Varicella and Herpes Zoster Vaccines

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses varicella and herpes zoster vaccines.

1. **Medical Necessity**

   Aetna considers varicella and herpes zoster vaccines medically necessary for the following indications:

   1. Varicella (chicken pox) vaccine as a preventive service according to the recommendations of the Centers for Disease Control's (CDC) Advisory Committee on Immunization Practices (ACIP);
   2. Combination measles, mumps, rubella, and varicella vaccine (MMRV) (ProQuad) as a preventive service alternative to individual measles, mumps and rubella (MMR) and varicella vaccines for children 12 months to 12 years of age where simultaneous administration of MMR and varicella vaccines is indicated;
   3. Varicella primary vaccination in HIV-infected, varicella zoster virus negative persons aged greater than 8 years with CD4 cell counts greater than 200 cells/µL and in HIV-infected children aged 1 to 8 years with CD4 percentages greater than 15 %;
   4. Recombinant herpes zoster vaccine (Shingrix) (given as a two-dose series) for *any* of the following indications:
      1. For the prevention of herpes zoster (HZ) (shingles) in adults aged 50 years and older; *or*
      2. For the prevention of HZ in adults aged 50 years and older who previously received zoster vaccine live (Zostavax); *or*
      3. For the prevention of HZ in adults aged 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy (e.g., autologous hematopoietic stem cell transplant, hematologic malignancies, solid organ transplant recipients, solid tumors receiving chemotherapy, HIV-infected adults, primary immunodeficiencies, autoimmune and inflammatory conditions, and taking immunosuppressive medications/therapies);

      Aetna considers repeat (booster) with recombinant herpes zoster vaccine (Shingrix) beyond the primary series of two Shingrix vaccinations as experimental, investigational, or unproven.

   5. Re-vaccination with recombinant herpes zoster vaccine (Shingrix) for hematopoietic stem-cell transplant (HSCT) recipients if 24 months have passed since HSCT, the recipient does not have graft-versus-host disease, and member is considered immunocompetent.

2. **Experimental, Investigational, or Unproven**

   Aetna considers recombinant herpes zoster vaccine (Shingrix) experimental, investigational, or unproven for treatment of zoster or postherpetic neuralgia (PHN), prevention of primary varicella infection (chickenpox), and for all other indications because its effectiveness for these indications has not been established.

Note: Zoster vaccine live (ZVL), Zostavax, is no longer available for use in the United States, as of November 18, 2020.

CPT Codes / HCPCS Codes / ICD-10 Codes

***Varicella (chicken pox) and combination varicella and measles, mumps and rubella vaccine (MMRV)*:**

Code	Code Description
CPT codes covered if selection criteria are met:	
90710	Measles, mumps, rubella, and varicella vaccine (MMRV), live, for subcutaneous use
90716	Varicella virus vaccine (VAR), live, for subcutaneous use
Other CPT codes related to the CPB:	
90707	Measles, mumps, and rubella vaccine (MMR), live, for subcutaneous use
ICD-10 codes covered if selection criteria are met:	
B20	Human immunodeficiency virus [HIV] disease [varicella zoster virus negative persons aged > 8 years with CD4 cell counts > 200 cells / µL and in HIV-infected children aged 1 - 8 years with CD4 cell percentages > 15%]
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status [varicella zoster virus negative persons aged > 8 years with CD4 cell counts > 200 cells / µL and in HIV-infected children aged 1 - 8 years with CD4 cell percentages > 15%]
Z23	Encounter for immunization

***Zoster vaccine*:**

CPT codes covered if selection criteria are met:	
90750	Zoster (shingles) vaccine (HZV), recombinant, sub-unit, adjuvanted, for intramuscular injection [Shingrix]
CPT codes not covered for indications listed in the CPB:	
90736	Zoster (shingles) vaccine (HZV), live, for subcutaneous injection [zostevax] [Zostavax will no longer be sold in the United States starting July 1, 2020. Some pharmacies and clinics may still have Zostavax in stock. This vaccine is considered safe and may be used until the supply expires (before or by November 18, 2020)]
Other CPT codes related to the CPB:	
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
ICD-10 codes covered if selection criteria are met:	
B20	Human immunodeficiency Virus [HIV] disease
C11.0 - C22.1, C23 - C31.9, C33 - C44.201, C46.1, C47.0 - C49.9, C50.011 - C57.02, C58 - C73, C7A.1 - C7A.8, C80.0 - C80.1	Malignant neoplasm [solid tumors]
D00.00 - D09.9	Carcinoma in situ [solid tumors]
E08.00 - E13.9	Diabetes mellitus
E84.0 – E84.9	Cystic fibrosis
G20.A1 - G20.C	Parkinson's disease
G30.0 - G30.9	Alzheimer's disease
G35	Multiple sclerosis
G40.001 - G40.919	Epilepsy

Code	Code Description
I10 - I16.9	Hypertensive diseases
J44.0 - J44.9	Other chronic obstructive pulmonary disease
J45.20 - J45.998	Asthma
M05.00 - M06.9	Rheumatoid arthritis
N18.1 - N18.9	Chronic kidney disease (CKD)
Z23	Encounter for immunization
Z79.51 - Z79.52	Long-term (current) use of steroids
Z79.899	Other long term (current) drug therapy
Z94.84	Stem cells transplant status

ICD-10 codes not covered for indications listed in the CPB:

B01.9	Varicella without complication [prevention of chickenpox]
B02.0 - B02.9	Zoster (herpes zoster)
C91.10 - C91.12	Chronic lymphocytic leukemia of B-cell type
C81.00 - C91.02, C91.30 - C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue
D89.810 - D89.813	Graft-versus-host disease

Background

Varicella Vaccine

Varicella vaccine (Varivax, Merck & Co., Whitehouse Station, NJ) immunization is recommended for children over 12 months of age who do not have a history of having had varicella (chicken pox). The Advisory Committee on Immunization Practices (ACIP) recommends that children be immunized with 2 doses of varicella vaccine, with the first dose administered between 12 and 15 months of age, and a second dose administered between 4 and 6 years of age. In addition, the ACIP recommends that other persons who have not been immunized and have no history of varicella receive 2 doses of vaccine. Children, adolescents and adults who previously received 1 dose of varicella vaccine should receive a second one.

Healthy adolescents past their 13th birthday and adults who have not been immunized and have no history of varicella may also be immunized and require 2 doses of vaccine. The Centers for Disease Control's (CDC) recommends vaccination of adolescents greater than or equal to 13 years of age and adults at high risk for exposure or transmission. Groups at high risk include:

- Adolescents and adults living in households with children; *and*
- International travelers[*] *and*
- Non-pregnant women of childbearing age; *and*
- Persons who live or work[*] in environments where transmission of chicken pox can occur (e.g., college students, inmates and staff members of correctional institutions, and military personnel); *and*
- Persons who live or work[*] in environments where transmission of chicken pox is likely (e.g., teachers of young children, day care employees, and residents and staff members in institutional settings).

[*]**Note**: Some Aetna plans exclude coverage of vaccinations for work or for travel. Please check benefit plan descriptions for details.

Very few people escape childhood without contracting chicken pox. The recommendation is that all individuals under 21 years of age who do not have a clear history of chicken pox should be assumed to be susceptible and can be immunized. Adults over 21 who have no history of chicken pox should be tested for immunity and, if they are susceptible, should be immunized. Five to 10 % of the adult population is probably susceptible; 70 % of 18 year olds have been found to be immune, even if they have no clear history of having had chicken pox.

Children 12 months to 12 years of age should receive a 0.5-ml dose of varicella vaccine administered subcutaneously. A second dose of varicella vaccine should be given a minimum of 3 months later. Adolescents and adults 13 years of age and older should receive a 0.5-ml dose administered subcutaneously at an elected date and a second 0.5-ml dose 4 to 8 weeks later.

Varicella vaccine is contraindicated in certain individuals, including persons with an immunodeficient condition or receiving immunosuppressive therapy, persons with active untreated tuberculosis, and women who are pregnant.

The Food and Drug Administration (FDA) has approved a combined attenuated live virus vaccine containing measles, mumps, rubella, and varicella viruses (MMRV) (ProQuad injection, Merck & Co., Whitehouse Station, NJ) for use in children aged 12 months to 12 years. It is also approved for use in this population if a second dose of measles, mumps, and rubella vaccine is to be administered.

The approval was based on study data showing the immunogenicity, antibody persistence, and safety of the combination vaccine to be similar with that of its previously approved components (measles, mumps, and rubella (MMR) and varicella). The incidence of adverse events including those most commonly reported (injection site reactions, nasopharyngitis, cough) was similar between the treatment groups.

Herpes Zoster Vaccines

Herpes zoster (HZ) is the consequence of re-activation of the varicella zoster virus (VZV) that remains latent since primary infection (varicella). The overall incidence of HZ is about 3 per 1,000 of the population per year increasing to 10 per 1,000 per year by age 80. Approximately 50 % of persons reaching age 90 years will have had HZ. In approximately 6 %, a second episode of HZ may occur; usually several decades after the first attack. The most common complication of HZ is post-herpetic neuralgia (PHN), defined as significant pain or dysaesthesia present 3 months or more following HZ. More than 5 % of the elderly have PHN at 1 year after acute HZ. Reduced cell-mediated immunity to HZ occurs with aging, which may be responsible for the increased incidence in the elderly and from other causes such as tumors, human immunodeficiency virus infection as well as immunosuppressant drugs. Diagnosis of PHN is usually clinical from typical unilateral dermatomal pain and rash. Prodromal symptoms, pain, itching and malaise, are common (Johnson and Whitton, 2004).

