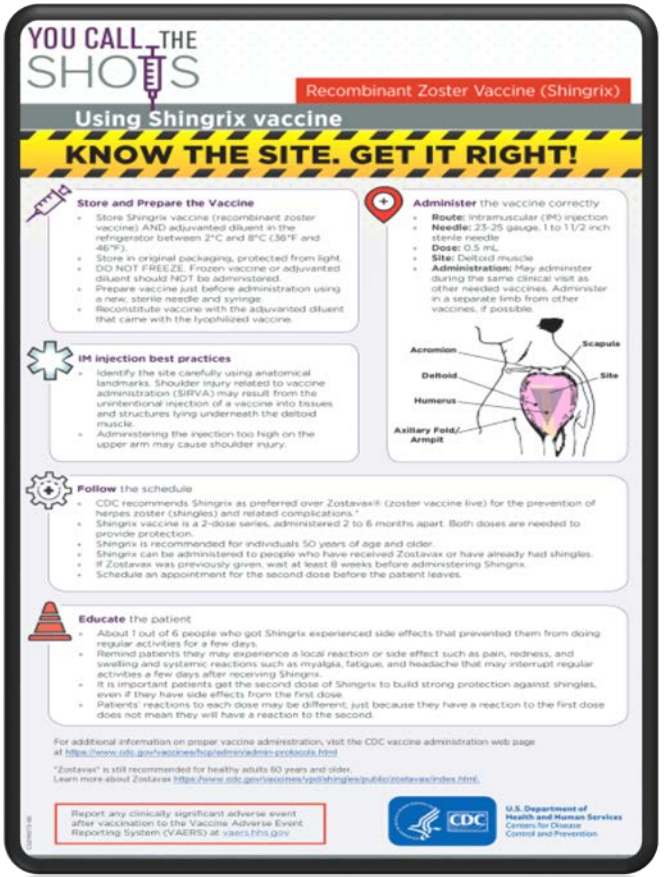
Cost and insurance

Shingrix is now covered by most health insurance plans. Tell your patients to contact their health insurance providers ahead of time to see if they will cover the vaccine

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

www.cdc.gov/shingles/vaccination
National Center for Immunization and Respiratory Diseases (NCIRD)

gov/shingles/multimedia



YOU CALL THE SHOTS

Recombinant Zoster Vaccine (Shingrix)

Using Shingrix vaccine

KNOW THE SITE. GET IT RIGHT!

Store and Prepare the Vaccine

- Store Shingrix vaccine (recombinant zoster vaccine) AND adjuvanted diluent in the refrigerator between 2°C and 8°C (36°F and 46°F).
- Store in original packaging, protected from light.
- DO NOT FREEZE. Frozen vaccine or adjuvanted diluent should NOT be administered.
- Prepare vaccine just before administration using a new, sterile needle and syringe.
- Reconstitute vaccine with the adjuvanted diluent that came with the lyophilized vaccine.

IM injection best practices

- Identify the site carefully using anatomical landmarks. Shoulder injury related to vaccine administration (SIRVA) may result from the unintentional injection of a vaccine into tissues and structures lying underneath the deltoid muscle.
- Administering the injection too high on the upper arm may cause shoulder injury.

Administer the vaccine correctly

- **Route:** Intramuscular (IM) injection
- **Needle:** 23-25 gauge, 1 to 1 1/2 inch sterile needle
- **Dose:** 0.5 mL
- **Site:** Deltoid muscle
- **Administration:** May administer during the same clinical visit as other needed vaccines. Administer in a separate limb from other vaccines, if possible.

Follow the schedule

- CDC recommends Shingrix as preferred over Zostavax® (zoster vaccine live) for the prevention of herpes zoster (shingles) and related complications.*
- Shingrix vaccine is a 2-dose series, administered 2 to 6 months apart. Both doses are needed to provide protection.
- Shingrix is recommended for individuals 50 years of age and older.
- Shingrix can be administered to people who have received Zostavax or have already had shingles.
- If Zostavax was previously given, wait at least 8 weeks before administering Shingrix.
- Schedule an appointment for the second dose before the patient leaves.

