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Review Article

Recommendations and guidance for herpes zoster vaccination for adults in Taiwan

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Abstract Herpes zoster (HZ) is a painful, vesicular, cutaneous eruption from reactivation of varicella zoster virus (VZV), which can lead to potentially debilitating complications. The lifetime risk of HZ is estimated to be 20%—30% in the general population, with an increased risk in the elderly and immunocompromised populations. The most effective strategy to prevent HZ and its complications is by vaccination. Two types of HZ vaccines, zoster vaccine live and recombinant zoster vaccine, have been approved for use. This guidance offers recommendations and suggestions for HZ vaccination in adults, aiming to reduce the disease burden of HZ and its complications. It is intended as a guide to first-line healthcare providers, but does not supersede clinical judgement when assessing risk and providing recommendations to individuals. The Working Group on Adult Immunization Practice was appointed by the Infectious Diseases Society of Taiwan (IDST) and recommendations were drafted after a full literature review, using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system. The recommendations were reviewed and revised by expert review panels during a series of consensus meetings and endorsed by the IDST, Taiwan Association of Family Medicine, the Taiwanese Dermatological Association, the Taiwan Oncology Society, the Taiwan Society of Blood and Marrow Transplantation, the Transplantation Society of Taiwan, the Taiwan AIDS Society, and the Taiwan College of Rheumatology. This guidance describes the epidemiology of HZ and provides recommendations for HZ vaccination in adults with varying levels of risk, differing history of previous VZV infection and past varicella or zoster vaccinations.

Introduction

Herpes zoster (HZ) is caused by the reactivation of the varicella zoster virus (VZV), which remains dormant in the dorsal root ganglia or sensory ganglia of the cranial nerve after a primary varicella infection or chickenpox.[1] While varicella usually occurs during childhood, HZ typically occurs in adults or the elderly when the cellular immune response fails to control the latent replication of VZV.[1] HZ manifests by a painful, vesicular, cutaneous eruption with a dermatomal distribution; and can lead to potentially debilitating complications, including postherpetic neuralgia (PHN), HZ ophthalmicus, bacterial superinfections, cranial and peripheral nerve palsies, and visceral involvement.[2] The most effective strategy to prevent varicella, HZ, and its related complications is by vaccination (Table 1).[3—7]

Table 1 Comparison of varicella and zoster vaccines.

Proprietary name	Varivax[3]	Varilrix[4]	Zostavax[5]	Shingrix[6]
Type of vaccine	*Varicella* virus vaccine, live attenuated	*Varicella* virus vaccine, live attenuated	Zoster vaccine, live attenuated	Zoster vaccine, recombinant, adjuvanted
First approval year	1984	2004	2006	2017
Disease prevention	Varicella	Varicella	HZ	HZ
Component	1350 PFUs (Oka/ Merck strain)	Not less than 2000 PFUs (Oka strain)	19400 PFUs (Oka/ Merck strain)	Glycoprotein E, $AS01_B$ adjuvant system
Live vaccine	Yes	Yes	Yes	No
Route of Administration	Subcutaneous	Subcutaneous	Subcutaneous	Intramuscular
Dosage in adults	2 doses administered at a minimum interval of 4 weeks	2 doses, preferable to administer the second dose at least 6 weeks after the first dose; but in no circumstances should the interval be less than 4 weeks.	Single dose	2 doses administered at an interval of 2—6 months
Approximate Costs per dose	NT$1400—2000		NT$3800-4842	NT$8680
Efficacy	Children, >90% Adolescents and adults, 80%	Children, 88—100%	HZ: Aged 50—59 years, 70% Aged ≥60 years, 51% PHN: Aged ≥60 years, 67%	HZ: Aged ≥50 years, 94% Aged ≥70 years, 92% PHN: Aged ≥50 years, 91% Aged ≥70 years, 89%
Duration of protection	At least 10—20 years[7]	At least 10—20 years[7]	5—10 years[26]	At least 10 years[30]
Routine immunization program in Taiwan	Yes	Yes	No	No
Approved indication in Taiwan	Active immunization for prevention of varicella	Active immunization for prevention of varicella	Prevention of HZ in adults aged 50—79 years of age	Prevention of HZ and associated complications such as PHN in: - adults aged 50 years and above - adults aged 18 years and above with higher risk of developing HZ
Contraindications	- History of severe allergic reaction to any component of the vaccine or to a previous dose - Immunosuppression - Moderate or severe febrile illness - Active untreated tuberculosis - Pregnancy	- Hypersensitivity to any component of the vaccine - Primary or acquired immunodeficiency states -Lack of cellular immune competence - Receiving immunosuppressive therapy - Pregnancy	- History of anaphylactic/ anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine - Immunosuppression or immunodeficiency - Pregnancy	- History of severe allergic reaction to any component of the vaccine or after a previous dose.

Abbreviations: HZ, herpes zoster; NT$, New Taiwan dollar; PFUs: plaque-forming units; PHN, post-herpetic neuralgia.

Varicella vaccine has been commercially available since 1984; however, individuals who have a history of varicella immunization remain at risk for HZ. The first licensed vaccine for prevention of HZ, Zostavax® (zoster vaccine live [ZVL], Merck & Co., Inc., Whitehouse Station, NJ, USA), is a live, attenuated vaccine. ZVL is approved for use as a single dose for adults 50—79 years of age, but contraindicated in individuals with primary or acquired immunodeficiency states due to a theoretical risk of serious disease that can be caused by the attenuated, live virus.[5] The second licensed HZ vaccine, Shingrix® (recombinant zoster vaccine [RZV], GlaxoSmithKline Biologicals, Rixensart, Belgium), is an inactivated, recombinant, subunit vaccine. Immunization with a 2 dose series of RZV is recommended for adults aged 50 years and older or adults aged at least 18 years, who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy.[6] The aim of this guidance is to develop strategies of HZ vaccination for adults, to further reduce the disease burden of HZ and its complications. This guidance is intended as a guide to first-line healthcare providers, and does not supersede clinical judgement when assessing risk and providing recommendations to the individuals.