There is reliable evidence that zoster vaccine significantly reduces morbidity from HZ and PHN among older adults. In a randomized, controlled, multi-center study, Oxman and colleagues (2005) examined if vaccination against VZV would decrease the incidence, severity, or both of HZ and PHN among older adults. A total of 38,546 adults aged 60 years or older were enrolled in this study. The vaccine used was a live attenuated Oka/Merck VZV vaccine. Herpes zoster (shingles) was diagnosed according to clinical and laboratory criteria. The pain and discomfort associated with HZ were measured repeatedly for 6 months. The primary end point was the burden of illness due to HZ, a measure affected by the incidence, severity, and duration of the associated pain and discomfort. The secondary end point was the incidence of PHN. More than 95 % of the subjects continued in the study to its completion, with a median of 3.12 years of surveillance for HZ. A total of 957 confirmed cases of HZ (315 among vaccine recipients and 642 among placebo recipients) and 107 cases of PHN (27 among vaccine recipients and 80 among placebo recipients) were included in the efficacy analysis. The use of the zoster vaccine reduced the burden of illness due to HZ by 61.1 % ($p < 0.001$), reduced the incidence of PHN by 66.5 % ($p < 0.001$), and reduced the incidence of HZ by 51.3 % ($p < 0.001$). Reactions at the injection site were more frequent among vaccine recipients but were generally mild. These researchers concluded that the zoster vaccine significantly reduced morbidity from HZ and PHN among older adults.

Zostavax

In May 2006, the FDA approved Zostavax (Merck & Co., Inc., Whitehouse Station, NJ), a vaccine for use to reduce the risk of HZ in people aged 60 years and older. Zostavax is administered subcutaneously in one single injection, preferably in the upper arm. The most common adverse effects in individuals who received Zostavax were redness, pain and tenderness, swelling at the site of injection, itching, as well as headache.

The FDA approved prescribing information indicates that zoster vaccine is not indicated for the treatment of herpes zoster or PHN. Zoster vaccine is a live attenuated virus vaccine, and the labeling states that zoster vaccine is contraindicated in the following persons:

- Persons with active untreated tuberculosis;
- Persons on immunosuppressive therapy, including high-dose corticosteroids;
- Those with a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine;
- Those with a history of primary or acquired immunodeficiency states including leukemia; lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; or AIDS or other clinical manifestations of infection with human immunodeficiency viruses;
- Women who are or may be pregnant.

Zostavax is a live attenuated virus vaccine and is contraindicated in immunosuppressed persons, including persons with a history of primary or acquired immunodeficiency states including leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; with AIDS or other clinical manifestations of infection with human immunodeficiency viruses; and with active untreated tuberculosis. Zostavax is also contraindicated in persons on immunosuppressive therapy, including high-dose corticosteroids, and in women who are or may be pregnant.

Zostavax (zoster vaccine) is given as a single 0.65 mL dose by subcutaneous injection (not intramuscularly). Studies are ongoing to assess the duration of protection from a single dose of zoster vaccine and the need, if any, for booster doses. Zostavax (zoster vaccine) is stored frozen and requires reconstitution prior to administration. The product should be reconstituted immediately upon removal from the freezer. The diluent should be stored separately at room temperature or in the refrigerator. The reconstituted vaccine should be discarded if it is not used within 30 minutes; the reconstituted vaccine should not be frozen.

Wutzler (2010) stated that although the efficacy of zoster vaccine against HZ declined with advancing age of the vaccinees, subjects older than 70 years also benefited from vaccination because the burden of illness was considerably reduced. The protective effect of zoster vaccine persists for at least 7 years post-vaccination. The author stated that the need for, or timing of, re-vaccination has not yet been determined. Zostavax has been well-tolerated. It can be concomitantly administered with inactivated influenza vaccine at separate sites. The author stated that zoster and pneumococcal vaccines should not be given concomitantly.

According to the CDC (2011), zoster vaccine is administered subcutaneously as a single dose. The vaccine should not be injected intra-muscularly. However, it is not necessary to repeat vaccination if the shingles vaccine is administered intra-muscularly. Studies are ongoing to assess the duration of protection from 1 dose of zoster vaccine and the need, if any, for booster doses.

The ACIP currently recommends Zostavax for all adults aged 60 years and older with no contraindications and for adults older than 80 years with chronic illnesses (Splete, 2011). No changes were made to the current recommendation of herpes zoster vaccination for adults aged 60 years and older, the CDC's ACIP reported. The FDA licensed Zostavax for use in adults aged 50 to 59 years in March 2011. However, the working group did not currently propose changes to the current ACIP recommendations. Data from studies conducted by Merck have shown vaccine efficacy in the 50 to 59 age group, but there is insufficient evidence regarding the duration of vaccine protection when it is given well before the peak age for zoster incidence. The working group observed that it might be inappropriate to expand recommendations while the vaccine remains in short supply, and the incidence could increase if limited supply is used at time of low incidence. The ACIP published updated their recommendations for shingles vaccine in August 2014 and maintained their current recommendation for shingles vaccine for persons age 60 years and older (Hale, et al., 2014).

Guidelines for preventing infections in hematopoietic cell transplant (HCT) recipients by the Center for International Blood & Marrow Transplant Research, National Marrow Donor Program, European Group for Blood and Marrow Transplantation, American Society for Blood and Marrow Transplantation, Canadian Blood and Marrow Transplant Group, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, Association of Medical Microbiology and Infectious Disease, and the CDC (Ljungman et al, 2009) indicated that zoster vaccine (Zostavax, live) should not be given to HCT recipients.

The British Society for Haematology’s guidelines on "The diagnosis, investigation and management of chronic lymphocytic leukaemia" (Oscier et al, 2012) states that "live vaccines such as polio, herpes zoster, and yellow fever should be avoided".

Zhang et al (2012) stated that methotrexate (MTX) has become the foundation disease-modifying anti-rheumatic drug (DMARD) for rheumatoid arthritis (RA). However, concern exists regarding its possible association with infectious complications including VZV and HZ. Furthermore, no consensus exists regarding pre-MTX VZV screening or the use of VZV vaccine. These researchers undertook systematic literature review (SLR) investigating the relationship between the use of MTX in patients with RA and VZV and HZ infection. Additionally, the European Centre for Disease Prevention and Control, HPA, the CDC, Rheumatology societies and WHO web sites and publications were consulted. A total of 35 studies fulfilled the inclusion criteria comprising 29 observational studies and 6 case reports. The case reports and 13 observation studies considered the association between MTX and HZ. Three of the observational studies reported a positive association although in 5 cases, patients were concurrently treated with prednisolone. Five studies concluded that there was no association between HZ and MTX. Three studies comparing the infection rates of MTX with other RA therapies found that MTX did not result in higher HZ infection rates. Three studies examining the association between HZ and MTX treatment duration failed to show a link. The authors concluded that no evidence exists to support an association between MTX and VZV infection in RA patients and the data regarding the role of MTX in HZ development is conflicting. The role of pre-MTX VZV screening is controversial and, as it may delay initiation of RA treatment, these investigators suggested against VZV screening in this context.

Guthridge et al (2013) noted that patients with systemic lupus erythematosus (SLE) are at increased risk of HZ. Although Zostavax has been approved by the FDA, its use in immunocompromised individuals remains controversial because it is a live-attenuated virus vaccine. In a pilot study, these researchers examined the immunogenicity of Zostavax in patients with SLE. A total of 10 patients with SLE and 10 control subjects aged 50 years or older participated in this open-label vaccination study. All were sero-positive for VZV. Patients with SLE were excluded for SLE Disease Activity Index (SLEDAI) greater than 4, or use of mycophenolate mofetil, cyclophosphamide, biologics, or greater than 10 mg prednisone daily. Follow-up visits occurred at 2, 6, and 12 weeks. Clinical outcomes included the development of adverse events, particularly HZ or vesicular lesions, and SLE flare. Immunogenicity was assessed with VZV-specific interferon-gamma-producing enzyme-linked immunospot (ELISPOT) assays and with antibody concentrations. All subjects were women. Patients with SLE were slightly older than controls (60.5 versus 55.3 years, $p < 0.05$). Median baseline SLEDAI was 0 (range of 0 to 2) for patients with SLE. No episodes of HZ, vesicular rash, serious adverse events, or SLE flares occurred. Three injection site reactions occurred in each group: mild

erythema or tenderness. The proportion of subjects with a greater than 50 % increase in ELISPOT results following vaccination was comparable between both groups, although absolute SLE responses were lower than controls. Antibody titers increased only among controls following vaccination ($p < 0.05$). The authors concluded that HZ vaccination yielded a measurable immune response in this cohort of patients with mild SLE taking mild-moderate immunosuppressive medications; no herpetiform lesions or SLE flares were seen in this small cohort of patients. This was a pilot study testing the immunogenicity of Zostavax in SLE patients; the clinical value of Zostavax in these patients needs to be further-evaluated in well-designed studies.

Son et al (2010) assessed the effectiveness of varicella virus in clinically stable HIV-infected children. The investigators assessed its effectiveness by reviewing the medical records of closely monitored HIV-infected children, including those receiving highly active antiretroviral therapy (HAART) between 1989 and 2007, noting both varicella immunization and development of varicella or herpes zoster. Effectiveness was calculated by subtracting from 1 the rate ratios for the incidence rates of varicella or herpes zoster in vaccinated versus unvaccinated children. The results showed the effectiveness of the vaccine was 82% (95% confidence interval [CI], 24%-99%; P = .01) against varicella and was 100% (95% CI, 67%-100%; P < .001) against herpes zoster. The authors further noted that when the analysis was controlled for receipt of HAART, vaccination remained highly protective against herpes zoster.

Taweesith et al (2011) stated that the live attenuated varicella vaccine is recommended for HIV-infected children who are not severely immunosuppressed. The authors conducted a study aimed to assess the immunogenicity and safety of varicella vaccination among HIV-infected children who had severe immunosuppression before receiving antiretroviral therapy. A total of 60 HIV-infected children with no history of chickenpox or herpes zoster infection with CD4 T lymphocyte counts ≥ 15 % or ≥ 200 cell/mm were enrolled and administered two doses of varicella vaccine, the first at the time of enrollment and the second at 3 months. The analysis showed a median (interquartile range) of age, CD4 nadir, and current CD4 percentage were 11.2 (8.5 to 12.8) years, 9.5 % (3 to 14), and 28 % (22 to 32), respectively and that 57 children (95 %) received anti-retroviral therapy for a median of 27 months. The results showed that among 34 children (57 %) who were VZV sero-negative at baseline, 11.8 % (95 % CI: 3.3 % to 27.5 %) and 79.4 % (95 % CI: 62.1 % to 91.3 %) were VZV seroconverted after first and second dose of vaccine, respectively. Children who had VZV sero-conversion were found to be more likely to have HIV RNA less than 1.7 copies/mL (92.6 % versus 71.4 %, p = 0.18) and among 26 children who were sero-positive at baseline, the geometric mean titers were increased from 56.7 to 107.9 and 134.6 unit/mL, respectively. Local and systemic reactions of grade 1 and 2 were reported in 13 % and 4 % of children, respectively. There was a trend toward better response among children with younger age, high CD4, and viral suppression. Thus, the authors concluded that administration of the 2 doses of varicella vaccine resulted in high sero-conversion rates without serious adverse reactions. Varicella vaccination for HIV-infected children should be encouraged.

