Clinical Policy Bulletin:
Varicella and Herpes Zoster Vaccines

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Policy

I. Aetna considers varicella (chicken pox) vaccine a medically necessary preventive service according to the recommendations of the Centers for Disease Control's (CDC) Advisory Committee on Immunization Practices (ACIP).

II. Aetna considers combination measles, mumps, rubella, and varicella vaccine (MMRV) (ProQuad) a medically necessary 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.

III. Aetna considers varicella primary vaccination medically necessary in HIV-infected, 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 percentages > 15%.

IV. Aetna considers zoster vaccine (Zostavax) a medically necessary preventive service to reduce the risk of herpes zoster (shingles) in members 60 years of age and older. Aetna considers repeat (booster) zoster vaccination as experimental and investigational.
Aetna considers Zostavax experimental and investigational for all other indications (e.g., autologous and allogeneic hematopoietic transplant recipients, individuals with chronic lymphocytic leukemia) because its effectiveness for these indications has not been established.

**Background**

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 1st dose administered between 12 and 15 months of age, and a 2nd 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 2nd 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 2nd 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 2nd 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 2nd 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 (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 dysesthesia 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.

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.

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.

No changes were made to the current recommendation of herpes zoster vaccination for adults aged 60 years and older, the CDC's ACIP reported at its latest meeting. The FDA licensed Zostavax for use in adults aged 50 to 59 years in March 2011, said Dr. Paul Cieslak, chair of the zoster working group. However, the working group does not currently propose changes to the current 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. Also, "it might be inappropriate to expand recommendations while the vaccine remains in short supply," he said, adding that the incidence could increase "if limited supply is used at time of low incidence". He also pointed out, however, that "the decision of the working group at this time is not intended to prejudice future deliberations". 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 (Splett, 2011).

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. Sixty 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 (8.5-12.8) years, 9.5% (3-14), and 28% (22-32), respectively and that fifty-seven children (95%) received antiretroviral therapy for a median of 27 months. The results showed that among 34 children (57%) who were VZV seronegative at baseline, 11.8% (95% CI, 3.3%-27.5%) and 79.4% (95% CI, 62.1%-91.3%) were VZV seroconverted after first and second dose of vaccine, respectively. Children who had VZV seroconversion were found to be more likely to have HIV RNA <1.7 copies/mL (92.6% vs. 71.4%, P = 0.18) and among 26 children who were seropositive 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 seroconversion 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, multicenter 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 < .0001), 2.23 (P = .004), 1.76 (P = .026), and 9.01 (P = NA), respectively. Similarly, antibody GMFR were 2.35 (P < .0001), 1.28 (P = .003), 1.37 (P = .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 / microL 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 percent 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 cells/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).

CPT Codes / HCPCS Codes / ICD-9 Codes

Varicella (chicken pox) and combination varicella and measles, mumps and rubella vaccine (MMRV):
CPT codes covered if selection criteria are met:

90710
90716

Other CPT codes related to the CPB:

90707

ICD-9 codes covered if selection criteria are met:

V05.4  Need for other prophylactic vaccination and inoculation against varicella

V06.8  Need for other prophylactic vaccination and inoculation against other combinations of diseases

Other ICD-9 codes related to the CPB:

052.0 - 052.9  Chickenpox

V06.4  Need for other prophylactic vaccination and inoculation against measles-mumps-rubella [MMR]

Zoster vaccine:

CPT codes covered if selection criteria are met:

90736

ICD-9 codes covered if selection criteria are met:

V05.8  Need for other prophylactic vaccination and inoculation against other specified disease

ICD-9 codes not covered for indications listed in the CPB:

204.10 - 204.12  Chronic lymphoid leukemia

Other ICD-9 codes related to the CPB:

053.0 - 053.9  Herpes zoster

ICD-9 codes contraindicated for this CPB:

011.0 - 011.9  Pulmonary tuberculosis

042  Human immunodeficiency Virus [HIV] disease

200.00 - 208.91  Malignant neoplasm of lymphatic and hematopoietic tissue
630 - 669.94 Complications of pregnancy and childbirth
V08 Asymptomatic human immunodeficiency virus [HIV] infection status
V10.79 Personal history of other lymphatic and hematopoietic neoplasms
V14.7 Personal history of allergy to serum or vaccine
V22.0 - V23.9 Supervision of normal or high-risk pregnancy
V42.81 - V42.82 Organ or tissue replaced by transplant, bone marrow or peripheral stem cells
V58.65 Long-term (current) use of steroids

The above policy is based on the following references:

11. Merck & Co., Inc. ProQuad [measles, mumps, rubella and varicella (Oka/Merck) virus vaccine live. Prescribing Information. 9633800.
Varicella and Herpes Zoster Vaccines


41. Taweesith W, Puthanakit T, Kowitdamrong E, et al. The immunogenicity and safety of live attenuated varicella-zoster virus vaccine in human

43. Hibbard, PL. Immunizations in HIV-infected patients. UpToDate [serial online]. Waltham, MA: UpToDate; June 3, 2014.

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