Epidemiology

The lifetime risk of HZ is estimated to be about 20%—30% in the general population, and the risk may increase to 50% among those aged >85 years.[8] In Europe and the United States (US), the incidence of HZ in the general adult population varies across countries, ranging from 1.2 to 4.8 cases per 1000 person-years (PY).[9] In Taiwan, the overall incidence of HZ was 4.97 cases per 1000 PY, based on the National Health Insurance Research Database (NHIRD) from 2000 to 2005, with a significantly higher incidence in women compared with men (5.20 vs 4.72 per 1000 PY). The estimated lifetime risk of HZ occurrence is 32.2% and the yearly medical expenditures related to HZ treatment increased from 250 to 319 million New Taiwan dollars from 2000 to 2004.[10] PHN is the most common and debilitating complication of HZ, particularly in the elderly. The proportion of PHN among HZ cases aged >75 years is 4%. Moreover, patients with PHN are shown to have an association with a higher consumption of healthcare services, including outpatient, emergency room visits, and hospital admissions.[11]

The risk for HZ and related complications is increased in immunocompromised adults. In a systematic review evaluating the risk of HZ among adults with immunocompromised conditions in the US, the incidence rate of HZ ranged from 9 to 95 cases per 1000 PY. The incidence estimates were the highest in patients with hematopoietic stem cell transplantation (HSCT), followed by those with hematologic malignancies, solid organ transplantation (SOT), and solid cancers, and were the lowest in people living with HIV (PLWH).[12] The incidence of HZ also increased with age within different immunocompromised populations, except for PLWH. The incidence of HZ for patients aged 18—49 years vs 60—64 years was 40 vs 51 per 1000 PY in patients with HSCT, 13 vs 20 per 1000 PY in patients with SOT, 8 vs 13 per 1000 PY in patients with cancers and 18 vs 16 per 1000 PY in PLWH, respectively.[13] Another meta-analysis showed that a slightly smaller increased risk (risk ratio [RR] range, 1.23—2.08) was observed in those with comorbidities such as diabetes mellitus, rheumatoid arthritis (RR, 1.51; 95% confidence interval [CI], 1.31—1.75), cardiovascular diseases, renal disease, systemic lupus erythematosus (SLE) (RR, 2.08; 95% CI, 1.56—2.78), and inflammatory bowel disease.[14] In addition, COVID-19 was also identified as a factor associated with developing HZ in patients aged ≥ 50 years (adjusted incidence rate ratio [IRR], 1.15; 95% CI, 1.07—1.24; $P < 0.001$).[15] In Taiwan, a study based on the NHIRD from 2000 to 2006 found that patients with HZ were more likely to have diabetes mellitus (RR, 1.52; 95% CI, 1.48—1.57), lymphoma/leukemia (RR, 1.91; 95% CI, 1.67—2.18), breast cancer (RR, 1.57; 95% CI, 1.40—1.76), liver cancer (RR, 1.19; 95% CI, 1.08—1.32), SLE (RR, 2.12; 95% CI, 1.88—2.39), and HIV/AIDS (RR, 1.53; 95% CI, 1.17—1.99).[16]

Methods

Working group, expert panels, and process of guidance development

The "Working Group on Adult Immunization Practice" of the Infectious Diseases Society of Taiwan (IDST) was established in 2021 and aims to develop updated recommendations and guidance for adult immunization, which are supplementary to those provided by Taiwan Advisory Committee on Immunization Practices (ACIP). The working group is comprised of a steering committee and a guidance working committee. The steering committee included 3 infectious diseases specialists who were responsible for setting the purpose and scope of the working group and inviting members of the guidance working committee and the expert review panel. The guidance working committee, comprised of 19 infectious diseases specialists (including 8 pediatricians) and 1 pharmacist, recommended and selected from 13 hospitals across Taiwan, was tasked with reviewing the literature and drafting recommendations. The external review panel was invited by the IDST to provide suggestions and critical review of the guidance. The external review panel included experts representing the Taiwan Association of Family Medicine, the Taiwanese Dermatological Association, the Taiwan Oncology Society, the Taiwan Society of Blood and Marrow Transplantation, the Transplantation Society of Taiwan, the Taiwan AIDS Society, and the Taiwan College of Rheumatology. The final recommendations were endorsed by the medical associations listed above.

During May to October 2022, 6 committee meetings were held to identify relevant, clinical questions and search strategies, to perform comprehensive literature reviews, to rate the quality of the evidence, to decide the strength of recommendations, and to synthesize the draft recommendations. The external expert review panels were invited to join the final 2 meetings to provide suggestions and critical review of the draft recommendations, and the final version of the recommendations was reviewed and endorsed by the IDST and all involved medical associations in November,

2022. All committee members agreed to disclose conflicts of interest before initiation of the guidance development process and after completion of the final draft of recommendations.

Literature review

The working group performed a comprehensive literature search through PubMed, Medline, Embase, Cochrane Database, and Clinicaltrial.gov database. The keywords included HZ, PHN, adult, immunocompromised, solid cancer, hematologic malignancy, transplantation, human immunodeficiency virus (HIV), autoimmune, zoster vaccine live, live attenuated zoster vaccine, recombinant zoster vaccine, adjuvant zoster vaccine, efficacy, safety, immunogenicity, immune response, and concomitant. Included studies were randomized controlled trials and observational studies, and were limited to English articles published before June 30, 2022.

Rating of the evidence and recommendation

The working group adopted the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system to assess the quality of evidence and the strength of recommendations.[17] The GRADE system classified the quality of evidence as high (A), moderate (B), low (C), or very low (D) based on the risk of bias, consistency of results, directness of evidence, precision, and publication bias of included studies. These levels infer a gradient of confidence in estimates of the treatment effect.[18] Although vaccine efficacy was regarded as the critical outcome, vaccine immunogenicity without efficacy data in immunocompromised populations was not considered to affect the directness of evidence during the guidance development by expert consensus, since evidence in this population was limited. The strength of recommendations are classified as either strong (1) or weak (2) after evaluating the balance between benefit and harm, cost and resources, values and preferences, and feasibility and acceptability of the intervention.[19] While a strong recommendation indicates that the desirable effects of adherence to a recommendation outweigh the undesirable effects, a weak recommendation indicates that the undesirable effects of adherence to a recommendation may outweigh its desirable effects. However, the strength of a recommendation may not be necessarily correlated with its priority for implementation. The GRADEpro Guideline Development Tool was used to create concise summary tables to facilitate guidance development.[20] The recommendations and guidance for HZ vaccination are summarized in Table 2.

What is the recommendation for HZ vaccination in immunocompetent adults?

Recommendations

1. HZ vaccination is recommended for immunocompetent adults aged $\geq$ 50 years, unless contraindicated. *(Strong recommendation, moderate quality of evidence) (1B)*
2. Both RZV and ZVL are recommended for immunocompetent adults aged $\geq$ 50 years, with a preference for RZV. *(Weak recommendation, low quality of evidence) (2C)*