Mullane et al (2013) conducted a randomized, double-blind, placebo-controlled, multi-center study on the safety and immunogenicity of heat-treated zoster vaccine (ZVHT). Four doses of ZVHT or placebo were administered approximately 30 days apart to adults with either solid tumor malignancy (STM); hematologic malignancy (HM); human immunodeficiency virus (HIV) with CD4(+) < 200; autologous hematopoietic stem-cell transplant (HCT) or allogeneic-HCT recipients. The results indicated that no safety signals were found in any group. The investigators also found that IFN-gamma ELISPOT geometric mean fold rises (GMFR) after dose 4 in STM, HM, HIV, and autologous-HCT patients were 3.00 ($p < 0.0001$), 2.23 ($p = 0.004$), 1.76 ($p = 0.026$), and 9.01 (p = NA), respectively. Similarly, antibody GMFR were 2.35 ($p < 0.0001$), 1.28 ($p = 0.003$), 1.37 ($p = 0.017$), and 0.90 (p = NA), respectively. Thus, the authors concluded that ZVHT was generally safe and immunogenic through 28 days post-dose 4 in adults with STM, HM, and HIV and that autologous-HCT but not allogeneic-HCT patients had a rise in T-cell response. Antibody responses were not increased in either HCT population.

Aberg et al (2014) reported on the 2013 update on primary care guidelines for management of HIV infected persons by the HIV Medicine Association of the Infectious Diseases Society of America. New information based on literature published from 2009 to 2013 was incorporated into this updated version of the guidelines. The recommendations stated that varicella primary vaccination may be considered in HIV-infected, varicella zoster virus seronegative persons aged > 8 years with CD4 cell counts > 200 cells / microliter and in HIV-infected children aged 1 to 8 years with CD4 cell percentages > 15% due to moderate quality evidence in the peer-reviewed literature.

A 2014 UpToDate report on immunizations in HIV-infected patients reported results of a trial of 295 HIV-infected individuals with CD4 cell counts ≥ 200 cells/microL and virologic suppression on antiretroviral therapy who received varicella zoster vaccine. Individuals with CD4 cell counts > 350 cells / microL had the highest post-vaccination zoster antibody level, but there were high rates of injection site reactions in the zoster group (42 versus 12.4 % in the placebo group). The UpToDate report concluded that although these data are promising, further research is needed to determine which HIV-infected individuals at what age should receive the zoster vaccine. However, the authors noted that it is reasonable to vaccinate those with CD4 counts > 200 cels/microL if they are aged 60 years or older. The UpToDate report also states that "zoster vaccine is specifically not recommended for HIV-infected patients with a CD4 cell count < 200 cells/microL" (HIbberd, 2014).

The live attenuated virus vaccine Zostavax has been FDA approved for prevention of herpes zoster (shingles) inn individuals 50 years of age and older. The FDA package insert further notes that Zostavax is not indicated for the treatment of zoster or postherpetic neuralgia, nor is it indicated for prevention of primary varicella infection (Chickenpox) (FDA, 2006).

In a clinical study, Levin and colleagues (2016) noted that herpes zoster vaccine (ZV) was administered as a second dose to 200 participants greater than or equal to 70 years of age who had received a dose of ZV greater than or equal to 10 years previously. Varicella zoster virus (VZV) antibody titers (measured by a VZV glycoprotein-based enzyme-linked immunosorbent

assay [gpELISA]) and levels of interferon γ (IFN-γ) and interleukin 2 (IL-2; markers of VZV-specific cell-mediated immunity [CMI], measured by means of ELISPOT analysis) in individuals aged greater than or equal to 70 years who received a booster dose of ZV were compared to responses of 100 participants aged 50 to 59 years, 100 aged 60 to 69 years, and 200 aged greater than or equal to 70 years who received their first dose of ZV. The study was powered to demonstrate non-inferiority of the VZV antibody response at 6 weeks in the booster-dose group, compared with the age-matched first-dose group. Antibody responses were similar at baseline and after vaccination across all age and treatment groups. Both baseline and post-vaccination VZV-specific CMI were lower in the older age groups. Peak gpELISA titers and their fold rise from baseline generally correlated with higher baseline and post-vaccination VZV-specific CMI; IFN-γ and IL-2 results for subjects greater than or equal to 70 years old were significantly higher at baseline and after vaccination in the booster-dose group, compared with the first-dose group, indicating that a residual effect of ZV on VZV-specific CMI persisted for greater than or equal to 10 years and was enhanced by the booster dose. The authors concluded that these findings supported further investigation of ZV administration in early versus later age and of booster doses for elderly individuals at an appropriate interval after initial immunization against HZ.

Lal and associates (2015) stated that in previous phase I and phase II clinical trials involving older adults, a subunit vaccine containing varicella-zoster virus glycoprotein E and the AS01B adjuvant system (called HZ/su) had a clinically acceptable safety profile and elicited a robust immune response. These researchers performed a randomized, placebo-controlled, phase III clinical trial in 18 countries to examine the safety and effectiveness of HZ/su in older adults (greater than or equal to 50 years of age), stratified according to age group (50 to 59, 60 to 69, and greater than or equal to 70 years). Participants received 2 intramuscular doses of the vaccine or placebo 2 months apart. The primary objective was to evaluate the effectiveness of the vaccine, as compared with placebo, in reducing the risk of HZ in older adults. A total of 15,411 participants who could be evaluated received either the vaccine (7,698 participants) or placebo (7,713 participants). During a mean follow-up of 3.2 years, HZ was confirmed in 6 participants in the vaccine group and in 210 participants in the placebo group (incidence rate, 0.3 versus 9.1 per 1,000 person-years) in the modified vaccinated cohort. Overall vaccine effectiveness against HZ was 97.2 % (95 % CI: 93.7 to 99.0; $p < 0.001$). Vaccine effectiveness was between 96.6 % and 97.9 % for all age groups. Solicited reports of injection-site and systemic reactions within 7 days after vaccination were more frequent in the vaccine group. There were solicited or unsolicited reports of grade 3 symptoms in 17.0 % of vaccine recipients and 3.2 % of placebo recipients. The proportions of participants who had serious adverse events (AEs) or potential immune-mediated diseases or who died were similar in the 2 groups. The authors concluded that the HZ/su vaccine significantly reduced the risk of HZ in adults who were 50 years of age or older; and vaccine effectiveness in adults who were 70 years of age or older was similar to that in the other 2 age groups.

Cunningham and colleagues (2016) noted that a trial involving adults 50 years of age or older (ZOE-50) showed that the HZ subunit vaccine (HZ/su) containing recombinant varicella-zoster virus glycoprotein E and the AS01B adjuvant system was associated with a risk of herpes zoster that was 97.2 % lower than that associated with placebo. A second trial was performed concurrently at the same sites and examined the safety and effectiveness of HZ/su in adults 70 years of age or older (ZOE-70). This randomized, placebo-controlled, phase III clinical trial was conducted in 18 countries and involved adults 70 years of age or older. Participants received 2 doses of HZ/su or placebo (assigned in a 1:1 ratio) administered intramuscularly 2 months apart. Vaccine effectiveness against HZ and PHN was assessed in subjects from ZOE-70 and in participants pooled from ZOE-70 and ZOE-50. In ZOE-70, 13,900 participants who could be evaluated (mean age of 75.6 years) received either HZ/su (6,950 participants) or placebo (6,950 participants). During a mean follow-up period of 3.7 years, HZ occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 versus 9.2 per 1,000 person-years). Vaccine effectiveness against HZ was 89.8 % (95 % CI: 84.2 to 93.7; $p < 0.001$) and was similar in participants 70 to 79 years of age (90.0 %) and participants 80 years of age or older (89.1 %). In pooled analyses of data from participants 70 years of age or older in ZOE-50 and ZOE-70 (16,596 participants), vaccine effectiveness against HZ was 91.3 % (95 % CI: 86.8 to 94.5; $p < 0.001$), and vaccine effectiveness against PHN was 88.8 % (95 % CI: 68.7 to 97.1; $p < 0.001$). Solicited reports of injection-site and systemic reactions within 7 days after injection were more frequent among HZ/su recipients than among placebo recipients (79.0 % versus 29.5 %). Serious AEs, potential immune-mediated diseases, and deaths occurred with similar frequencies in the 2 study groups. The authors concluded that HZ/su was found to reduce the risks of HZ and PHN among adults 70 years of age or older.

In a Cochrane review, Gagliardi and co-workers (2016) evaluated the safety and effectiveness of vaccination for preventing HZ in older adults. For this 2015 update, these investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 9), Medline (1948 to the third week of October 2015), Embase (2010 to October 2015), CINAHL (1981 to October 2015) and LILACS (1982 to October 2015). Randomized controlled trials (RCTs) or quasi-RCTs comparing zoster vaccine with placebo or no vaccine, to prevent HZ in older adults (mean age greater than 60 years). Two review authors independently collected and analyzed data using a data extraction form. They also performed "Risk of bias" assessment. These researchers identified 13 studies involving 69,916 participants. The largest study included 38,546 participants. All studies were conducted in high-income countries and included only healthy Caucasian individuals greater than or equal to 60 years of age without immunosuppressive co-morbidities. A total of 10 studies used live attenuated varicella zoster virus (VZV) vaccines; 3 studies tested a new type of vaccine not yet available for clinical use. These researchers judged 5 of the included studies to be at low risk of bias. The incidence of HZ, at up to 3 years of follow-up, was lower in participants who received the vaccine than in those who received a placebo: risk ratio (RR) 0.49; 95 % CI: 0.43 to 0.56, risk difference (RD) 2 %, number needed to treat to benefit (NNTB) 50; GRADE: moderate quality evidence. The vaccinated group had a higher incidence of mild-to-moderate intensity AEs. These date came from 1 large study that included 38,546 people aged 60 years or older. A study including 8,122 participants compared the new vaccine (not yet available) to the placebo; the group that received the new vaccine had a lower incidence of HZ at 3.2 years of follow-up: RR 0.04, 95 % CI: 0.02 to 0.10, RD 3 %, NNTB 33; GRADE: moderate quality

evidence. The vaccinated group had a higher incidence of AEs; but most them were of mild-to-moderate intensity. The authors concluded that HZ vaccine is effective in preventing HZ disease and this protection can last 3 years. In general, zoster vaccine is well-tolerated; it produces few systemic AEs and injection site AEs of mild-to-moderate intensity. There are studies of a new vaccine (with a VZV glycoproteic fraction plus adjuvant), which is currently not yet available for clinical use.