Educate the patient

- About 1 out of 6 people who got Shingrix experienced side effects that prevented them from doing regular activities for a few days.
- Remind patients they may experience a local reaction or side effect such as pain, redness, and swelling and systemic reactions such as myalgia, fatigue, and headache that may interrupt regular activities a few days after receiving Shingrix.
- It is important patients get the second dose of Shingrix to build strong protection against shingles, even if they have side effects from the first dose.
- Patients' reactions to each dose may be different; just because they have a reaction to the first dose does not mean they will have a reaction to the second.

For additional information on proper vaccine administration, visit the CDC vaccine administration web page at https://www.cdc.gov/vaccines/hcp/admin/admin-protocols.html

*Zostavax® is still recommended for healthy adults 60 years and older.
Learn more about Zostavax https://www.cdc.gov/vaccines/vpd/shingles/public/zostavax/index.html.

Report any clinically significant adverse event after vaccination to the Vaccine Adverse Event Reporting System (VAERS) at vaers.hhs.gov

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

RZV Effectiveness

RZV Effectiveness

- CDC and partners are exploring opportunities to study the real-world vaccine effectiveness of RZV via:
  - Large health systems
  - Administrative claims data

- Objectives: to evaluate vaccine effectiveness of 1 & 2 doses of RZV among:
  - Adults ≥50 years
  - ZVL recipients
  - Immunocompromised

Zoster Vaccine Coverage & 2 dose Completion

Coverage and 2 dose Completion

Monitoring System	Description	Coverage/ Uptake	2-dose Completion
TIPS Trendsin Immunization Practice System	Immunization Information Systems	✓	✓
NHIS National Health Interview Survey	Survey	✓	✓
BRFSS Behavioral Risk Factor Surveillance System	Survey	✓	
VSD Vaccine Safety Datalink	Electronic Health Record	✓	✓

RZV Vaccine Supply Status

- Due to high levels of demand for RZV (Shingrix), GSK has implemented order limits and providers have experienced shipping delays which will continue throughout 2018

- GSK indicates they have increased the number of doses available for the U.S. market in 2018
  - GSK plans to release doses to all customer types on a consistent, predictable schedule for the remainder of the year
  - Supply of RZV is sufficient to support the vaccination of more patients in the U.S. than were vaccinated against shingles last year

CDC Clinical Guidance for Herpes Zoster Vaccination

- **Recombinant Zoster Vaccine** (Shingrix, GSK) is the preferred shingles vaccine. Every effort should be made to ensure that two doses are administered within the recommended interval. If more than 6 months have elapsed since the first dose of RZV, administer the second dose when possible. Do not restart the vaccine series and do not substitute Zoster Vaccine Live (ZVL) for the second dose of RZV.

- **Zoster Vaccine Live** (Zostavax™, Merck) is a recommended shingles vaccine for immunocompetent adults ≥60 years. A decision to vaccinate with ZVL may be made after an informed discussion between patient and healthcare provider, considering factors such as patient preference for ZVL or a desire for immediate vaccination when RZV is unavailable. Persons who have received ZVL are recommended to subsequently receive RZV. Age and time since receipt of ZVL may be considered to determine when to vaccinate with RZV (minimum interval of 8 weeks).

Summary

- Safety- VAERS, VSD
- Effectiveness- large health systems and administrative claims
- Coverage & Adherence- Immunization Information Systems, surveys, electronic health records

➢ Evidence of safety and effectiveness of herpes zoster vaccine use in immunocompromised persons is currently being reviewed

Questions?

Reports to VAERS of death following RZV, Oct 20, 2017-Apr 27, 2018 (n=5)

Age (years)	Sex	Time from vaccination to death (days)	Other co-administered vaccines	Cause of death as listed by death certificate or autopsy report
60	Male	30	None	Acute respiratory distress syndrome; MRSA sepsis; zoster (chronic immunosuppression)
83	Female	2	None	Myocardial infarction
65	Female	1	None	Hypertensive and atherosclerotic vascular disease
62	Male	0	None	Probable complications of coronary artery disease
65	Female	0	None	Hypertensive and atherosclerotic vascular disease