Summary of the evidence

The first licensed vaccine for prevention of HZ is Zostavax® (ZVL), which is approved for use in adults aged 50—79 years. Vaccine efficacy of ZVL in preventing HZ and PHN was 51.3% and 66.5%, respectively, in the Shingles Prevention Study (SPS) which included individuals aged $\geq$ 60 years.[21] In the Zoster Efficacy and Safety Trial (ZEST) enrolling those aged between 50 and 59 years, the vaccine efficacy of ZVL in preventing HZ was 69.8%.[22] The vaccine efficacy of ZVL decreased with increasing age and waned over time.[21—25] The vaccine efficacy was 70%, 64%, 41% and 18% in those aged 50—59, 60—69, 70—79 and $\geq$ 80 years, respectively. The vaccine efficacy decreased from 51.3% to 21.2% for HZ incidence and 66.5%—35.4% for incidence of PHN, during follow up from 7 through 11 years post-vaccination. The pooled analysis of safety data revealed that vaccination did not significantly increase deaths or vaccine-associated serious adverse events (SAEs), whereas vaccine-associated systemic (RR, 1.29; 95% CI, 1.06—1.57) and injection-site adverse events (RR, 2.99; 95% CI, 2.75—3.26) were more frequently reported in the vaccinated group.[26] The recombinant zoster vaccine, Shingrix® (RZV), was approved by the US Food and Administrative agency (FDA) in 2017. The pivotal studies of RZV included the ZOE-50 and ZOE-70 trials.[27,28] The ZOE-50 trial enrolled individuals aged $\geq$ 50 years, and the vaccine efficacy was 97.2% which was comparable across all age groups.[27] The ZOE-70 trial included individuals aged $\geq$ 70 years, and reduced HZ incidence by 89.8%.[28] The pooled analysis of participants 70 years of age or older from the ZOE-50 and ZOE-70 trials demonstrated a vaccine efficacy of 91.3% against HZ and 88.8% against PHN.[28] Persistence of protection conferred by RZV was maintained above 83.3% for up to 8 years, and decreased to 73% at 10 years.[29] Safety data from the ZOE-50 and ZOE-70 trials showed that there was no difference between the vaccinated and placebo groups in the incidence of SAEs and deaths, however, the vaccinated group had a significantly higher incidence of grade 3 injection site reactions (9.5% vs 0.4%) and systemic symptoms (11.4% vs 2.4%) compared to the placebo group.[27] Based on the efficacy and safety of ZVL and RZV, we recommend that immunocompetent adults, aged $\geq$ 50 years, may receive either ZVL or RZV to prevent HZ and PHN, with a preference for RZV.

Although there were no head-to-head, clinical trials that directly compared the vaccine efficacy between ZVL and RZV, one network meta-analysis estimated the relative efficacy and safety of ZVL and RZV based on evidence derived from randomized controlled trials.[30] This meta-analysis demonstrated that RZV was significantly more effective in preventing HZ and PHN compared with ZVL. The adjuvanted vaccine, RZV, was associated with a significantly higher rate of injection-site and systemic reactions compared to ZVL; however, there were no differences in SAEs between RZV and ZVL. The preferred HZ vaccine recommended in the

Table 2 Recommendations and guidance for herpes zoster vaccination in adults.

Risk group/Clinical Condition	Recommendations	GRADE Strength of Recommendation/ Quality of Evidence	Comments
General adult population (Age ≥ 50 years)	Shingrix Zostavax Shingrix is preferred	Strong/Moderate (1B) Weak/Low (2C)	Both vaccines are suggested for adult population aged ≥ 50 years.
Immunocompromised adults (Age ≥ 18 years)			
Solid cancer	Shingrix	Weak/High (2A)	
Hematologic malignancy	Shingrix	Strong/High (1A)	
Autologous HSCT	Shingrix	Strong/High (1A)	For recipients of HSCT and solid organ transplantation, use of live attenuated zoster vaccine is not suggested.
Allogeneic HSCT	Shingrix	Weak/Moderate (2B)	
Kidney solid organ transplantation	Shingrix	Weak/High (2A)	
Solid organ transplantation other than kidney	Shingrix	Weak/Very low (2D)	
People living with HIV	Shingrix	Strong/High (1A)	
	Zostavax	Weak/High (2A)	Zostavax may only be considered for people living with HIV who are receiving antiretroviral therapy and virologically suppressed with CD4 counts ≥ 200 cells/ mm^3.
Autoimmune inflammatory rheumatic diseases	Shingrix	Weak/High (2A)	
Concomitant vaccination			
General population	Shingrix	Weak/Moderate (2B)	• Shingrix can be given concomitantly with seasonal influenza vaccine, PCV, PPSV23, or Tdap. • The adverse reactions occurred more frequently when PPSV23 is co-administered with Shingrix.
		Good practice statement	Inactivated vaccines may in general be administered concomitantly with, or at any time before or after, other inactivated vaccines or live vaccines.
	Zostavax	Weak/Moderate (2B)	• Zostavax can be given concomitantly with seasonal influenza vaccine and PPSV23.
		Good practice statement	• Live vaccines can be given concomitantly with other inactivated vaccines or live vaccines • If two different live vaccines are not administered on the same day, they must be separated by an interval of at least 4 weeks.
Previous history of vaccination			
Previously received varicella vaccine	Shingrix Zostavax	Weak/Low (2C)	
Previously received Zostavax > 5 years ago	Shingrix	Strong/Moderate (1B)	
Previously received Zostavax ≤ 5 years ago	Shingrix	Weak/Moderate (2B)	The shortest interval between Zostavax and Shingrix is 8 weeks.
Previous history of VZV infection			
After a prior episode of herpes zoster	Shingrix Zostavax	Weak/Low (2C)	A minimal interval of 2 months between an episode of herpes zoster and the zoster vaccine is suggested.
Persons who do not have a history of varicella or have an unclear history of varicella	Shingrix Zostavax	Weak/Low (2C)	Shingrix is preferred

Strength of recommendations: 1 — Strong, 2 — Weak; Quality of evidence: A — High, B — Moderate, C — Low, D — Very Low.
Abbreviations: HSCT, hematopoietic stem cell transplantation; PCV, valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Tdap, Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine; VZV, varicella zoster virus.

national guidelines vary across countries. While the use of ZVL is no longer recommended in the US and some western European countries, a preference for RZV is clearly stated in the national guidelines of Canada and the United Kingdom, in contrast to other countries, such as the Czech Republic and Italy, where no particular preference is stated.[30] Because RZV has a promising vaccine efficacy across different age groups and provides higher efficacy as well as longer protection compared with ZVL, the panel therefore recommends RZV as the preferred HZ vaccine in immunocompetent adults aged ≥ 50 years.

Which HZ vaccine is recommended for immunocompromised adults with solid cancers?

Recommendations

1. RZV is suggested as the preferred vaccine for immunocompromised adults with solid cancers. *(Weak recommendation, high quality of evidence) (2A)*

Summary of the evidence

Studies evaluating the efficacy and safety of ZVL in the immunocompromised population were limited since ZVL may increase the risk of attenuated VZV related serious disease.[5] To date, the efficacy of HZ vaccines has not been evaluated in patients with solid cancers, however, immunogenicity was demonstrated in a phase 2/3, randomized controlled trial comparing RZV to placebo in 232 adults aged ≥ 18 years.[31] Vaccination was administered at either 8—30 days or within 1 day before the initiation of a chemotherapy course. The immunogenicity remained greater in the vaccination group compared with the placebo group, with a geometric mean concentration (GMC) ratio of anti-glycoprotein E (gE) humoral immune response in RZV vs placebo group of 14.4 (95% CI, 10.7—19.5). The safety profile showed a similar frequency of SAEs in the RZV vs placebo group (25.6% vs 27.0%). However, local symptoms were reported more frequently in the RZV vs placebo group, with grade 3 AEs in 11.6% vs 0%, and general symptoms in 22.3% vs 15.5%, respectively. Based on the immunogenicity and safety data, we suggest an RZV as the preferred vaccine for patients with solid cancers. The timing of the first vaccination is preferably at a minimum of 8 days before the start of the chemotherapy cycle. The expert panel suggests that if HZ vaccination cannot be administered before chemotherapy, vaccination during or after the course of chemotherapy may be acceptable when there is sufficient recovery of immunity. The timing of HZ vaccination should be individualized.