According to the CDC (2018b), Zostavax will no longer be sold in the United States starting July 1, 2020. Some pharmacies and clinics may still have Zostavax in stock. This vaccine is safe and may be used until the supply expires (before or by November 18, 2020). Merck & Co., Inc. issued a notification letter informing healthcare professionals that the decision is not related to any product safety or manufacturing issues with Zostavax, and will only affect cutomers in the United States (Merck, 2020).

Shingrix

Shingrix is a non-live, recombinant subunit vaccine that combines an antigen, glycoprotein E, and an adjuvant system, AS01B, intended to generate a strong and long-lasting immune response. The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC, 2017) recommended the use of the new Shingrix vaccine (GlaxoSmithKline) over the existing Zostavax vaccine (Merck) for the prevention of shingles in immunocompetent adults 50 years of age and older. The Advisory Committee on Immunization Practices (ACIP) also recommended that adults who previously received Zostavax be given Shingrix. The previous ACIP recommendation applied to adults 60 years of age and older.

The FDA approved Shingrix (zoster vaccine recombinant, adjuvanted) on October 20, 2017 for the prevention of herpes zoster (shingles) in adults aged 50 years and older. The approval was based on a comprehensive phase 3 clinical trial program involving 38,000 adults to evaluate the vaccine's efficacy, safety, and immunogenicity.

In a pooled analysis of these studies, Shingrix demonstrated efficacy against shingles greater than 90% across all age groups, as well as sustained efficacy over a follow-up period of four years. By preventing shingles, Shingrix also reduced the overall incidence of post-herpetic neuralgia (PHN),

The Prescribing Information for Shingrix states that it is not indicated for the prevention of primary varicella infection (chickenpox). It is contraindicated in persons with a history of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of Shingrix.

Shingrix is available as suspension for injection supplied as a single-dose vial of lyophilized varicella. Two doses (0.5 mL each) administered intramuscularly according to the following schedule: First dose at Month 0 followed by a second dose administered anytime between 2 and 6 months later (GSK, 2017).

Lal and colleagues (2018) noted that in phase-III clinical trials, 2 doses of a HZ subunit vaccine (HZ/su; 50 µg varicella-zoster virus glycoprotein E [gE] and AS01B Adjuvant System) administered 2-months apart in older adults (greater than or equal to 50 and greater than or equal to 70 years) demonstrated greater than 90 % efficacy in preventing HZ and had a clinically acceptable safety profile. In a phase-III, open-label, clinical trial, these investigators reported immunogenicity, reactogenicity and safety following administration of 2 HZ/su doses at intervals longer than 2 months. This trial was conducted in the U.S. and Estonia; a total of 354 adults greater than or equal to 50 years were randomized 1:1:1 to receive 2 HZ/su doses 2, 6, or 12 months apart; gE-specific humoral immune responses were evaluated at pre-vaccination, 1 and 12 months post-dose 2. Co-primary objectives were to compare immune responses to HZ/su 1 month post-dose 2 when given 6-months or 12-months apart to those administered 2-months apart. For each participant, safety information was collected from dose 1 to 12 months post-dose 2; 346 participants completed the study and 343 were included in the according-to-protocol cohort for immunogenicity. One month post-dose 2, vaccine response rates were 96.5 % (97.5 % CI: 90.4 to 99.2) and 94.5 % (97.5 % CI: 87.6 to 98.3) for the 0, 6- and 0, 12-month schedules, respectively; both schedules meeting the pre-defined criterion. Non-inferiority of anti-gE geometric mean concentrations was demonstrated for HZ/su administered on 0, 6-month compared to a 0, 2-month schedule; however, HZ/su administered on a 0, 12-month schedule did not meet the non-inferiority criterion. Injection site pain was the most commonly reported solicited AE; 26 participants each reported at least 1 serious AE; none was assessed as related to vaccination. The authors concluded that immune responses to HZ/su administered at 0, 6-month were non-inferior to those elicited by a 0, 2-month schedule; HZ/su exhibited a clinically acceptable safety profile for all dosing intervals.

Weinberg and associates (2018) stated that live attenuated (ZV) and recombinant adjuvanted (HZ/su) zoster vaccines differ with respect to efficacy, effect of age, and persistence of protection. In a randomized, double-blind, placebo-controlled trial, these investigators compared cell-mediated immunity (CMI responses to ZV and HZ/su. Participants in this study were stratified by age (50 to 59, and 70 to 85 years) and by HZ vaccination status (received ZV greater than or equal to 5 years before entry or not). Varicella zoster virus (VZV)- and gE-specific CMI were analyzed by interleukin 2 (IL-2) and interferon gamma (IFN-γ) FluoroSpot and flow cytometry at study days 0, 30, 90, and 365. Responses to ZV peaked on day 30 and to HZ/su (administered in 2 doses separated by 60 days) peaked on day 90. Age and vaccination status did not affect peak responses, but higher baseline CMI correlated with higher peak responses. HZ/su generated significantly higher VZV-specific IL-2+ and gE-specific IL-2+, IFN-γ+, and IL-2+/IFN-γ+ peak and 1-year baseline-adjusted responses compared with ZV. VZV-specific IFN-γ+ and IL-2+/IFN-γ+ did not differ between vaccines. HZ/su generated higher memory and effector-memory CD4+ peak responses and ZV generated higher effector CD4+ responses . The authors concluded that the higher IL-2 and other memory responses generated by HZ/su compared with ZV may contribute to its superior efficacy.

ACIP recommends the recombinant zoster vaccine, Shingrix, for adults with chronic medical conditions (e.g., chronic renal failure, diabetes mellitus, rheumatoid arthritis, and chronic pulmonary disease) (Dooling et al., 2018).

While Shingrix is not contraindicated in immunocompromised persons, as of August 2020, it is not recommended by ACIP at this time. ACIP will begin reviewing evidence for Shingrix in immunocompromised people as soon as it becomes available and will modify vaccine policy as necessary. ACIP does; however, recommend Shingrix to someone who is taking low-dose immunosuppressive medication (e.g., <20 mg/day of prednisone or equivalent or using inhaled or topical steroids), anticipating immunosuppression, or has recovered from an immunocompromising illness. Immunocompromised persons and those on moderate to high doses of immunosuppressive therapy were excluded from the efficacy studies, and thus, ACIP has not made recommendations regarding the use of Shingrix in these patients. This topic is anticipated to be discussed at upcoming ACIP meetings as additional data become available (CDC, 2018b; Dooling et al., 2018).

In July 2021, the U.S. FDA approved the expansion of Shingrix to allow for the prevention of shingles in adults aged 18 years and older who are or who will be at increased risk of shingles due to immunodeficiency or immunosuppression caused by known disease or therapy. In October 2021, the CDC Advisory Committee on Immunization Practices (ACIP) voted unanimously to recommend two doses of Shingrix for the prevention of herpes zoster and its complications in adults 19 years of age and older who are or will be immunodeficient or immunosuppressed due to disease or therapy. Approval was based on clinical studies examining the safety and efficacy of Shingrix in adults (≥18 years of age) who had undergone an autologous hematopoietic stem cell transplant (auHSCT) and those undergoing treatment for hematological malignancies (post-hoc analysis). Further safety and immunogenicity data were generated in adults who were, or were anticipated to be, immunodeficient or immunosuppressed due to known disease or therapy, including patients with HIV, solid tumours, and renal transplants. For immunocompetent adults, Shingrix is intended to be administered in two doses, 2 to 6 months apart. However, for adults who are or will be immunodeficient or immunosuppressed due to known disease or therapy and who would benefit from a shorter vaccination schedule, the second dose can be administered 1 to 2 months after the first dose (GSK, 2021).

Herpes Zoster Vaccine and Chronic Kidney Disease

Hamad and colleagues (2021) stated that chronic kidney disease (CKD) is a risk factor for HZ infection; and few studies have examined HZ vaccine (HZV) in this population. In a systematic review and meta-analysis, these investigators examined the safety and effectiveness of HZV in patients with renal disease (CKD, dialysis, and transplant). They searched Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases (up to May 2020) for RCTs and non-RCTs evaluating HZV in patients with CKD for effectiveness and AEs risks. Studies without a control group (placebo or no vaccine) were excluded. Extraction of pre-specified data and risk of bias assessments using the Newcastle-Ottawa scale for cohort studies and the Cochrane Risk of Bias Tool for RCTs were carried out by 3 authors. Random-effects meta-analysis was used to generate pooled treatment effects and 95 % CIs. A total of 404,561 individuals from 8 studies (3 RCTs and 5 non-RCTs) were included in this study. All 8 studies examined HZ as an outcome, with 3 reporting AEs. Risk of HZ was lower in patients who received HZV compared with controls (HR, 0.55; 95 % CI: 0.37 to 0.82; $p < 0.01$); however, heterogeneity was high ($I2 = 88$ %, $p < 0.01$). There was no significant difference in AEs associated with HZV (HR, 1.03; 95 % CI: 0.54 to 1.28; $p = 0.8$). The authors concluded that HZV compared with control significantly lowered the risk of HZ without an increase in AEs in CKD patients; however, significant heterogeneity was present. Moreover, these researchers stated that HZV should be actively considered in CKD patients because the prevalence of HZ is higher in this population.