Which HZ vaccine is recommended for immunocompromised adults with hematologic malignancies not scheduled for HSCT?

Recommendations

1. RZV is recommended for immunocompromised adults, aged ≥ 18 years, with hematologic malignancies, either during or after the course of cancer therapy. (*Strong recommendation, high quality of evidence) (1A)*

Summary of the evidence

One small, retrospective study with 62 subjects, suggested that ZVL can be given safely to adult patients with hematologic malignancies and in HSCT recipients on minimal or not under immunosuppressive therapy.[32] A consensus of the European Myeloma Network recommends RZV as the preferred vaccine for patients with multiple myeloma (MM), based on 2 studies involving small numbers of patients with MM, with favorable results when given 2 doses of RZV at 2—6 months apart.[33—36]

Two randomized, placebo-controlled trials, studied the efficacy and immunogenicity of RZV among adult patients with hematologic malignancies.[36—38] One multinational study randomized 569 patients to RZV or placebo administered during or after cancer therapy.[36] The RZV group had a reduced incidence of HZ of 8.5 per 1000 PY compared to 66.2 per 1000 PY in the placebo group. The reported SAEs up to 30 days after the last vaccination were similar between the RZV versus placebo group (17/283, 6.0% vs 29/279, 10.4%).

In the ZOE-HSCT study, 1846 patients were randomized to RZV or placebo with the first dose given at 50—70 days after autologous HSCT.[37,38] A second dose of vaccination was given 1—2 months later. The vaccine efficacy was 68.2% with a 90% reduction in PHN in the ZOE-HSCT trial. The humoral and cell-mediated immune responses of RZV recipients were superior to those receiving placebo at 1 month after the second dose of vaccination. Similar findings were observed in participants aged 18—49 years and ≥50 years. During the development of this guidance, experts raised concerns involving factors influencing vaccination decision-making, such as poor immune responses or thrombocytopenia during active hematologic malignancies or patients undergoing chemotherapy. Therefore, the panel recommends that RZV should be considered for adult patients with hematologic malignancies after shared decision-making between the patient and their hematologist-oncologist.

Which HZ vaccine is recommended for adult transplant recipients?

Recommendations

1. For recipients of autologous HSCT, vaccination with RZV is recommended at least 2 months post-transplantation *(Strong recommendation, high quality of evidence) (1A)*.
2. For recipients of allogeneic HSCT, vaccination with RZV may be considered at least 9 (6—12) months post-transplantation *(Weak recommendation, moderate quality of evidence) (2B)*.
3. For recipients of kidney transplantation, vaccination with RZV may be considered at least 4 months post-transplantation *(Weak recommendation, high quality of evidence) (2A)*.
4. For recipients of SOT other than the kidney, vaccination with RZV may be considered, and the interval between transplant and vaccination depends on the regimen of immunosuppressants given and the clinical condition.

(Weak recommendation, very low quality of evidence) (2D)

5. For recipients of HSCT and SOT, use of ZVL is not suggested. *(Weak recommendation, very low quality of evidence) (2D).*

Summary of the evidence

Recipients of autologous HSCT

There are 2 randomized controlled trials in autologous HSCT recipients receiving RZV vaccination. Vaccination was given at 50—70 days post-transplant in both studies. The first trial was a phase 1/2a, randomized controlled trial enrolling 120 adults with hematologic malignancies, including multiple myeloma (63.3%), non-Hodgkin B-cell lymphoma (23.3%), Hodgkin lymphoma (7.5%), non-Hodgkin T-cell lymphoma (5%), and acute myeloid leukemia (0.8%).[39] The participants underwent HSCT in the previous 50—70 days and were divided into 4 groups, to receive 3 doses of RZV with full-dose adjuvant, 3 doses of RZV with half-dose adjuvant, 2 doses of RZV with full-dose adjuvant, and 3 doses of saline as placebo. Both humoral and cellular immune responses were robust in the groups receiving RZV. The GMCs of anti-VZV gE antibody peaked at 4 months post-vaccination in the gE adjuvanted with AS01 groups, reaching up to 25-55-fold higher than before vaccination, and remained high for at least 1 year. The response rates at 4 months were also high, reaching 76.9%, in the gE/AS01 groups, and were similar after the second and third doses. At 15 months, over 54.5% of subjects remained above the response rate threshold. VZV-specific CMI, measured by the geometric mean frequencies of gE-specific CD4 T-cell was significantly higher in the gE/AS01 adjuvanted groups compared to the placebo group at 4 months with a 9-32-fold increase, and persisted up to 15 months with an 11-15-fold increase. Although the rates of 7-day injection site reaction were higher in the vaccination groups (75.9—90.0% for the 3-dose groups, 85.7% for the 2-dose group) vs the placebo group (23.3%), the rates of SAE were similar (27.8% in the vaccination groups and 26.7% in the placebo group).

The second trial randomized 1846 participants to receive 2 doses of RZV or placebo 50—70 days after autologous HSCT.[37] RZV had a vaccine efficacy of 68.2%, with a 67% humoral immune response rate at 1 month, dropping to 45% at 24 months after 2 doses; and cellular immune response rates of 93% at 1 month, and maintaining 71% at 24 months after 2 doses. There was a significant 90% reduction in the incidence of PHN (IRR, 0.11; 95% CI, 0.00—0.78; P = 0.02) and a 38% reduction in the duration of severe worst HZ pain (hazard ratio [HR], 0.62; 95% CI, 0.42—0.89; P = 0.01). The safety profile between the vaccinated vs placebo group was similar with comparable rates of reported SAEs (28% vs 26%). Local and general reactions were more frequently observed in the vaccinated group versus the placebo group, with significantly more injection site reactions (86% vs 10%), grade 3 pain intensity (11% vs 0%) and grade 3 myalgia (6.2% vs 2.1%). In summary, RZV significantly reduced the incidence of HZ, PHN, and duration of severe HZ pain; and induced strong immune responses among autologous HSCT recipients. The safety profile was similar to results from the clinical trials conducted in the general population. Based on limited evidence from these 2 studies, the panel recommends vaccination with RZV in recipients of autologous HSCT at least 2 months post-transplantation. The US Centers for Disease Control and Prevention (CDC) guidelines recommend administering RZV at least 3—12 months after transplantation, and advise vaccination prior to discontinuation of prophylactic antiviral therapy.[40] The panel cautions that the optimal time interval for vaccination post-transplantation remains uncertain.

Recipients of allogeneic HSCT

There were one retrospective and 2 prospective cohort studies evaluating the immune responses and safety of RZV among allogeneic HSCT recipients. Timing of vaccination after transplantation ranged from 7 to 37 months, and 9 months after transplantation in one single arm study with 150 patients. In a retrospective study of 30 HSCT recipients (17 allogeneic and 13 autologous),[41] the median time from HSCT to the first dose of RZV was 8 months (interquartile range [IQR], 7—12 months). At the time of vaccination, the majority of these patients either did not receive immunosuppressive agents or were under single-agent immunosuppression. The immune response was defined as seroconversion in previously seronegative individuals or a fourfold increase from baseline VZV immunoglobulin G (IgG) titers. Humoral vaccine response was achieved in 11 patients (37%) measured at a median time of 4 months from the second dose of RZV. A higher response rate was found in autologous (8/13, 62%) compared with allogeneic HSCT recipients (3/17, 18%). The only significant variable associated with a poor vaccine response in a multivariate model adjusted for age was recipients of allogeneic HSCT.

In a single-arm, prospective study enrolling 150 allogeneic HSCT recipients, 2 doses of RZV were administered between 9 and 24 months after the transplantation.[42] Injection site pain within 7 days developed in 86% patients, but SAEs occurred in only 1.3% patients. Most of the patients received immunosuppressants at the time of vaccination (71% and 60% at the first and second dose, respectively). Vaccination did not increase the risk of developing graft-versus-host disease. The incidence rate of HZ was 28.3 per 1000 PY in allogeneic HSCT recipients receiving RZV, which was similar to that observed in autologous HSCT recipients receiving RZV (30.0 per 1000 PY).[37] It is important to remark on the occurrence of HZ in 4 of 34 patients who discontinued antiviral prophylaxis, even after completing 2-dose vaccination. This occurred within a median follow-up of 113 days. The higher incidence rate of HZ (295 per 1000 PY) suggested that antiviral prophylaxis should be continued for some time after completing RZV vaccination. Another single-arm, prospective study which included 79 allogeneic HSCT recipients, demonstrated a significant, 2-fold increase in VZV-specific cellular immune response when vaccinated with 2 doses of RZV.[43] The median interval between allogeneic HSCT and the first dose of vaccination was 37 months.

In summary, allogeneic HSCT recipients receiving 2 doses of RZV vaccination can achieve immunogenicity, with both significant humoral and cellular immune responses and had safety profile similar to autologous HSCT recipients. RZV vaccination may lower the incidence of HZ when compared to historical controls, however, high-quality evidence

supporting the use of RZV in allogeneic HSCT recipients is lacking and a longer follow-up period is needed. Based on the above limited evidence, the panel recommends that vaccination with RZV may be considered, at least 9 months post-transplantation in recipients of allogeneic HSCT. The US CDC guidelines recommend administering RZV at least 6—12 months after transplantation, and advise vaccination prior to discontinuation of prophylactic antiviral therapy.[40] The panel cautions that the optimal time interval for vaccination post-transplantation remains uncertain.

Recipients of kidney transplantation

Currently, there is only one prospective RCT evaluating immunogenicity and none reporting the vaccine efficacy of RZV in recipients of kidney transplants. A phase 3, randomized controlled trial evaluated immunogenicity in 264 recipients of kidney transplantation who received 2 doses of RVZ or placebo, 1—2 months apart, at 4—18 months post-transplantation.[44] The vaccine response rate was high at 2 months for both humoral (80.2%; 95% CI, 71.9%—86.9%) and cellular mediated immunity (71.4%; 95% CI, 51.3%—86.8%). Both the humoral and cellular immunity increased significantly at 2 months post-vaccination and persisted through to 13 months. At 2 months post-vaccination, the GMC ratio of anti-gE antibody was 14.0 (95% CI, 10.9—18.0), and gE-specific CD4 T-cell frequencies was 17.3 (95% CI, 5.9—50.4). The humoral and cellular immune responses appeared higher in the 18—49 years cohort compared to the $\geq$ 50 years cohort. The rate of 7-day injection site reaction was higher in the vaccination group compared to the placebo group (87.8% vs 9.1%), but the rates of SAEs, including allograft rejections, were similar between the 2 groups (19.7% vs 25.0% in the RZV vs placebo group). This trial showed that recipients of kidney transplantation can have robust immunogenicity after RZV vaccination. Based on this one study, the panel recommends that RZV may be considered in recipients of kidney transplantation at least 4 months post-transplantation. The panel cautions that the optimal time interval for vaccination post-transplantation remains uncertain.

Recipients of SOT other than kidney

Two single-arm, prospective studies were conducted to evaluate the immunogenicity of RZV for recipients of other SOT. One study enrolled 23 patients, with the majority receiving lung (8), liver (7), and also kidney (4) transplantation.[45] The median time between transplantation and a 2-dose RZV was 3.8 years, and the median interval between the 2 vaccine doses was 2.7 months. Although the majority of enrolled patients (78.3%) received 3 immunosuppressants at vaccination, a significant increase in humoral and cellular responses were achieved, with only mild adverse events and without rejection episodes. The other study included 49 lung transplantation recipients seropositive for VZV IgG.[46] The median time between transplantation and a 2-dose RZV was 3 years, and the median interval between the 2 vaccine doses was 63 days. The rate of 7-day injection site reaction was 83.0% and SAEs at 3 months of vaccination was 28.5%, which were similar to that observed in kidney transplant recipients.[44] Significant immunogenicity was observed after vaccination, with significant increases in both humoral (anti-gE antibody) and cellular immune responses (median gE-specific CD4 T-cell frequencies). No cases of HZ occurred during a 2-year follow-up period. Based on the significant immunogenicity demonstrated in these small studies, the panel recommends that RZV may be considered in recipients of SOT other than kidney.

ZVL for recipients of all types of transplants

There are 3 retrospective, cohort studies including HSCT recipients given ZVL vaccination. One study enrolled 31 HSCT recipients (26 allogeneic and 5 autologous), with a median time from post-transplantation to vaccination of 658 days.[32] No vaccine-related adverse events were reported during a median follow-up period of 268 days. One patient developed HZ after vaccination. The other study included 110 HSCT recipients (58 allogeneic and 52 autologous) with ZVL vaccination 2 years after transplantation.[47] Only 2 patients (1.8%) developed zoster-like skin rash, which subsided after antiviral agent use. In both studies, it was not determined whether the rash was due to the vaccine virus or wild-type virus. Another study analyzed 70 autologous HSCT recipients, with a median time to vaccination from post-transplant of 25 months.[48] No rashes or other adverse events related to the vaccines were identified. A phase I, randomized controlled trial was conducted in 34 adult patients with end-stage renal disease prior to or awaiting renal transplantation, and evaluated vaccination with ZVL (n = 26) or placebo (n = 4) given at least 4 weeks prior to transplantation.[49] None of the subjects developed zoster rash, rejection, or elevation of anti-human leukocyte antigens (HLA) antibody. Twelve patients who received ZVL subsequently underwent renal transplantation. A significant 2.1-fold rise in geometric mean titer of anti-VZV IgG antibody at 5 weeks after vaccination was noted. The titers gradually waned with time, but remained higher than that at baseline.

In general, ZVL is contraindicated for immunocompromised patients due to the risk of infection by the vaccine virus strain. Despite the low rates of zoster rash in the above studies, there are case reports of incident disseminated HZ in recipients of kidney or other solid organ transplants.[50] In view of the concern for safety and lack of vaccine efficacy, the panel suggests against vaccination with ZVL for recipients of any types of transplants.