Herpes Zoster Vaccine and Hematopoietic Stem Cell Transplant Recipients

The Centers for Disease Control (CDC, 2018) notes that "A hematopoietic cell transplant (HCT) results in immunosuppression because of the hematopoietic ablative therapy administered before the transplant, drugs used to prevent or treat graft-versus-host disease, and, in some cases, from the underlying disease process necessitating transplantation. HCT involves ablation of the bone marrow followed by reimplantation of the person’s own stem cells or stem cells from a donor. Antibody titers to vaccine-preventable diseases (e.g., tetanus, poliovirus, measles, mumps, rubella, and encapsulated bacteria) decrease 1 to 4 years after autologous or allogeneic HCT if the recipient is not revaccinated. HCT recipients of all ages are at increased risk for certain vaccine-preventable diseases, including diseases caused by encapsulated bacteria (i.e., pneumococcal, meningococcal, and Hib infections). As a result, HCT recipients who received vaccines prior to their HCT should be revaccinated routinely after HCT, regardless of the source of the transplanted stem cells. Vaccination or revaccination doses of pneumococcal vaccines, DTaP vaccine, Hib vaccine, hepatitis A vaccine, hepatitis B vaccine, meningococcal vaccines, IPV, inactivated influenza vaccines, and human papillomavirus (HPV) vaccines (for individuals aged 9-26 years) are recommended after HCT. Varicella, zoster, and MMR vaccines may be administered after HCT if 24 months have passed since HCT, the patient does NOT have graft-vs-host disease, and is considered immunocompetent".

Winston and associates (2018) stated that recipients of autologous haemopoietic stem-cell transplants (auto-HSCT) have an increased risk of herpes zoster and herpes zoster-related complications. In a randomized, double-blind, placebo-controlled, phase-III clinical trial, these researchers examined the safety and efficacy of an inactivated varicella zoster vaccine for the prevention of herpes zoster following auto-HSCT. Participants of this trial were recruited from 135 medical centers (i.e., stem-cell transplant centers and hospitals) in North America, South America, Europe, and Asia. Patients were eligible if they were aged 18 years or older, scheduled to receive an auto-HSCT within 60 days of enrolment, and had a history of varicella infection or were sero-positive for antibodies to varicella zoster virus, or both. Exclusion criteria included a history of herpes zoster within

the previous year of enrolment, and intended anti-viral prophylaxis for longer than 6 months after transplantation. Participants were randomly assigned according to a central randomization schedule generated by the trial statistician, to receive either the inactivated-virus vaccine from 1 of 3 consistency lots, a high-antigen lot, or placebo, stratified by age (less than 50 versus greater than or equal to 50 years) and intended duration of anti-viral prophylaxis after transplantation (less than or equal to 3 months versus greater than 3 to less than or equal to 6 months). Participants, investigators, trial staff, and the funder's clinical and laboratory personnel were masked to group assignment. Participants were given 4 doses of inactivated vaccine or placebo, with the first dose 5 to 60 days before auto-HSCT, and the second, third, and fourth doses at about 30, 60, and 90 days following transplantation. The primary efficacy end-point was the incidence of herpes zoster, confirmed by PCR or adjudication by a masked clinical committee, or both, assessed in all participants randomly assigned to the vaccine consistency lot group or placebo group who received at least 1 dose of vaccine and had auto-HSCT. Safety was assessed in all randomized participants who received at least 1 dose of vaccine and had follow-up data. A pre-specified vaccine efficacy success criterion required the lower bound of the 95 % CI be higher than 25 % for the relative reduction of the hazard ratio (HR) of herpes zoster infection in participants given the vaccine from one of the consistency lots compared with those given placebo. Between December 7, 2010, and April 25, 2013, a total of 560 participants were randomly assigned to the vaccine consistency lot group, 106 to the high-antigen lot group, and 564 to the placebo group; 249 (44 %) of patients in the vaccine consistency lot group, 35 (33 %) in the high-antigen lot group, and 220 (39 %) in the placebo group discontinued before study end, mostly because of death or withdrawal; 51 participants were excluded from the primary efficacy end-point analyses because they did not undergo auto-HSCT or were not vaccinated, or both (22 [4 %] in the vaccine consistency lot group, and 29 [5 %] in the placebo group). Mean follow-up for efficacy was 2.4 years (SD 1.3) in the vaccine consistency lot group and 2.3 years (SD 1.3) in the placebo group; 42 (8 %) of 538 participants in the vaccine consistency lot group (32.9 per 1,000 person-years) and 113 (21 %) of 535 in the placebo group (91.9 per 1,000 person-years) had a confirmed case of herpes zoster. The estimated vaccine efficacy was 63.8 % (95 % CI: 48.4 to 74.6), meeting the pre-specified success criterion. For the combined vaccine groups versus the placebo group, the proportion of patients with serious AEs (216 [33 %] of 657 versus 181 [33 %] of 554; risk difference 0.2 %, 95 % CI: -5.1 to 5.5) and serious vaccine-related AEs (5 [1 %] versus 5 [1 %]; risk difference 0.1 %, -1.4 to 1.1) were similar. Vaccine-related injection-site AEs occurred more frequently in participants given vaccine than those given placebo (191 [29 %] versus 36 [7 %]; risk difference 22.6 %, 95 % CI: 18.5 to 26.6; $p < 0.0001$). The authors concluded that the findings of this study showed for the first time in a large phase-III clinical trial that early vaccination of auto-HSCT recipients during the peri-transplant period could be effective for the prevention of an opportunistic infection like herpes zoster and that the vaccine was well-tolerated.

Bastidas and colleagues (2019) noted that herpes zoster, a frequent complication following auto-HSCT, is associated with significant morbidity. A non-live adjuvanted recombinant zoster vaccine has been developed to prevent post-transplantation zoster. In a phase-III, randomized, observer-blinded study, these researchers examined the efficacy and AE profile of the recombinant zoster vaccine in immunocompromised auto-HSCT recipients. This trial was conducted in 167 centers in 28 countries between July 13, 2012, and February 1, 2017, among 1,846 patients aged 18 years or older who had undergone recent auto-HSCT. Participants were randomized to receive 2 doses of either recombinant zoster vaccine (n = 922) or placebo (n = 924) administered into the deltoid muscle; the first dose was given 50 to 70 days after transplantation and the second dose 1 to 2 months thereafter. The primary end-point was occurrence of confirmed herpes zoster cases. Among 1,846 auto-HSCT recipients (mean age of 55 years; 688 [37 %] women) who received 1 vaccine or placebo dose, 1,735 (94 %) received a second dose and 1,366 (74 %) completed the study. During the 21-month median follow-up, at least 1 herpes zoster episode was confirmed in 49 vaccine and 135 placebo recipients (incidence, 30 and 94 per 1,000 person-years, respectively), an incidence rate ratio (IRR) of 0.32 (95 % CI: 0.22 to 0.44; $p < 0.001$), equivalent to 68.2 % vaccine efficacy. Of 8 secondary end-points, 3 showed significant reductions in incidence of PHN (vaccine, n = 1; placebo, n = 9; IRR, 0.1; 95 % CI: 0.00 to 0.78; $p = 0.02$) and of other pre-specified herpes zoster-related complications (vaccine, n = 3; placebo, n = 13; IRR, 0.22; 95 % CI: 0.04 to 0.81; $p = 0.02$) and in duration of severe worst herpes zoster-associated pain (vaccine, 892.0 days; placebo, 6,275.0 days; HR, 0.62; 95 % CI: 0.42 to 0.89; $p = 0.01$); 5 secondary objectives were descriptive. Injection site reactions were recorded in 86 % of vaccine and 10 % of placebo recipients, of which pain was the most common, occurring in 84 % of vaccine recipients (grade 3: 11 %). Unsolicited and serious AEs, potentially immune-mediated diseases, and underlying disease relapses were similar between groups at all time-points. The authors concluded that among adults who had undergone auto-HSCT, a 2-dose course of recombinant zoster vaccine compared with placebo significantly reduced the incidence of herpes zoster over a median follow-up of 21 months.

Herpes Zoster Vaccine and Hematologic Malignancies / Solid Tumors

Vink and colleagues (2019) stated that the adjuvanted recombinant zoster vaccine (RZV) has demonstrated greater than 90 % efficacy against HZ in adults greater than or equal to 50 years of age and 68 % efficacy in auto-HSCT recipients greater than or equal to 18 years of age. In a multi-center, observer-blind, phase-II/III clinical trial, these investigators examined the immunogenicity and safety of RZV administered to patients with solid tumors (STs) before or at the start of a chemotherapy cycle. Subjects were randomized (1:1) to receive 2 doses of RZV or placebo 1 to 2 months apart and stratified (4:1) according to the timing of the first dose with respect to the start of a chemotherapy cycle (first vaccination 8 to 30 days before the start or at the start [± 1 day] of a chemotherapy cycle). Anti-glycoprotein E (gE) antibody concentrations, gE-specific CD4+ T cell frequencies, and vaccine response rates (VRRs) were assessed 1 month after dose 1 and 1 and 12 months after the second dose. Reactogenicity and safety were assessed in the total vaccinated cohort through 12 months after dose 2. There were 232 subjects in the total vaccinated cohort, 185 in the according-to-protocol cohort for humoral immunogenicity, and 58 in the according-to-protocol cohort for cell-mediated immunogenicity. Post-vaccination anti-gE antibody concentrations, gE-specific CD4+ T cell frequencies and VRRs were higher in RZV recipients than in placebo recipients. Solicited AEs were more frequent

among RZV recipients than placebo recipients. Incidence of unsolicited AEs, serious AEs, fatalities, and potential immune-mediated diseases were similar between RZV and placebo recipients. The authors concluded that RZV was immunogenic in patients with STs receiving immunosuppressive chemotherapies. Humoral and cell-mediated immune responses persisted 1 year after vaccination. No safety concerns were identified.

Mullane and co-workers (2019) noted that patients who are immunocompromised because of malignancy have an increased risk of HZ and HZ-related complications. In a randomized, multi-center, double-blind, placebo-controlled, 2-arm phase-III clinical trial, these investigators examined the safety and efficacy of an inactivated varicella zoster virus (VZV) vaccine for HZ prevention in patients with ST or hematological malignancies. This trial was carried out in 329 centers across 40 countries, and it included adult patients with ST malignancies receiving chemotherapy and those with hematological malignancies, either receiving or not receiving chemotherapy. Subjects were randomly assigned (1:1) to receive 4 doses of VZV vaccine inactivated by gamma irradiation or placebo approximately 30 days apart. The subjects, investigators, trial site staff, clinical adjudication committee, and sponsor's clinical and laboratory personnel were masked to the group assignment. The primary efficacy end-point was HZ incidence in patients with ST malignancies receiving chemotherapy, which was assessed in the modified intention-to-treat (ITT) population (defined as all randomly assigned patients who received at least 1 dose of inactivated VZV vaccine or placebo). The primary safety end-point was serious AEs up to 28 days after the 4rth dose in patients with ST malignancies receiving chemotherapy. Safety end-points were evaluated in all patients who received at least 1 dose of inactivated VZV vaccine or placebo and had follow-up data. Between June 27, 2011 and April 11, 2017, a total of 5,286 patients were randomly assigned to receive VZV vaccine inactivated by gamma irradiation (n = 2,637) or placebo (n = 2,649). The hematological malignancy arm was terminated early because of evidence of futility at a planned interim analysis; thus, all pre-specified hematological malignancy end-points were deemed exploratory. In patients with ST malignancies in the modified ITT population, confirmed HZ occurred in 22 of 1,328 (6.7 per 1,000 person-years) VZV vaccine recipients and in 61 of 1,350 (18.5 per 1,000 person-years) placebo recipients. Estimated vaccine efficacy against HZ in patients with ST malignancies was 63.6% (97.5 % CI: 36.4 to 79.1), meeting the pre-specified success criterion. In patients with ST malignancies, serious AEs were similar in frequency across treatment groups, occurring in 298 (22.5 %) of 1,322 patients who received the vaccine and in 283 (21.0 %) of 1,346 patients who received placebo (RD 1.5 %, 95 % CI: -1.7 to 4.6). Vaccine-related serious AEs were less than 1 % in each treatment group. Vaccine-related injection-site reactions were more common in the vaccine group than in the placebo group. In the hematological malignancy group, VZV vaccine was well-tolerated and estimated vaccine efficacy against HZ was 16.8 % (95 % CI: -17.8 to 41.3). The authors concluded that the inactivated VZV vaccine was well-tolerated and effective for HZ prevention in patients with ST malignancies receiving chemotherapy, but was not effective for HZ prevention in patients with hematological malignancies.

Dagnew and colleagues (2019) noted that Shingrix can prevent HZ in the elderly and autologous HSCT recipients. These researchers examined the safety and immunogenicity of this vaccine in adults with hematological malignancies receiving immunosuppressive cancer treatments. In a randomized, observer-blind, placebo-controlled phase-III clinical trial, carried out at 77 centers worldwide, these researchers randomly assigned (1:1) patients with hematological malignancies aged 18 years and older to receive 2 doses of the adjuvanted recombinant zoster vaccine or placebo 1 to 2 months apart during or after immunosuppressive cancer treatments, and stratified participants according to their underlying diseases. The co-primary objectives of the study were the evaluation of safety and reactogenicity of the adjuvanted recombinant zoster vaccine compared with placebo from the first vaccination up to 30 days after last vaccination in all participants; evaluation of the proportion of participants with a vaccine response in terms of anti-glycoprotein E humoral immune response to the adjuvanted recombinant zoster vaccine at month 2 in all participants, excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukemia (CLL); and evaluation of the anti-glycoprotein E humoral immune responses to the vaccine compared with placebo at month 2 in all participants, excluding those with non-Hodgkin B-cell lymphoma and CLL. They evaluated immunogenicity in the per-protocol cohort for immunogenicity and safety in the total vaccinated cohort. Between March 1, 2013, and September10, 2015, these researchers randomly assigned 286 participants to adjuvanted recombinant zoster vaccine and 283 to placebo; 283 in the vaccine group and 279 in the placebo group were vaccinated. At month 2, 119 (80.4 %, 95 % CI: 73.1 to 86.5) of 148 participants had a humoral vaccine response to adjuvanted recombinant zoster vaccine, compared with 1 (0.8 %, 0.0 to 4.2) of 130 participants in the placebo group, and the adjusted geometric mean anti-glycoprotein E antibody concentration was 23,132.9 mIU/ml (95 % CI 16,642.8 to 32,153.9) in the vaccine group and 777.6 mIU/ml (702.8 to 860.3) in the placebo group (adjusted geometric mean ratio 29.75, 21.09 to 41.96; $p < 0.0001$) in all patients, excluding those with non-Hodgkin B-cell lymphoma and CLL. Humoral and cell-mediated immune responses persisted above baseline until month 13 in all strata and, as expected, vaccine was more reactogenic than placebo (within 7 days after vaccination pain was reported by 221 [79.5 %] of 278 vaccine group participants and 45 [16.4 %] of 274 placebo group participants; fatigue was reported by 162 [58.3 %] of 278 vaccine group participants and 102 [37.2 %] of 274 placebo group participants). Incidences of unsolicited or serious adverse events (AEs), potential immune-mediated diseases, disease-related events, and fatal serious AEs were similar between the groups. The authors concluded that immunocompromised adult population with hematological malignancies is at high risk for HZ. The adjuvanted recombinant zoster vaccine, which is currently licensed in certain countries for adults aged 50 years and older, is likely to benefit this population.

Racine and associates (2020) noted that the adjuvanted recombinant zoster vaccine (RZV) is indicated for prevention of HZ in adults aged greater than or equal to 50 years. Questions regarding the use of RZV in immunocompromised patients less than 50-year of age, who are at increased risk for HZ, were raised. In a systematic review, these investigators examined existing evidences on safety, immunogenicity and efficacy of RZV in immunocompromised adults aged 18 to 49 years. A total of 4 data-bases were searched. Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines

were followed. Screening and classification of search items was performed using the web-based platform DistillerSR. The search identified 1,389 potentially relevant records; 6 studies fulfilled inclusion criteria. The proportion of patients aged 18 to 49 varied between 23 % and 62 %. Pain at injection site (98.6 %) and fatigue (75.3 %) were the most common AEs. The proportion of patients reporting serious AEs (SAEs) ranged between 8.1 % and 30.8 % in RZV and between 4.1 % and 36.5 % in placebo groups. SAEs deemed related to vaccination were reported in less than 1 % of patients in both RZV and placebo groups. The proportion of patients that experienced clinically significant underlying disease-related events ranged between 0.0 and 20.0 % in RZV and 0.0 and 26.7 % in placebo groups. The humoral and cell-mediated immune response rate ranged between 65.4 % and 96.2 % and 50.0 % to 93.0 %, respectively. Vaccine efficacy in HSCT patients was 72 % (95 % CI: 39 % to 88 %) in 18- to 49-year old subjects and 67 % (95 % CI: 53 % to 78 %) in greater than or equal to 50-year old subjects (median follow-up of 21 months). Vaccine efficacy in greater than or equal to 18-year old patients with hematologic malignancies was estimated at 87.2 % (95 % CI: 44.3 % to 98.6 %) up to 13 months post-vaccination. The authors concluded that the findings of this study suggested that RZV had an acceptable safety profile and induced immunity in an important proportion of greater than or equal to 18-year old immunocompromised patients. Moreover, these researchers stated that longer follow-up studies are needed to examine the duration of RZV induced immunity in immunocompromised patients.

Herpes Zoster Vaccine and Inflammatory Bowel Disease

Kopylov et al (2012) noted that VZV is a severe and preventable infection in immunosuppressed inflammatory bowel disease (IBD) patients. The European Crohn's and Colitis Organization (ECCO) guidelines recommend VZV immunization in patients with negative VZV exposure history. The value of patient-reported VZV exposure history for prediction of seropositivity in IBD patients remains unknown. Moreover, data on VZV immunity in adult IBD patients or accuracy of VZV serological testing under immunomodulator treatment is sparse. These researchers determined the prevalence of seropositivity for VZV-IgG in immunomodulator-treated IBD patients. A secondary aim was to establish the value of patient-reported history of past VZV infection for prediction of immunity, to validate the current vaccination strategy. History of VZV-related illness was accessed by epidemiological questionnaire, and serological testing for VZV-IgG was performed. Serum anti-TNF medications levels were measured when applicable. A total of 121 IBD (86 % Crohn's disease [CD], mean age of 37 ± 12.8 years) patients were included in the study. Immunomodulator therapy was received by 87 % (anti-TNFs: 71 %) of the patients. Previous exposure to VZV was reported by 104 patients, and 97/104 (93 %) were VZV-IgG seropositive; 17 patients, all seropositive, reported negative exposure history. The calculated positive and negative predictive values (PPVs and NPVs) for the reported history of VZV exposure were 93 % and 0 %, respectively. The authors concluded that negative history of VZV exposure was a poor predictor of seronegativity. History-positive patients may still be seronegative and exposed to VZV infection. These investigators suggested serological testing of all IBD patients with subsequent immunization of the seronegative patients before initiation of immunosuppressive therapy.

The American College of Gastroenterology (ACG) clinical guideline on "Preventive care in inflammatory bowel disease" (Farraye et al, 2017) noted that recent data suggested that IBD patients do not receive preventive services at the same rate as general medical patients. Patients with IBD often consider their gastroenterologist to be the primary provider of care. To improve the care delivered to IBD patients, health maintenance issues need to be co-managed by both the gastroenterologist and the primary care team. Gastroenterologists need to explicitly inform the primary care provider of the unique needs of the IBD patient, especially those on immunomodulators and biologics or being considered for such therapy. In particular, documentation of up-to-date vaccinations are crucial as IBD patients are often treated with long-term immunosuppressive therapies and may be at increased risk for infections, many of which are preventable with vaccinations. Health maintenance issues addressed in this guideline include identification, safety and appropriate timing of vaccinations, screening for osteoporosis, cervical cancer, melanoma and non-melanoma skin cancer as well as identification of depression and anxiety and smoking cessation. To accomplish these health maintenance goals, coordination between the primary care provider, gastroenterology team and other specialists is necessary.

Mir and Kane (2018) stated that patients with IBD are not receiving preventative care services at the same rate as the general population. IBD patients are at increased risk for infections, osteoporosis, and certain malignancies secondary to their disease and as they are on immunosuppressive therapy. They are a younger population and often times consider their gastroenterologist as their primary care physician. These researchers discussed up-to-date evidence pertaining to vaccine-preventable illnesses in the immunosuppressed IBD patient, screening for bone health, cervical cancer, skin malignancies, psychological wellbeing, and smoking cessation. Vaccinations are recommended in the IBD population as they are immunosuppressed and at increased risk for acquiring influenza and pneumonia. Not only are they at greater risk to acquire it but they also have a much severe complicated course. Ideally, IBD patients should be vaccinated prior to initiating immunosuppression and most inactive vaccines can be administered to them while they are on therapy. All IBD patients should be encouraged to stop smoking and have adequate vitamin D intake along with appropriate applicable cancer screenings. Gastroenterologists must work in collaboration with primary care providers along with other specialists to help provide their IBD patients with well-rounded care.