Which HZ vaccine is recommended for adult people living with HIV?

Recommendations

1. RZV is recommended for adult people living with HIV. *(Strong recommendation, high quality of evidence) (1A)* Deferring vaccination until patients are receiving antiretroviral therapy (ART) and virologically suppressed with CD4 counts $\geq$ 200 cells/mm^3 may be considered to ensure a robust immune response.

2. ZVL may be considered for adult people living with HIV who are receiving ART and virologically suppressed with CD4 counts $\geq$ 200 cells/mm^3. *(Weak recommendation, high quality of evidence) (2A)*

Summary of the evidence

Live attenuated vaccine (ZVL) is contraindicated in PLWH with advanced immunosuppression (CD4 cell count $<$ 200 cells/mm^3) due to concerns that it may cause VZV-related diseases. However, in Taiwan, the highest risk of developing HZ after initiation of ART is a baseline CD4 cell count of $<$ 200 cell/mm^3 (odds ratio [OR], 2.03; 95% CI, 1.02—4.06) and a history of prior zoster (OR, 3.14; 95% CI, 1.39—7.13).[51] In a large cohort study in the US, risk factors for developing HZ include those with CD4 cell counts $<$ 350 cells/mm^3 (adjusted OR [aOR], 2.46; 95% CI, 1.42—4.23) and detectable plasma HIV RNA $>$ 400 copies/mL (aOR, 1.49; 95% CI, 1.00—2.24).[52] A randomized, placebo-controlled trial of ZVL conducted in 395 adult PLWH found that 2 doses of ZVL, at a 6 weeks' interval, was immunogenic and safe.[53] Participants were virally suppressed with CD4 cell counts $\geq$ 200 cells/mm^3. The primary composite safety endpoints, included SAEs or Division of AIDS (DAIDS) grade 3 and 4 signs and symptoms within 42 days, were similar between the ZVL and placebo groups (5.1% vs 2.1%). ZVL induced a significantly higher humoral responses (glycoprotein enzyme-linked immunosorbent antibody [gpELISA] titers) and numerically higher cellular immune responses (geometric mean fold rise (GMFR) in interferon-gamma [IFN- γ] enzyme-linked immunospot [ELISPOT] responses) than placebo at both 6 and 12 weeks. There were no differences in VZV antibody titers after 1 or 2 doses of ZVL. Participants with the higher CD4 cell counts had significantly higher VZV antibody titers. This was not observed for ELISPOT responses. Only 2 participants developed polymerase chain reaction-confirmed HZ (1 ZVL, 1 placebo recipient). Based on this evidence, the panel suggests that ZVL may be considered for adult PLWH who are receiving ART with CD4 cell counts $\geq$ 200 cells/mm^3 and virologically suppressed.

The immunogenicity and safety of 3 doses of RZV in adult PLWH was evaluated in a phase 1/2, randomized, placebo-controlled trial.[54] The majority of participants (94/123, 76.4%) were under a stable ART regimen with a CD4 cell count of $\geq$ 200 cells/mm^3, 14 (11.4%) had a CD4 count of 50—199 cells/mm^3, and 15 (12.2%) were ART-naive with a CD4 count of $\geq$ 500 cells/mm^3. Both humoral (serum anti-gE antibody concentrations) and cellular immune responses (frequencies of gE-specific CD4 T cells) were higher following RZV vaccination compared to placebo. The administration of a third dose did not provide additional benefit. Higher humoral and cell-mediated immune responses were observed in the high CD4 group compared to that in the low CD4 and ART-naïve/high CD4 cohorts. No vaccination-related SAEs were reported and only 1 RZV recipient developed HZ after the first vaccine dose. Based on the immunogenicity and safety data, the panel recommended RZV for adult people living with HIV. To ensure a robust immune response, the panel recommends to consider deferring vaccination until patients are under ART, virologically suppressed, and attain a CD4 count $\geq$ 200 cells/mm^3.

Which HZ vaccine is recommended for immunocompromised adults with autoimmune inflammatory rheumatic diseases?

Recommendations

1. RZV is suggested for adult patients with autoimmune inflammatory rheumatic diseases. *(Weak recommendation, high quality of evidence) (2A)*

Summary of the evidence

Several randomized, controlled trials evaluated the immunogenicity of ZVL in adults with various autoimmune rheumatic diseases. The VaricElla zosteR VaccinE (VERVE) trial was conducted in 601 patients, aged $\geq$ 50 years, who received tumor necrosis factor inhibitors for any indication, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and others. Both humoral and cellular immunogenicity was demonstrated by a significant mean increase in the GMFR of anti-gE antibody by ELISA (1.33; 95% CI, 1.17—1.51) and VZV-specific IFN- γ-secreting spot-forming cells by ELISPOT (1.39; 95% CI, 1.07—1.82) at 6 weeks after vaccination.[55] Another trial recruited 90 adult patients with SLE under stable immunosuppressive treatment, and demonstrated both humoral and cellular immunogenicity after ZVL vaccination compared to placebo. At 6 weeks after vaccination, there was a significant 59.8% increase in level of anti-VZV IgG, and a greater number of IFN-γ secreting T-cell spots (42% increase) in the vaccinated compared to the placebo group.[56] A retrospective cohort study among 463,541 persons aged $\geq$ 60 years, with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease, showed that the incidence rate of HZ was significantly lower in vaccinated individuals compared with unvaccinated individuals (7.8 vs 11.6 cases per 1000 PY).[57] None developed varicella or HZ eruption within 6 weeks post-vaccination. The American College of Rheumatology guideline for vaccinations conditionally recommends holding immunosuppressive medication for an appropriate period before and 4 weeks after live attenuated virus vaccination.[58] These studies support the administration of ZVL in patients with autoimmune rheumatic diseases with low disease activity and under stable immunosuppressive treatment.

The efficacy and safety profile of RZV among patients with autoimmune inflammatory rheumatic diseases were evaluated in the pooled, post hoc analysis on ZOE-50 and ZOE-70. Eligible participants included those having pre-existing potential immune-mediated diseases and not under immunosuppressive medication; the most frequent pre-existing conditions including psoriasis, spondyloarthropathy, and rheumatoid arthritis. The overall vaccine efficacy against HZ was 90.5% (95% CI, 73.5—97.5%) and rates of reported SAEs were similar between the RZV and placebo groups.[59] The panel suggests RZV as the recommended HZ vaccine for adult patients with autoimmune inflammatory rheumatic diseases.

Can HZ vaccine be administered concomitantly with other vaccines?

Recommendations

1. In general, inactivated vaccines, including RZV, may be administered concomitantly with, or at any time before or after, other inactivated vaccines or live vaccines protecting against a different disease. *(Good practice statement)*
2. RZV can be given concomitantly with seasonal influenza vaccine, pneumococcal vaccines (pneumococcal conjugate vaccine, PCV; or 23-valent pneumococcal polysaccharide vaccine, PPSV23) or tetanus, diphtheroid, pertussis vaccines (Tdap). *(Weak recommendation, moderate quality of evidence) (2B)*
3. In general, live vaccines given by the parenteral route, including ZVL, may be administered concomitantly with other injected live vaccines. If they are not administered concomitantly, a minimum interval of 4 weeks should be maintained between two live parenteral vaccines. *(Good practice statement)*
4. ZVL can be given concomitantly with seasonal influenza vaccine, or PPSV23. *(Weak recommendation, moderate quality of evidence) (2B)*

Summary of the evidence

Simultaneous or concomitant administration, defined as giving more than 1 vaccine on the same day, is recommended as an effective approach to increase immunization rates by the US Advisory Committee on Immunization Practices (ACIP).[60] Vaccines can be divided into 2 general categories: live and inactivated. In general, simultaneously administered vaccines (either >1 inactivated vaccine or > 1 live-virus or inactivated plus live-virus vaccines) are safe, effective, and routinely recommended.[61] There is no evidence that inactivated vaccines interfere with the immune responses to other inactivated vaccines or to live vaccines. However, data indicates that administering 2 or more live-virus vaccines parenterally within 28 days of each other, rather than simultaneously, may result in an impaired immune response.[60] Live vaccines included in the Taiwan Centers for Disease Control immunization schedules include measles, mumps, and rubella (MMR) vaccine, Japanese encephalitis chimeric virus vaccine (JE-CV), and ZVL. Inactivated vaccines that are commonly used in Taiwan are tetanus, diphtheria toxoids, acellular pertussis (Tdap) vaccine, inactivated seasonal influenza vaccine, hepatitis B vaccine, hepatitis A vaccine, pneumococcal conjugate vaccine (PCV), 23-valent pneumococcal polysaccharide vaccine (PPSV23), human papillomavirus (HPV) vaccine, COVID-19 vaccine, and RZV.

The guidance from the ACIP recommends that injected live vaccines may be administered concomitantly with other injected live vaccines if indicated. If vaccines are not administered concomitantly, the recommended minimum interval between 2 live, parenteral vaccines should be at least 4 weeks. Although the immune responses have been shown to be adequate when vaccines are given on the same day, a retrospective study showed a significant increase in breakthrough infections when varicella vaccine was administered within 30 days of MMR vaccine. This suggests that MMR vaccine may attenuate the immune response to varicella vaccine. This recommendation has been extrapolated to ZVL and MMR vaccines.[62]

There exists some controversy concerning the co-administration of ZVL with PPSV23, which may induce a reduced immunogenicity of ZVL. A randomized trial demonstrated that that the immune response induced by ZVL when administered concomitantly with PPSV23 was inferior to when non-concomitantly given (geometric mean titers ratio of VZV antibodies was 0.70, 95% CI, 0.61—0.80).[63] Nevertheless, 2 large, retrospective, cohort studies compared the incidence of HZ following concomitant vs non-concomitant administration of ZVL and PPSV23, and did not find a statistically significant difference.[64,65] Therefore, some countries, such as Canada, recommends that ZVL may be given with PPSV23 at the same time.[66]

Concomitant administration of ZVL with trivalent and quadrivalent inactivated influenza vaccines has been studied in 2 randomized trials, which showed similar immune responses to both vaccines at 4 weeks after vaccination in both the concomitant and non-concomitant groups.[67,68]

The ACIP stated a best practice statement that inactivated vaccines may be administered concomitantly with, or at any time before or after, other inactivated vaccines or live vaccines protecting against a different disease. For concomitant parenteral injections, different injection sites and separate needles and syringes should be used.[60] Studies have evaluated the concomitant administration of RZV with unadjuvanted, inactivated, seasonal influenza vaccine,[69] Tdap vaccine,[70] 13-valent PCV (PCV13),[71] and PPSV23.[72] The immune responses of the co-administered vaccines were unaffected, with an exception of a lower GMC for one of the pertussis antigens when RZV is co-administered with the Tdap vaccine. The humoral immune response to RZV in the co-administration group was noninferior to the control group, with an adjusted GMC ratio (control/co-administration) of 1.11 (95% CI, 1.02—1.21).[70] Adverse reactions were more frequently reported when PPSV23 was co-administered with RZV, such as shivering, which was reported in 31.9% vs 23.0% in the co-administration vs the control group, respectively.[72]

A cohort study found no significant difference in the risk of HZ among individuals who received RZV with and without concomitant vaccination. Influenza vaccine (65.9%) was the most common concomitant vaccine (adjusted HR [aHR], 0.75; 95% CI, 0.53—1.08).[73] Another cohort study evaluated influenza vaccine uptake in the subsequent year, following concurrent vs separate administration of influenza and zoster vaccines. Those who received concurrent influenza and zoster vaccines were significantly less likely to receive an influenza vaccine the following year (87.3% vs 91.3%; aOR 0.74; 95% CI, 0.71—0.78). The reduced willingness to receive influenza vaccine in subsequent years may possibly be due to misattribution of the systemic side effects caused by the zoster vaccine to the influenza vaccine. Therefore, primary healthcare practitioners may need to spend more time to discuss expected vaccine side effects and reassure individuals who experience side effects.[74]

Can persons who had a prior varicella vaccine receive HZ vaccination?

Recommendations

1. Either ZVL or RZV is suggested for persons who were previously vaccinated with varicella vaccines. *(Weak recommendation, very low quality of evidence) (2D)*

Summary of the evidence

Varicella vaccine was commercially available since 1984; therefore, individuals who have received varicella vaccine are currently less than 50 years of age. As ZVL is approved for those aged $\geq$ 50 years, there is insufficient information to answer the question of whether persons previously vaccinated with varicella vaccines can receive zoster vaccines. Following the recommendations from the US CDC, the panel also suggests that RZV can be administered even if persons have received a varicella vaccine in the past.[75]

Can persons who had a prior ZVL receive an RZV?

Recommendations

1. RZV is recommended for persons who were previously vaccinated with a ZVL after an interval of more than 5 years *(Strong recommendation, moderate quality of evidence) (1B)*; however, it is also suggested for those vaccinated with a ZVL within 5 years. *(Weak recommendation, moderate quality of evidence) (2B)*
2. A minimal interval of 8 weeks is suggested between administering a ZVL and an RZV, however, the optimal interval between these two vaccines is currently unknown. *(Weak recommendation, very low quality of evidence) (2D)*

Summary of the evidence

Previous studies showed that the vaccine efficacy of ZVL waned over time.[23,24] The vaccine efficacy against HZ declined from 62.0% (95% CI, 49.6%—71.6%) within 1 year of ZVL vaccination to $<$ 50.0% after year 2.[76] At year 10, the vaccine efficacy against HZ was only 14.1% (95% CI, −11.3%-34.9%).[24] Results from observational cohort studies showed a similar trend of vaccine effectiveness. A meta-analysis, which included 5 observational cohort studies with a maximum follow-up duration of 8 years, showed that the pooled vaccine effectiveness against HZ was 60.0% (95% CI, 13.6%—77.6%) in the first year after vaccination and declined to 50.8% (95% CI, 11.4%—72.9%) at 6 years after vaccination.[77]

In 2 cohort studies which enrolled participants aged $\geq$50 years and $\geq$65 years, RZV may further lower the incidence of HZ in persons who have previously been vaccinated with ZVL.[78,79] Complete vaccination with 2 doses of RZV is strongly suggested, since it induces stronger immunogenicity and confers better vaccine effectiveness compared to one dose.[79—81] The optimal interval between administering ZVL and RZV is currently unknown. Clinical trials only included participants who received ZVL $\geq$ 5 years before RZV vaccination,[80] however, several cohort studies evaluated the vaccine effectiveness of RZV in those with a history of ZVL vaccination within 5 years.[78,79] Currently, none of the few, available studies indicate that RZV would be less safe or less effective when administered at an interval of less than 5 years. The expert panel in the US ACIP suggests a minimum of 2 months between receipt of ZVL and RZV.[82]

Compared to persons who received ZVL only, additional vaccination with RZV lowered the incidence rate of HZ from 7.54 to 2.39 per 1000 PY in a cohort study.[78] A meta-analysis of 2 large cohort studies in the US showed that the pooled vaccine effectiveness against HZ was 75.5% (95% CI, 41.5%—89.7%) in adults aged $\geq$ 50 years who received ZVL within 5 years before RZV.[77—79] In individuals who had previously been vaccinated with ZVL, RZV induced immunogenicity with high anti-gE antibody titers and frequencies of gE-specific CD4 T-cell through 1 year after 2 doses of RZV vaccination. The strong humoral and cell-mediated immune responses observed in those with prior ZVL vaccination were non-inferior to those without prior ZVL vaccination. In addition, revaccination with RZV was well-tolerated without increased safety concerns, with comparable reactogenicity and safety profile.[80,81]

ZVL does offer some protection against HZ and PHN within 5 years of vaccination, albeit with considerable waning in vaccine efficacy after 2 years post-vaccination.[24,76,77,83,84] Considering the relatively high cost of 2 doses of RZV, the panel gave a lower strength of recommendation for persons who received ZVL within 5 years compared to those who received ZVL more than 5 years ago.

Should persons with a prior episode of HZ receive HZ vaccination?

Recommendations

1. Persons with a prior episode of HZ are suggested to receive HZ vaccine, either ZVL or RZV, after a minimal interval of 2 months. *(Weak recommendation, low quality of evidence) (2C)*

Summary of the evidence

In a safety study, severe adverse reactions were not increased significantly after ZVL vaccination in 420 subjects with a prior history of HZ in comparison to those without a prior history of HZ.[85] A previous study conducted in Japan revealed that the interval between the prior and recurrent episodes of HZ among 1125 cases ranged from 2 months to 73 years with a mean interval of 13.71 $\pm$ 10.96 years, and peaking at 3—11 years.[86] In a Korean study with a follow-up period of over 4.4 years, the recurrence rate was 12.0 per 1000 person years. A total of 2358 episodes of recurrent HZ occurred in 2100 cases, including 232 cases with a second recurrence and 26 cases with a third recurrence. The estimated overall recurrence rate was 5.3% and the interval between initial HZ episode and first recurrence ranged from 181 to 3815 days, with a mean of 1063 days.[87] In a more

recent study in the US, with an average 5.6 years of follow-up, the cumulative incidence of recurrence (defined as having HZ at ≥ 6 months after the most recent diagnosis of HZ), at 2, 4, 6, 8, and 10 years was 2.5%, 4.8%, 6.6%, 8.0%, and 10.3%, respectively.[88] Recommendations regarding the time frame for vaccination following an episode of HZ varied between different countries, and ranged from waiting until the acute stage of HZ has resolved and symptoms abated, in Germany and USA, to at least 2 months in Austria, and up to at least 1 year later in Canada, Ireland and Australia.[89] Based on the high rates of HZ recurrence after a prior episode of HZ, the panel recommends vaccination with zoster vaccine, either ZVL or RZV, after a prior episode of HZ. A minimal of 2-month interval between an episode of HZ and zoster vaccination is recommended based on the documented minimal interval between an episode of HZ and recurrence of 2 months.

Should HZ vaccine be given to persons who do not have a history of varicella or have an unclear history of varicella?

Recommendations

1. Adults ≥ 50 years old who do not have a history of varicella or have an unclear history of varicella are suggested to receive HZ vaccine, and RZV is preferred. *(Weak recommendation, low quality of evidence) (2C)*
2. For persons who are known to be seronegative for varicella zoster virus, immunization with 2 doses of varicella vaccine with an interval of 4 weeks is suggested. *(Weak recommendation, low quality of evidence) (2C)*.

Summary of the evidence

Studies in Taiwan showed that the seroprevalence of varicella was up to 88% in the general population aged 21—30 years, in the era before varicella vaccine was introduced into the national immunization program.[90] In the post-varicella vaccine era, varicella seropositivity reached 91.4% by 11 years of age.[91] In a more recent study among 2406 healthcare workers in a medical center in central Taiwan, the varicella seroprevalence decreased from 88.0% in 2011 to 72.2% in 2017.[92] Both ZVL and RZV has been shown to be safe and immunogenic in VZV-seronegative individuals. A small study which enrolled 21 healthy adults, aged ≥ 30 years, who were either seronegative for VZV or had low VZV antibody titers; showed that ZVL was both immunogenic and well tolerated.[93] Another small study was conducted in 23 VZV-seronegative transplant patients, and showed that RZV was both safe and immunogenic.[45] Canadian and German guidelines recommend against screening for a history of varicella, whether through medical history review or laboratory testing, before administering the HZ vaccination. This recommendation is supported by seroprevalence studies and the absence of any known safety risks associated with immunization of individuals susceptible to VZV.[89] The US CDC also recommends not screening for a history of varicella or conducting laboratory testing for serologic evidence of prior varicella when vaccinating immunocompetent adults aged 50 years and older.[94] For immunocompromised adults, the US CDC guidelines recommend healthcare providers to take into account various factors, such as a patient's age, recall and documentation (e.g., of prior varicella, varicella vaccination, or HZ), and serology testing results, when deciding whether to administer RZV vaccination.[40] For individuals who are known to be VZV-seronegative, immunization with a varicella vaccine is recommended in Canada, Germany and the US.[94] Austrian guidelines recommend that immunization with RZV can be carried out in VZV-seronegative individuals in high-risk groups, after a careful risk-benefit assessment.[89] The Australian immunization guideline suggests that adults who are VZV-seronegative and have no history of age-appropriate varicella vaccination may receive either 2 doses of varicella vaccine (preferable) or 1 dose of ZVL (if aged ≥ 50 years). Following the recommendation from other guidelines, we suggest that adults aged ≥ 50 years old who do not have a history of varicella or have an unclear history of varicella can receive HZ vaccine, with a preference for RZV. For immunocompromised adults aged under 50 years, a history of varicella vaccination and serology testing should be considered before administering RZV vaccination. For persons who are known to be seronegative for VZV, we suggest immunization with 2 doses of varicella vaccine with an interval of 4 weeks.

CRediT authorship contribution statement

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Declaration of competing interest

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