However, in a review on "Updates in vaccination: Recommendations for adult inflammatory bowel disease patients", Chaudrey et al (2015) recommended a single-dose of zoster vaccine for all IBD adults 60 years and older, regardless of previous shingles. HZ vaccine is contraindicated in immunosuppressed patients. However, the current ACIP recommendations reported that patients receiving short-term (i.e., less than 14 days) or low-to-moderate dose (i.e., less than 20 mg/day) corticosteroid therapy are not considered to be sufficiently immunosuppressed to justify avoiding the live zoster vaccine. This is also applicable to

patients on low-dose methotrexate (i.e., less than or equal to 0.4 mg/kg per week), azathioprine (less than or equal to 3.0 mg/kg per day), or 6-mercaptopurine (less than or equal to 1.5 mg/kg per day). This opinion does not extend to other live vaccines and patients on anti-TNF therapy.

Furthermore, an UpToDate review on "Medical management of low-risk adult patients with mild to moderate ulcerative colitis" (Al Hashash and Regueiro, 2020) states that "Patients who are not up to date with other routinely recommended vaccines (based on age or other risk factors) should receive any needed inactivated (non-live) vaccines regardless of immunosuppression. Any needed live vaccines (e.g., measles or zoster vaccines) should ideally be administered greater than or equal to 4 weeks prior to the start of immunosuppression. The approach to immunizations for patients with IBD is similar to the care of patients with autoimmune inflammatory rheumatic conditions …".

Live Varicella-Zoster Vaccine in Persons Receiving Tumor Necrosis Factor Inhibitor Therapy

Curtis and colleagues (2021) stated that the safety and effectiveness of live virus vaccines, such as the VZV, are unknown in patients with inflammatory diseases receiving immunomodulatory therapy such as tumor necrosis factor inhibitors (TNFis). In a randomized, blinded, placebo-controlled trial, these researchers examined the safety and immunogenicity of the live attenuated zoster vaccine (ZVL) in patients receiving TNFis. Subjects were adults aged 50 years or older receiving TNFis for any indication; and were randomly assigned to ZVL versus placebo; ELISpot and gpELISA from serum and peripheral blood mononuclear cells were measured at baseline and 6 weeks after vaccination. Suspected varicella infection or HZ was clinically assessed using digital photographs and polymerase chain reaction (PCR) on vesicular fluid. Between March 2015 and December 2018, a total of 617 subjects were randomly assigned in a 1:1 ratio to receive ZVL (n = 310) or placebo (n = 307) at 33 centers. Mean age was 62.7 years (SD, 7.5); 66.1 % of subjects were women, 90 % were White, 8.2 % were Black, and 5.9 % were Hispanic. The most common TNFi indications were rheumatoid arthritis (57.6 %) and psoriatic arthritis (24.1 %); TNFi medications were adalimumab (32.7 %), infliximab (31.3 %), etanercept (21.2 %), golimumab (9.1 %), and certolizumab (5.7 %). Concomitant therapies included methotrexate (48.0 %) and oral glucocorticoids (10.5 %). Through week 6, no cases of confirmed varicella infection were found; cumulative incidence of varicella infection or shingles was 0.0 % (95 % CI: 0.0 % to 1.2 %). At 6 weeks, compared with baseline, the mean increases in geometric mean fold rise as measured by gpELISA and ELISpot were 1.33 percentage points (CI: 1.17 to 1.51 percentage points) and 1.39 percentage points (CI: 1.07 to 1.82 percentage points), respectively. The authors concluded that this study informed safety concerns related to use of live virus vaccines in patients receiving biologics. Moreover, these researchers stated that this study was potentially limited generalizability to patients receiving other types of immunomodulators.

SARS-CoV-2 Vaccine and the Risk of Re-Activation of Varicella Zoster

Desai and colleagues (2021) noted that although the COVID-19 vaccination is deemed safe, exact incidence and nature of adverse effects, especially dermatological ones, are still unknown. In a systematic review, these investigators described the demographic, clinical, morphological characteristics, outcomes, and timing of development of herpes zoster (HZ) to the various COVID-19 vaccines. In addition, they examined if COVID-19 vaccine has temporal relationship between development of HZ. They carried out a review of studies from PubMed and Embase using MeSH and keywords like "Shingles", "Herpes zoster", "Varicella zoster", "COVID-19", "Vaccine", and "SARS-CoV-2". No filters (including country of publication, language, type of articles) were applied. Individual case report references were filtered for any pertinent cases. A total of 54 cases of HZ consisting of 27 male and 27 female patients have been reported. There were cases with known risk factors for HZ, which included age more than 50 years (n = 36), immunological disorders (n = 10), chronic disease (n = 25), metabolic disorder (n = 13), malignancy (n = 4), and psychiatric disorder (n = 2). The mean (SD) period between development of HZ and COVID-19 vaccination was 7.64 (6.92) days. Majority of the cases were from the high-income and/or middle-income countries; 86.27 % of the cases of HZ were reported due to mRNA vaccine; and 36 patients 36/45 (80 %) developed HZ following the priming dose of COVID-19 vaccine among those who received mRNA vaccine. The authors could not establish definite link; however, there may be possible association between COVID-19 vaccine and shingles. These researchers stated that large-scale immunological, epidemiological, and clinical studies may help to understand the cause-effect relationship. Based on the criteria of temporal connection with vaccination and a plausible biological link, HZ appears to be a "possible" but uncommon AE following vaccination. Furthermore, these findings may be therapeutically relevant in deciding whether to use anti-viral as a temporary prophylactic prior to immunization for individuals who are at a greater risk of VZV re-activation following SARS-CoV-2 vaccination. These investigators stated that this study was limited by publication bias, small sample size, missing data, and lack of generalizability in demographics of the series analyzed. In the majority of the cases, diagnosis of HZ was pertinent to the HZ clinical findings.

Herpes Zoster Vaccine Live and Risk of Stroke

Yang et al (2021) noted that HZ is associated with increased risk of stroke, and zoster vaccine live (ZVL, Zostavax) reduces the risk of HZ. No study has examined the association between ZVL (Zostavax) and risk of stroke. In a population-based, cohort study, these investigators examined association between receipt of ZVL (Zostavax) and risk of stroke among older U.S. population. This trial included 1,603,406 U.S. Medicare fee-for-service beneficiaries aged 66 years or older without a history of stroke and who received ZVL (Zostavax) during 2008 to 2014, and 1,603,406 propensity score-matched unvaccinated beneficiaries followed through to December 31, 2017. These researchers used Cox proportional hazard models to examine

association between ZVL (Zostavax) and composite fatal or nonfatal incident stroke outcomes. During a median of 5.1 years follow-up (inter-quartile range [IQR], 3.9 to 6.7), these researchers documented 64,635 stroke events, including 43,954 acute ischemic strokes and 6,727 hemorrhagic strokes, among vaccinated beneficiaries during 8,755,331 person-years. The corresponding numbers among unvaccinated beneficiaries were 73,023, 50,476, and 7,276, respectively, during 8,517,322 person-years. Incidence comparing vaccinated to unvaccinated beneficiaries were 7.38 versus 8.57 per 1,000 person-years for all stroke, 5.00 versus 5.90 for acute ischemic stroke, and 0.76 versus 0.84 for hemorrhagic stroke ($p < 0.001$ for all difference). Adjusted HR comparing vaccinated to unvaccinated beneficiaries were 0.84 (95 % CI: 0.83 to 0.85), 0.83 (0.82 to 0.84), and 0.88 (0.85 to 0.91) for all stroke, acute ischemic stroke, and hemorrhagic stroke, respectively. The association between ZVL (Zostavax) and risk of stroke appeared to be stronger among younger beneficiaries, beneficiaries who did not take anti-hypertensive or statin medications and who had fewer co-morbid conditions ($p < 0.05$ for interaction) but largely consistent across sex, low-income status, and racial groups. The authors concluded that among Medicare fee-for-service beneficiaries, receipt of ZVL (Zostavax) was associated with lower incidence of stroke; these findings may encourage people to get vaccinated against HZ to reduce HZ and HZ-associated stroke risk.

Zoster Vaccine Effectiveness in the Elderly

Mbinta et al (2022) stated that given the substantial impact of herpes zoster on health and quality of life (QOL), as well as its considerable economic burden, prevention via vaccination is a priority. In a systematic review and meta-analysis, these investigators examined the effectiveness of the herpes zoster vaccines (RZV and ZVL) against incident herpes zoster PHN in the elderly. They reviewed studies examining the effectiveness of herpes zoster vaccines in adults aged 50 years or older, compared with no vaccination or another vaccine. These investigators searched published literature on Medline, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, ProQuest Central, and Dimensions, as well as unpublished studies, grey literature, and the reference lists of included studies. Observational studies published in any language between May 25, 2006, and December 31, 2020, were included. Eligible studies were appraised for methodological quality using standardized critical appraisal instruments from the Joanna Briggs Institute, and data were extracted from selected studies using a standardized tool. Random-effects meta-analysis models were employed to estimate pooled vaccine effectiveness for outcomes of interest (herpes zoster, herpes zoster ophthalmicus, and PHN) among clinically and methodologically comparable studies, with a fixed-effects model also used for herpes zoster ophthalmicus. Vaccine effectiveness was also assessed in individuals with co-morbidities. The search identified 1,240 studies, of which 1,162 were excluded based on title and abstract screening. A further 56 articles were excluded upon reading the full text; 22 studies (21 cohort studies and 1 case-control study, involving 9,536,086 subjects and 3.35 million person-years in the U.S., U.K., Canada, and Sweden) were included in the quantitative analysis. Of these, 13 studies were included in the meta-analysis. The overall quality of evidence was very low for all outcomes. The pooled vaccine effectiveness for ZVL against herpes zoster in adults was 45.9 % (95 % CI: 42.2 to 49.4; 7 studies). The vaccine effectiveness for ZVL against PHN was 59.7 % (58.4 to 89.7; t3 studies) and against herpes zoster ophthalmicus (in a fixed-effects model) was 30.0 % (20.5 to 38.4; 2 studies). ZVL was effective in preventing herpes zoster in individuals with co-morbidities, including diabetes (vaccine effectiveness 49.8 %, 45.1 to 54.1; 3 studies), chronic kidney disease (54.3 %, 49.0 to 59.1; 4 studies), liver disease (52.9 %, 41.6 to 62.1; 2 studies), heart disease (52.3 %, 45.0 to 58.7; 2 studies), and lung disease (49.0 %, 32.2 to 66.2; 2 studies). In a post-hoc analysis of 2 studies from the U.S. published after 2020, the pooled vaccine effectiveness for RZV against herpes zoster in adults was 79.2 % (57.6 to 89.7). Substantial heterogeneity ($I2 \geq 75$ %) was observed in 50 % of the meta-analyses. The authors concluded that ZVL and RZV were effective in preventing herpes zoster in routine clinical practice. ZVL also lowered the risk of PHN. Selection bias and confounding by unmeasured variables were inherent challenges of observational studies based on large health-care databases. Nevertheless, these findings would reassure policy makers, health practitioners, and the public that the vaccinations currently available for herpes zoster vaccination programs are effective at preventing herpes zoster and related complications.

Herpes Zoster Vaccine in Immunocompetent and Immunocompromised Subjects

In a systematic review and meta-analysis, Xia et al (2022) examined the safety, efficacy, and effectiveness of RZV and ZVL in immunocompetent and immunocompromised subjects. These investigators searched PubMed, Embase, Cochrane Library, and Web of Science databases (up to January 2022) to identify English articles. Search terms included RCTs, observational studies, herpes zoster, RZV, ZVL. Only RCTs examining vaccine safety and efficacy as well as observational studies examining vaccine effectiveness (after a vaccine was approved for marketing) were included. Two independent researchers screened the literature, extracted the data, and checked each other results. A total of 17 RCTs and 19 cohort studies were included in this review. Among immunocompetent subjects, RZV was superior to ZVL at wide intervals (relative vaccine efficacy: 84 %, 95 % CI: 53 % to 95 %; relative vaccine effectiveness: 49 %, 95 % CI: 21 % to 67 %), across genders and subjects aged 60 years or older. Among immunocompromised subjects, RZV was superior to placebo in terms of vaccine efficacy (60 %, 95 % CI: 49 % to 69 %). There was no difference between ZVL and placebo in those with selected immunosuppressive conditions. RZV was 45 % (95 % CI: 30 % to 59 %) superior to ZVL in real-world practice. Compared with placebo, AEs related to RZV were primarily related to injection-site and systemic, and RZV did not increase the risk of serious AEs (SAEs) or death. There was no difference in the incidence of AEs between groups with and without immunosuppression. The authors concluded that both RZV and ZVL could reduce the risk of herpes zoster in both immunocompetent and immunocompromised subjects; RZV was well-tolerated in the study population and demonstrated stronger protection than ZVL.

Cost-Effectiveness of an Adjuvanted Recombinant Zoster Vaccine in Adults with Inflammatory Bowel Disease

Caldera et al (2023) stated that recombinant zoster vaccine (RZV) is recommended for all adults 19 years of age or older who are at increased risk for HZ, including patients with inflammatory bowel disease (IBD). These investigators constructed a Markov model to compare the RZV cost-effectiveness with no vaccination in patients with Crohn's disease (CD) and ulcerative colitis (UC). A simulated cohort of 1 million patients was used for each IBD group at ages 18, 30, 40, and 50 years. The primary objective of this analysis was to compare RZV cost-effectiveness in patients with CD and UC, comparing vaccination to no vaccination. Overall, vaccination was cost-effective for both CD and UC, with the incremental cost-effectiveness ratio (ICERs) below $100,000/quality-adjusted life years (QALY) for all age cohorts. For patients with CD, 30 years of age and older, and those with UC 40 years and older, vaccination was both more effective and less expensive than the non-vaccinated strategy (CD 30 years or older: ICERs $6,183 to $24,878 and UC 40 years or older: ICERs $9,163 to $19,655). However, for CD patients under 30 (CD 18: ICER $2,098) and UC patients under 40 (UC = 18: ICER $11,609, and UC = 30: $1,343), costs were greater for vaccinated patients, but there was an increase in QALY. One-way sensitivity analysis of age indicated that cost break-even occurred at age 21.8 years for the CD group, and 31.5 years for the UC group. In probabilistic sensitivity analysis, 92 % of both CD and UC simulations indicated that vaccination was preferred. The authors concluded that in their model, vaccination with RZV was cost-effective for all adult patients with IBD.

Live-Attenuated Varicella Vaccine in Pediatric Solid Organ Transplant Recipients

Piche-Renaud et al (2023) examined the available evidence on the immunogenicity, safety, and effectiveness of live-attenuated varicella vaccine in solid organ transplant (SOT) recipients. Medline and Embase were searched using pre-defined search terms to identify relevant studies. The included articles reported varicella vaccine administration in the post-transplant period in children and adults. A pooled proportion of transplant recipients who sero-converted and who developed vaccine-strain varicella and varicella disease was generated. A total of 18 articles (14 observational studies and 4 case reports) were included, reporting on 711 transplant recipients who received the varicella vaccine. The pooled proportion was 88.2 % (95 % CI: 78.0 % to 96.0 %, 13 studies) for vaccinees who sero-converted, 0 % (0 % to 1.2 %, 13 studies) for vaccine-strain varicella, and 0.8 % (0 % to 4.9 %, 9 studies) for varicella disease. Most studies followed clinical guidelines for administering live-attenuated vaccines, with criteria that could include being at least 1 year post-transplant, 2 months post-rejection episode, and on low-dose immunosuppressive medications. The authors concluded that varicella vaccination in transplant recipients was overall safe in the included studies, with few cases of vaccine-strain-induced varicella or vaccine failure, and although it was immunogenic, the proportion of recipients who sero-converted was lower than that observed in the general population. These investigators stated that these findings support varicella vaccination in select pediatric SOT recipients.

Daniels et al (2024) noted that vaccinating pediatric SOT candidates against measles and varicella is very important due to the risk of severe disease in immune-suppressed recipients and general avoidance of live virus vaccines post-transplantation. The world saw a resurgence of measles starting 2012 prompting the American Society of Transplantation in 2015 to release guidelines on recognition, prevention, and post-exposure prophylaxis of this disease in SOT recipients. These investigators examined the extent of incomplete immunity to these viruses in SOT candidates and the approach to immunity optimization during a period of heightened awareness. This trial was a cross-sectional study from 2012 to 2016 at Cleveland Clinic Children's, and included pediatric SOT candidates. Data on vaccination history, serology, and demographics were collected. Incomplete immunity was defined by incomplete vaccination or sero-negativity. Among 91 candidates, 54.9 % had complete varicella vaccination. Serological varicella immunity among patients tested varied by age: less than 7 years, 50.0 % positive in patients with complete schedules, none in the incomplete; 7 years or older, 50.0 % positive in patients with complete schedules, 65.5 % in the incomplete. For measles, 69.2 % had complete vaccination, with immunity varying by age among those tested: less than 7 years, 84.6 % positive in patients with complete schedules, 42.9 % in the incomplete; 7 years or older, 81.0 % with complete, 62.5 % with incomplete. Only 31.1 % of those who qualified for a varicella additional dose and 28 % who qualified for an additional measles dose received it, respectively. The authors concluded that incomplete immunity to varicella and measles was prevalent in pediatric SOT candidates at their center during the study period. Despite an increase in global measles activity, their efforts to optimize immunity via additional vaccine doses were only partially successful. These researchers stated that future investigations should focus on addressing strategies and understanding barriers to ensure timely vaccination for this vulnerable population before transplantation, especially during periods of increased viral activity.

Orhan Kilic et al (2024) stated that SOT recipients are at an increased risk of severe infections due to their immune-suppressed state. Despite the recommendation of routine screening and vaccination before transplantation to mitigate this danger, vaccination rates in these patients are still below desirable levels. In a retrospective, single-center study, these investigators examined the prevalence of positive antibody rates for measles, mumps, rubella, and varicella among children who are candidates for kidney transplant. This trial included 144 pediatric renal transplant patients for the past 7 years. These researchers reviewed the medical records of all participants to examine their serologic status for measles, mumps, rubella, and varicella viruses before renal transplant. A total of 144 pediatric renal transplant candidates (mean age of 11.5 years, 56.9 % male) were enrolled, and the most frequent causes of the chronic renal disease were congenital anomalies of the kidney and urinary tract and glomerular diseases (32.6 %). Sero-positivity rates for measles, mumps, rubella, and varicella were 59.0 %, 31.9 %, 46.5 %, and 43.6 %, respectively, and all patients who tested negative for antibodies were vaccinated before transplant. Younger age at transplant (OR = 0.909, 95 % CI: 0.840 to 0.923; p = 0.017) and congenital anomalies of the kidney and urinary

tract (OR = 3.46, 95 % CI: 1.1548 to 7.735; p = 0.002) were significantly associated with increased measles sero-positivity, although no significant associations were observed for the other viruses.

The authors observed lower sero-positivity rates for measles, mumps, rubella, and varicella in pediatric renal transplant patients versus healthy children and other previous studies. These investigators stated that it is very important to address these sub-optimal rates to protect the health of these vulnerable patients; they stated that future research should focus on targeted interventions to improve vaccination rates and outcomes in this population.

Measles-Mumps-Rubella-Varicella Vaccine / Nursing Mothers

The CDC and several health professional organizations (No authors listed, 2024) state that vaccines given to a nursing mother do not affect the safety of breast-feeding for mothers or infants and that breast-feeding is not a contraindication to measles, mumps, rubella and varicella virus vaccine. Breast-fed infants should be vaccinated according to the routine recommended schedules. Although rubella vaccine virus might be excreted into milk, the virus usually does not infect the infant. If an infection does occur, it is well-tolerated because the viruses are attenuated. No clear evidence exists of live attenuated measles or mumps vaccine virus excretion into breast milk. Lack of exclusive breast-feeding until 5 months of age is a risk factor for an infant's poor response to measles vaccination.

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Policy History

- Last Review 04/04/2025

  Effective: 03/25/1996

  Next Review: 01/22/2026

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes