Official journal of the Spanish Society of Chemotherapy

Revista Española de Quimioterapia
doi:10.37201/req/004.2023 - Advance Access published February 8, 2023

Review

Status of Herpes Zoster and Herpes Zoster Vaccines in 2023: A position paper

José María Molero García[1]
Santiago Moreno Guillén[2]
Fernando Rodríguez-Artalejo[3]
Julián Ruiz-Galiana[4]
Rafael Cantón[5]
Pilar De Lucas Ramos[6]
Alejandra García-Botella[7]
Alberto García-Lledó[8]
Teresa Hernández-Sampelayo[9]
Javier Gómez-Pavón[10]
Juan González del Castillo[11]
Mari Cruz Martín-Delgado[15]
Francisco Javier Martín Sánchez[13]
Manuel Martínez-Sellés[14]
Emilio Bouza[15]

[1]Family Medicine. Infectious diseases. Madrid.
[2]Infectious Diseases Service. Ramón y Cajal Hospital. University of Alcalá de Henares. Madrid.
[3]Department of Public Health. Autonomous University. Madrid
[4]Internal Medicine Service. Ruber International Hospital. Madrid.
[5]Microbiology Service. Ramón y Cajal Hospital and Ramón y Cajal Institute for Health Research (IRYCIS). Spanish Network for Research in Infectious Pathology (REIPI). Madrid.
[6]Emeritus. Pneumology Service. Gregorio Marañón General University Hospital, Complutense University. Madrid
[7]General Surgery Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[8]Cardiology Service. Prince of Asturias Hospital. University of Alcalá. Madrid.
[9]Pediatrics and ACES Service. Gregorio Marañón General University Hospital, Complutense University. Madrid.
[10]Geriatrics Service. Central Hospital of the Red-Cross. Alfonso X el Sabio University. Madrid
[11]Emergency Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[12]Intensive Medicine Service. Torrejón University Hospital. Francisco de Vitoria University. Madrid
[13]Emergency Service. San Carlos University Clinical Hospital. Complutense University. Madrid.
[14]Cardiology Service. Gregorio Marañón General University Hospital, European University. Madrid
[15]Clinical Emeritus, Community of Madrid. Clinical Microbiology and Infectious Diseases Service of the Gregorio Marañón General University Hospital, Complutense University. CIBERES. Cyber of Respiratory Diseases. Madrid.

Article history
Received: 23 January 2023; Accepted: 3 February 2023; Published: 8 February 2023

ABSTRACT

Herpes zoster infection (HZ) is an important public health problem due to its high incidence and frequent complications, especially post-herpetic neuropathy . The incidence of HZ increases with age and is more frequent in immunocompromised patients. It is estimated that at least 60,000 people develop HZ each year in Spain.

The usual forms of HZ are so clinically characteristic that they do not usually require microbiological confirmation, which is reserved for cases without cutaneous manifestations or with atypical presentation.

There are currently two vaccines approved by the regulatory agencies and marketed in Spain to prevent the onset of HZ and its complications. The first (Zostavax®) was marketed by the company MSD and licensed in Europe in 2006 and is a live attenuated virus vaccine that is administered in a single dose, while the second (Shingrix®) is a recombinant vaccine, marketed in 2017 and requires two doses. While the former cannot be administered to immunocompromised persons, the latter can be prescribed to any group of adults.

The criteria for the indication and financing of these vaccines have not been uniform in the various autonomous communities of Spain.

These and other aspects of HZ have been discussed by a group of experts from the Illustrious Official College of Physicians of Madrid (ICOMEM) whose criteria and opinions are included in this paper.

Keywords: Zoster, Herpes zoster, Varicella-Zoster Virus, Postherpetic neuralgia, vaccines, Zostavax, Shingrix, Immunocompromised patients, elderly.

Situación del herpes zóster y de las vacunas contra el mismo en 2023: Un documento de opinión

RESUMEN

La infección por herpes zoster (HZ) es un importante problema de salud pública, por su elevada incidencia y frecuentes complicaciones; en especial la neuropatía post herpética. La incidencia de HZ aumenta con la edad y es más frecuente en inmunodeprimidos. Se calcula que, al menos, 60.000 personas desarrollan HZ cada año en España.

Las formas habituales de HZ son tan características clínicamente que no suelen requerir confirmación microbiológica que se reserva para casos sin manifestaciones cutáneas o con manifestaciones atípicas

En la actualidad, existen en España dos vacunas aprobadas por las agencias reguladoras y comercializadas para prevenir la aparición de HZ y sus complicaciones. La primera (Zostavax®) fue comercializada por la compañía MSD y autorizada en Europa en 2006 y es una vacuna de virus vivos atenuados que se administra en dosis única, mientras que la segunda (Shingrix®) es una vacuna recombinante, comercializada en 2017 y

Correspondence:
Emilio Bouza Servicio de Microbiología Clínica y Enfermedades Infecciosas del Hospital General Universitario Gregorio Marañón, Universidad Complutense. CIBERES. Ciber de Enfermedades Respiratorias. Madrid
E-mail: emilio.bouza@gmail.com

All authors belong to the Scientific Committee on COVID-19 of the Madrid College of Physicians (ICOMEM).

requiere dos dosis. Mientras la primera no puede ser administrada a inmunodeprimidos, la segunda puede administrarse a cualquier grupo de personas.

Los criterios de indicación y de financiación de estas vacunas no han sido uniformes en las diversas comunidades autónomas de España.

Estos y otros aspectos sobre HZ han sido discutidos por un grupo de expertos del Ilustre Colegio Oficial de Médicos de Madrid (ICOMEM) cuyo criterio y opinión recogemos en este trabajo.

Palabras clave: Zoster, Herpes zoster, Virus Varicela-Zoster, Neuralgia Postherpética, vacunas, Zostavax, Shingrix, Inmunodeprimidos, ancianos

INTRODUCTION

Herpes Zoster (HZ) is a common disease caused by reactivation of the varicella-zoster virus (VZV), kept in a latent state since the primoinfection causing varicella (chickenpox). Its incidence is very high, particularly after the age of 50 years, to the point that more than around 20% of the global population will suffer one or more episodes of HZ if they live long enough to do so. The infection usually manifests as a cutaneous rash, characterized by the presence of vesicles evolving into crusts on the skin innervated by a central or peripheral nerve root. The disease usually progresses to spontaneous resolution but a proportion of patients will develop postherpetic neuralgia (PHN). The tendency to develop PHN or extracutaneous forms of the disease is all the greater in patients with various forms of immunosuppression.

The pharmaceutical industry has incorporated in the last 2 decades two effective vaccines against HZ of different nature and indications that are slow to be introduced in daily clinical practice and recommended by health authorities to large groups of the population.

The Scientific Committee on COVID-19 and Emerging Pathogens of the Illustrious College of Physicians of Madrid (ICOMEM) has asked itself a series of questions on the risks of HZ in different population groups, on the indications of vaccines against HZ, their contraindications, the potential for co-administration with other vaccines and on the variable response of the health authorities of the different autonomous communities of Spain in these circumstances.

We offer below the deliberation of the Committee on a series of issues that we consider of interest in the case of HZ, not only for the medical profession, but also for other health professionals and for the general population.

WHAT IS THE INCIDENCE OF ZOSTER IN THE WORLD AND IN SPAIN?

HZ infection is an important public health problem due to its high incidence and frequent complications, especially PHN. These translate into loss of quality of life and disability, largely due to the accompanying pain; in addition, HZ and PHN require a high use of health services and cause productivity losses.

Interestingly, the epidemiological characteristics of this disease vary little in the western world, as the incidence is quite similar between countries [1], and always increases with age and is more frequent in women, and in people with chronic diseases and reduced immunity (especially cellular). Probably, due to the increased survival of older people with such disorders, in the period 2009-2019, there has been an increase in the incidence of HZ in Spain from 75 years of age onwards [2].

Epidemiological surveillance of HZ is still under development, as data are not available for all the autonomous communities in Spain [3]. However, from the available information (the most recent is from 2018), at least 60,000 people develop HZ, and approximately 3,000 of them are hospitalized each year for this cause. About 50-60% of all those ill and hospitalized are over 60 years of age. In practical terms, the incidence of HZ in the adult population is very high, with more than one in five men and one in four women suffering from the disease between the ages of 50 and 85. The good news is that there is preliminary evidence that the incidence of HZ and its complications has declined somewhat in cohorts of children who have received the varicella vaccine [2] .

In a systematic review of the international literature, the risk of developing PHN ranged from 5% to more than 30%, depending on the type of study design, age distribution of the populations evaluated, and definition. More than 30% of patients with PHN experienced persistent pain for more than 1 year. The risk of recurrence of HZ ranged from 1% to 6%, with long-term follow-up studies showing an increased risk (5-6%) [4].

WHAT IS THE CLINICAL EXPRESSION OF VZV INFECTION?

VZV or Human Herpes Virus-3 (HHV-3), shares with the other close members of the *Alphaherpesviridae* subfamily the high transmissibility, the persistence in the host in latent form after infection and its capacity of reactivation with symptomatic clinical expression.

Primoinfection determines varicella as a clinical entity, a highly contagious process that affects practically the entire susceptible infant population and is characterized by a febrile condition followed by a rapidly evolving skin rash. Before the vaccine was introduced, only 10% of the population had chickenpox after the age of 13.

Once the disease has passed, generally without serious complications, VZV remains latent in the neuronal cells of the posterior ganglia of the spinal cord and brain, with minimal genomic expression. Its replication is contained by the immune system, which generates a long-lasting control [5].

The decrease of the immune response, due to any cause, allows the reactivation of the viral genetic material, with the consequent replication, invasiveness (cell to cell by continuity) and pathogenicity, giving rise to a second clinical form of the

disease that we call HZ or Herpes Zona (one virus, two clinical presentations) [5,6].

HZ, unlike varicella, predominates in the adult population (its overall incidence is 30%) and, as one gets older, the occurrence increases. Seventy percent of HZ appear after the age of 40 and one in two nonagenarians will have HZ at some point.

The latency state and possible reactivations of the virus that do not reach clinical expression are fundamental in maintaining the validity of immunity. It also appears that re-exposure to the virus by new infection has a role in maintaining immunity. However, after the drastic reduction of varicella with the generalized introduction of the varicella vaccine in the mid-1990s, it seems that the re-exposure to the virus by new infection plays a role in maintaining immunity [7]. The incidence of HZ does not seem to differ between countries where vaccination is the norm and where there is very little chickenpox [8] and, therefore, re-exposure by wild virus, and those where vaccination cannot or is not strictly enforced and chickenpox remains endemic [9]. This reinforces the idea that viral latency plays a key role in immune support [10].

HZ can be seen in healthy children, if the primary infection occurred very early. There is HZ in the first two years of age in children who were infected in their fetal period.

The attenuated viral variant Oka, used in the vaccine against varicella (chickenpox) [4], and later and with more viral load in the vaccine for HZ, has a behavior that determines a latency similar to the wild-type virus. Although it has less tendency to reactivation, it plays a similar role in the maintenance of immunity and, if this fails, it can mimic the primary disease (chickenpox) or HZ.

Immunosenescence and consequent loss of specific protection against the virus is the most common cause of HZ. Despite the boosting of immunity achieved by reactivation with clinical translation, a second episode of HZ can occur in up to 4% of patients and a third in 2%.

The most frequent complication is PHN, which appears in 5-20% of HZ (it increases in frequency and intensity with age). It is an inflammatory and cytopathic process in the neurons of the dorsal medullary ganglia and their corresponding axons that causes pain, sometimes very intense and of long duration. It is not known why some patients develop PHN and others do not. The intensity of the damage during the inflammatory phase, the production of neurotoxic substances, the existence of viral strains that alter conduction in the sodium channels of the nerve cell, the persistence of viral replication, and genetic and racial response factors have been postulated.

Neurotoxicity can, much less frequently, affect the anterior motor ganglion of the metameres, causing flaccid paralysis of the involved motor area. There are facial paralysis and paralysis of any other motor territory, including atonic bladders due to lesion of the sacral roots. Recovery is estimated at 50%. VZV can also produce myelitis, Guillain-Barré syndrome and meningoencephalitis.

VZV has three preferential cell tropisms in its invasiveness: T lymphocytes; skin epithelial cells and neurons. In its lymphocytic localization it is transported throughout the organism and can cause visceral complications (vasculitis, retinitis, enteritis...).

Vascular involvement, especially in the central nervous system, is a new field of study in the pathogenesis of VZV. The increase in stroke after an episode of HZ seems clear [11] and especially after the one that occurs with ocular lesion [11].

The identification of VZV in the wall of the temporal arteries has raised another question in the pathogenesis of temporal arteritis and has raised the issue of whether antivirals should be used in addition to corticosteroids for its treatment [11].

Ocular involvement (severe keratitis) and retinitis, sometimes necrotizing, are more frequent after HZ, and especially the latter is usually a complication clearly related to severe cellular immunosuppression states; HIV infection is a clear example [12].

Complications of infection or reactivation (varicella or zoster) may occur without the characteristic skin lesions, which should be taken into account as etiology before their appearance (meningoencephalitis, facial paralysis, stroke in children...).

WHAT IS THE BODY'S IMMUNE RESPONSE TO VZV AND HOW DOES IT EVOLVE THROUGHOUT LIFE?

The specificity of the virus for humans has made it difficult to understand the pathogenesis of the disease and the immune response. Only in recent years, and thanks to experimental models, has it been possible to deepen the molecular mechanisms of pathogenicity and cellular response to the virus [10].

VZV enters the body via the respiratory route and, through the nasopharyngeal epithelium, infects the lymphoid tissue of the pharynx [13] from where it is disseminated and transported in T-lymphocytes [14]. It finally invades the epidermal epithelium (symptomatic target of primoinfection) and by its own viraemia and probably by retrograde progression from the skin, through the sensory axons, it reaches the neurons of the posterior ganglia, where it remains resident under the control of the immune system. It has a long prodromal period (10 to 21 days), during which it is able to evade the defensive response, partially inhibiting functions of the innate immune response [15]. Once this is overcome, it induces cellular damage and the inflammatory response occurs, where it is the specific cellular immunity (mediated by T lymphocytes) and most probably the local innate immunity, which manage to modulate and finally reach the latency of the virus, which remains resident in the country [16].

The T cellular immune response is essential in defense and is of long duration. Its loss or decrease is the key to reactivation. If there is viral reactivation, a new potentiation of cellular immunity is generated (on whose effect and control capacity depends the intensity and the presence of complications).

There is also a response of specific antibodies that occurs

late and in clear relation of magnitude with the virulence of the process. In this case, the maximum level of specific antibodies is dated in the third week of evolution of HZ and has more significance as a marker of the intensity of the process (the more antibodies the more severe and prolonged the HZ, the more severe the neuralgia and the older the patient) translating more antigenic stimulus. The initial levels of specific antibodies at the onset of HZ do not correlate with the clinical course [17].

Senescence is the most common cause of loss of cellular immune protection, in addition to all pathological states of immunosuppression. Humoral immunocompetence is less important in VZV disease. Specific antibodies (hyperimmune serum) can block primoinfection, but modulation and resolution of the disease (varicella or zoster) depends on specific T-cell immunity.

Vaccines (attenuated virus) and recombinant glycoprotein E induce and potentiate immunity in the same way as virus activity, although in very elderly patients endogenous reactivation seems more potent than the vaccine [18].

In any case, if the measures of cellular immunity that we know in the laboratory are equivalent to viral reactivation and vaccines, especially the recombinant gE vaccine, and since HZ can recur, it is likely that vaccines also require booster doses, including the recombinant gE vaccine. In this case, the antigenic stimulus is punctual and does not remain latent. Its efficacy is measured and contrasted at 10 years and it seems that at that point both cell-mediated immunity (CMI) and antibody titer begin to decrease [19].

The search for vaccines against VZV has not been completed. As with other immunogens, we are looking for platforms that guarantee greater persistence of the antigenic stimulus (gE encoded in Calmette-Guérin bacilli), mRNA encodings that seem as effective as the recombinant one already in force and antigenic encodings in other vector viruses [20].

HOW IS HERPES ZOSTER DIAGNOSED? WHEN IS MICROBIOLOGICAL CONFIRMATION NECESSARY?

The clinical manifestations of HZ with skin lesions are usually so clear that in immunocompetent patients, microbiological confirmation is not required. The presence of a rash with vesicles distributed on a metamere, usually with dysesthesias or frank pain, are very characteristic.

Microbiological confirmation is necessary when the skin lesions are atypical as in the case of hemorrhagic lesions and without frank vesicles. Microbiological confirmation is also needed when there are no characteristic clinical lesions such as in patients presenting with acute neuritis (before the rash appears), atypical ocular manifestations, aseptic meningitis, myelitis, retinal necrosis, etc. Ramsay Hunt syndrome includes the triad of ipsilateral facial paralysis, otalgia and vesicles in the ear canal or pinna. It may be associated with dysgeusia, hypo- or hyperacusis, lacrimation and tongue lesions.

Laboratory confirmation is usually made on material aspirated from vesicles in the case of skin lesions or in other usually sterile fluids such as CSF. The most commonly used test today is PCR, followed by fluorescent antibody staining (direct fluorescence) and less frequently by viral isolation in cell culture.

PCR is more sensitive than the culture itself. In a study evaluating 1,479 clinical samples from 1,220 patients with suspected HZ, real-time PCR was more sensitive than culture isolation (92% vs. 53%) [21,22]. Culture, however, is necessary when sensitivity studies against antivirals are required.

WHAT HZ VACCINES ARE CURRENTLY AVAILABLE AND HOW MUCH PROTECTION DO THEY CONFER?

Currently, there are two vaccines approved by regulatory agencies and marketed to prevent the onset of HZ and its complications, essentially PHN (Table 1). They are indicated in persons over 50 years of age [20]. The first of these (Zostavax®), marketed by MSD and licensed in Europe in May 2006, is a live attenuated virus vaccine and is administered in a single dose [23-27]. It is contraindicated in states of primary or acquired immunodeficiency due to the risk of virus replication.

The second (Shingrix®) is more recent [28-33]. It was authorized in March 2018, is marketed by the company GSK and is the one that is included in the vaccination strategies by the different autonomous communities of Spain at the present time [2]. It is a recombinant vaccine containing the glycopro-

Table 1 | **Immunization vaccines against Herpes zoster marketed in Spain.**

Vaccine	Characteristics	Doses	Indications
Zostavax MSD	Live attenuated viruses	1 dose 0.65 ml	Prevention of herpes zoster and post-herpetic neuralgia in adults. Post-herpetic neuralgia in adults > 50 years
Shingrix GSK	Recombinant	2 doses of 0.5 ml each, separated two months apart	Prevention of herpes zoster and postherpetic neuralgia in: - adults >50 years - adults >18 years of age at increased risk for herpes zoster

tein E of the VZV virus and the adjuvant AS01B. The latter is a compound extracted from the bark of *Quillaja saponaria*, a tree native from Chile, which has also been used in some of the SARS-CoV-2 vaccines (NVX-CoV2373 vaccine, Novavax, USA), and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) [33,34]. In the indication of the Shingrix vaccine, the age of the target population is reduced by adding the prevention of HZ and PHN in adults 18 years of age and older with immunodeficiency conditions. In all cases included in the indication for vaccination with Shingrix, administration consists of two doses of 0.5 ml each, with a minimum interval of two months between doses.

Both vaccines have a good safety profile. However, the recombinant Shingrix vaccine has greater reactogenicity, both locally and systemically. No significant differences in serious adverse effects have been demonstrated between the two vaccines. The Shingrix vaccine is more efficient and its effectiveness against HZ and subsequent neuralgia, especially in immunocompromised patients, does not decrease with age, a situation that is common with the attenuated virus vaccine (Zostavax) [35]. In addition, since it is a recombinant vaccine, virus replication is not possible, making it safe in immunocompromised patients.

Like the efficacy (derived from clinical trials), the effectiveness (assessed in real life) of vaccination with Zostavax decreases with time after vaccination. In vaccinated persons followed for at least 4 years after vaccination, the incidence of HZ ranged from 14% to 49% of that expected. When PHN was analyzed, it ranged from 45% to 62% of expected [36]. With the Shingrix vaccine, the efficacy in adults over 70 years of age was 91% for HZ and 89% for PHN, with an effectiveness of over 70% in those who had received the complete regimen. The recombinant vaccine has also been shown to be highly effective against other complications of HZ infection such as vasculitis, disseminated disease, ophthalmic disease, neurological disease, stroke and visceral disease. The efficacy of the recombinant Shingrix vaccine is not affected by underlying diseases such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, depression or chronic kidney disease and shows high efficacy in immunosuppressed individuals.

In clinical trials, Shingrix has shown superiority over the attenuated vaccine, demonstrating an elevated humoral and cellular immune response that is maintained up to 10 years after receiving the vaccine [20]. Mathematical models predict that the immune response generated after the initial vaccination with the usual two doses can be maintained for 20 or more years, so there is no consensus on the need for revaccination [19]. However, persons who have previously received the attenuated virus vaccine (Zostavax) can be vaccinated with the recombinant Shingrix vaccine [37]. The first dose with Shingrix can be administered two months after the administration of the Zostavax vaccine, although taking into account the duration of efficacy of this vaccine, it is recommended to administer the Shingrix vaccine 5 years after the previous one, and both doses should also be administered.

WHAT ARE THE INDICATIONS FOR VACCINATION AGAINST ZOSTER BY AGE CRITERIA? ARE THERE INDICATIONS TO VACCINATE IMMUNOCOMPETENT POPULATIONS OF LOW OR MIDDLE AGE?

Epidemiology alone justifies that the age criterion is one of the criteria for the indication of vaccination in the prevention of HZ and its complications [2,37]: its incidence indicates that from the age of 50 years one in five men and one in four women will suffer from HZ with a risk of suffering from it at the age of 85 years of 50%. Furthermore, by the age of 80, it is estimated that 33% of those who have suffered from HZ will develop the dreaded and disabling PHN. Hospitalization, although low, is progressively required with age: 63.1% of hospitalizations for HZ and 83.2% for PHN are in patients aged 60 years and older, with a maximum in those over 85 years. Finally, 97.2% of deaths from HZ, also exceptional, occur in persons over 65 years of age. Based on all these data, there is no doubt that the priority indication for vaccination in the immunocompetent population against HZ is all those over 65 years of age and especially all those over 80 years of age [2,37] .

The community of Madrid [37] according to the doses available has indicated to vaccinate two cohorts in 2022, on the one hand those over 80 years old and on the other hand those who will be 65 years old in 2022, being available privately with a medical prescription for the rest of the population ("the imperfect ethics of vaccines") [38]. The choice of the 65-year-old cohort is due to the fact that most of them will have had chickenpox without previous vaccination, thus placing them in an age of increasing risk, being a cohort older than the rest of the age groups.

In younger, immunocompetent adults, the recommendation for vaccination is not clear. However, some studies indicate some population groups with a higher risk of suffering from HZ regardless of age. These may include adults with COPD on inhaled or oral corticosteroids [39]. Similarly, they could also be recommended for adults suffering from COPD [40] associated with type 1 or type 2 diabetes mellitus [41,42]. Finally, hemodialysis patients should also be included. [43]. Other conditions such as dementia [44] o depression [45], although these factors alone increase the risk of HZ, there is no clear indication for vaccination at this time in age groups below 65 years.

WHICH IMMUNOSUPPRESSED PATIENTS SHOULD RECEIVE VACCINES AGAINST ZOSTER?

There are several arguments supporting the administration of the HZ vaccine in the immunocompromised population. Firstly, the incidence of HZ is higher in immunocompromised patients than in the general population. In a study carried out in the Valencian Community, the mean incidence rate in the immunocompromised population was 9.15 cases per 1,000 people in the population with different immunosuppressive diseases, compared to 4.64 cases in the general popu-

lation, reaching figures of 56 cases per 1,000 patients in those undergoing hematopoietic stem cell transplantation [46].

In addition, immunocompromised patients are at higher risk of HZ complications and more severe disease (viremia, pneumonitis, hepatitis, meningoencephalitis) than immunocompetent patients [47,48]. PHN is the most frequent complication in immunocompromised patients, with the highest rate, again, in patients undergoing hematopoietic stem cell transplantation [46]. Finally, immunocompromised patients are more likely to suffer from recurrent HZ than immunocompetent patients [49].

Immunocompromised patients were excluded from pivotal studies with HZ vaccines. Later, studies have been conducted to assess the efficacy, immunogenicity and safety of the vaccine in certain groups of immunocompromised patients (autologous hematopoietic stem cell transplantation (TaPH), hematological malignancies during immunosuppressive chemotherapy, renal transplantation, solid tumor during immunosuppressive chemotherapy and HIV infection. In TaPH recipient patients, a 68% and 89% reduction in the incidence of HZ and PHN was demonstrated, respectively, with an adverse effect rate similar to that of placebo [50]. In patients with hematologic malignancies, the vaccine achieved an 87% reduction in the incidence of HZ vs. placebo [51]. In the case of patients with solid tumors undergoing chemotherapy, with renal transplantation or HIV infection, it was shown that humoral and protective cellular immunity were achieved in very high percentages of patients, similar to those found in similar population groups without immunocompromising conditions [52-54], although no efficacy data were obtained. In all cases, the vaccine showed an acceptable safety profile.

Based on all these data, vaccination with the HZ vaccine is recommended in most countries for adult patients with various diseases that cause immunosuppression and, therefore, a much higher risk of developing the disease than the general population. Among the most frequent indications, based on the data presented, the vaccine is recommended for people with solid organ transplants, patients with HSCT, patients with solid tumors receiving chemotherapy and in patients with HIV infection, in addition to other comorbidities that may result from the disease itself or its treatment in immunodeficiency.

WHAT ARE THE MOST APPROPRIATE VACCINATION RECOMMENDATIONS? AND WHAT ARE THE CONTRAINDICATIONS OF ZOSTER VACCINES?

The recommended guidelines for vaccination against HZ are included in a document issued by the Spanish Ministry of Health [2]:

- Zostavax vaccine is administered in a single dose. It is contraindicated in immunosuppressed patients as it is a live virus vaccine. It is not indicated in patients under 50 years of age [2,55] and can be applied in people who have previously suffered from HZ, after recovery from acute HZ.
- The Shingrix vaccine is administered in a two-dose schedule, with a minimum interval of two months between doses [33]. The second dose can be administered 2 to 6 months after the first one. This vaccine is recombinant, so it is not contraindicated in immunocompromised patients, and it can also be used in adults from 18 years of age, with a high risk of suffering HZ.
- People with special risk conditions for HZ can be vaccinated with Shingrix from 18 years of age onwards, respecting the following vaccination guidelines according to the patient's underlying pathology:
  - Hematopoietic stem cell transplantation (HSCT). Vaccination from 18 years of age. Two doses will be administered, with an interval of two months. In persons who are vaccinated in the immediate post-transplant period, the first dose should be administered 2 months after transplantation.
  - Solid organ transplantation (SOT). Vaccination from 18 years of age. Two doses will be administered two months apart. If vaccinated after transplantation, the first dose of vaccine will be administered 4-8 months after transplantation.
  - Treatment with anti-JKA drugs. Vaccination from 18 years of age. Two doses will be administered two months apart, if possible vaccination should be given before starting treatment.
  - HIV-infected persons. Vaccination will be carried out in stable persons who have been on antiretroviral treatment for at least one year. Two doses will be administered with an interval of two months.
  - Hematological malignancies. Two doses will be administered, with an interval of two months. In persons who are going to start chemotherapy treatment, the first dose of vaccine should be administered at least 10 days before starting the first cycle of treatment.
  - Solid tumors undergoing chemotherapy. Two doses will be administered, with an interval of two months. The first dose can be administered after completion of chemotherapy, or in window periods without active antitumor treatment.
- Other situations to consider are those individuals previously vaccinated with Zostavax, and those who have a history of HZ, or repeated HZ, prior to vaccination:
  - Individuals who have previously received Zostavax vaccine may be revaccinated with recombinant vaccine, respecting an interval of at least 5 years between this vaccine and the first dose of Shingrix.
  - Regarding patients who have suffered HZ prior to vaccination, there are data from a clinical trial showing that the Zostavax vaccine is immunogenic and well tolerated in patients who have previously undergone HZ [56]. The safety of the HZ/su vaccine in people who have suffered a previous episode of HZ,

before being vaccinated, is not questioned, although there are no specific studies on the subject [57].

Specific contraindications for these vaccines affect only Zostavax, which is contraindicated in immunocompromised patients and in those under 50 years of age. There are no contraindications for the Shingrix vaccine.

Both vaccines are safe. Although HZ/su is associated with greater local and systemic reactogenicity compared to the ZVL vaccine, no significant differences have been demonstrated between the two vaccines in the detection of serious adverse effects, nor when compared to the placebo group [58].

CAN THE ZOSTER VACCINE BE COMBINED WITH OTHER VACCINES?

Among the interactions described in the Shingrix technical data sheet, it is specified that it can be administered concomitantly with the inactivated non-adjuvanted vaccine against seasonal influenza, with the 23-valent polysaccharide (PPV23) and 13-valent pneumococcal vaccines or with the reduced antigenic content (dTpa) diphtheria, tetanus and anti-Tetanus and Pertussis vaccine (acellular component). Caution should be taken to administer them at different injection sites. In three phase III clinical trials randomized adults ≥ 50 years of age received 2 doses of Shingrix 2 months apart, administering the first dose concomitantly or not concomitantly with an inactivated seasonal influenza vaccine, with a PPV23 vaccine, or with a dTpa vaccine, immune responses to the co-administered vaccines were not affected [59-62]. Adverse reactions, fever and chills were more frequent when Shingrix was co-administered with PPV23.

In the absence of precise data, concomitant use of the HZ vaccine with the COVID vaccine is not recommended but could be scheduled one month apart.

After the COVID-19 pandemic, it seems necessary to create a global system that can support both routine immunization and epidemic immunization in adults [59,60].

New strategies are being advanced to address the context of immunosenescence, which can reduce the efficacy of vaccines and affect susceptibility to new infections in older adults [61]. High-dose, adjuvanted and recombinant specific influenza vaccines, pneumococcal conjugate vaccines and a recombinant adjuvanted HZ vaccine have demonstrated increased efficacy and effectiveness in older adults [62,63]. Many studies have shown that vaccines against influenza, pneumococcus and HZ [64,65-68] are cost-effective when administered to older adults in a variety of settings.

WHAT IS THE BEST TREATMENT FOR ACUTE ZOSTER?

The main goals of HZ treatment are to reduce the extent and duration of skin lesions, the intensity and duration of acute pain and the incidence of PHN. In immunocompromised and other vulnerable patients, treatment aims to reduce the

Table 2 | **Indications for antivirals in acute herpes zoster infection**

a) Situations in which treatment with oral antiviral drugs is recommended
- HZ with any location in persons ≥ 50 years*.
- HZ of non-truncular involvement, in areas of the head and/or neck that seat on any cranial nerve (ophthalmic, otic or other cranial nerves), in the extremities or perineum.
- HZ at any location with:
  - Moderate to severe HZ pain
  - Hemorrhagic or necrotic lesions
  - Affection of more than one dermatome
  - Atypical/satellite vesicles
  - Mucous membrane involvement
- HZ in immunocompromised patients.
- HZ in patients with predisposing skin diseases (e.g., atopic dermatitis).
- HZ in children and adolescents with prolonged treatment with salicylic acid or corticosteroids.

b) Situations in which treatment with intravenous acyclovir is recommended
- HZ in head and/or neck areas, especially in very elderly patients.
- HZ with hemorrhagic/necrotic lesions, with involvement of more than one dermatome, with atypical/satellite vesicles, with mucosal involvement or generalized HZ.
- HZ in immunocompromised patients
- HZ with signs of visceral or CNS involvement (stepwise dose increase up to 15 mg/kg b.w., three times daily, for up to 21 days)
- Acute retinal necrosis (complication of ocular herpes): induction with IV acyclovir for 7-10 days, followed by oral acyclovir (3-4 months), and topical and systemic treatment with corticosteroids.

Modified from references 1, 2

*Initiate within 72 hours after rash onset, but may be considered for patients presenting more than 72 hours after rash onset when there are skin, motor, neurological or ocular complications or in patients with advanced age or severe pain

Table 3 Recommended drugs for antiviral treatment of herpes zoster.

Drug	Dosage, frequency of administration and duration*
Valaciclovir (PO)	1000 mg, tid x 7 days
Aciclovir (PO)**	800 mg. 5 times/day x 7 days
Aciclovir (IV)	8–10 mg/kg, tid x 7-10 days
Famciclovir (VO)	250 mg, tid x 7 days
Brivudine (VO)	125 mg, qd x 7 days
Topical antiviral therapy is not recommended.	

Modified from reference 2

* Patients with recurrent shingles should receive antiviral treatment at a dose and duration similar to the treatment of their initial episode.

** Acyclovir and its analogues depend on renal function for their elimination and dose adjustment is necessary in case of moderate to severe renal insufficiency.

frequency and severity of complications [69]. In the absence of risk factors for the development of complications, HZ is usually a self-limited disease that does not require specific antiviral treatment. The different clinical practice guidelines agree on the indications for antiviral treatment in immunocompetent persons ≥ 50 years of age [69,70]. In addition, it would be indicated regardless of age, in cases of non-truncular involvement (such as HZ affecting the neck, extremities or perineum), in immunosuppressed patients, in cases of moderate or severe pain, in the presence of a non-mild skin rash or in patients with skin disease predisposing to complications (Table 2) [69].

Currently, there are four orally effective nucleoside analogues against HZ (Table 3) [70]. Antiviral drugs accelerate the resolution of acute HZ-related pain and may reduce the duration of the rash, but have not been shown to decrease the incidence of PHN [71]. Nor have statistically significant differences in pain cessation and resolution of skin symptoms been observed in different studies among the different antivirals [72].

Acute pain associated with HZ occurs in more than 95% of patients over 50 years of age [71]. Initially, this pain is nociceptive, but later a neuropathic component may appear. The treatment of acute pain depends on its severity and impact. Mild to moderate pain is treated with systemic analgesics. The application of cold, wet compresses over the blisters may help relieve pain. Severe cases may require opioids [70]. In the absence of acute pain control, and when a neuropathic component is suspected, analgesics can be combined with anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, venlafaxine or duloxetine as a second-line treatment [69]. It is unusual to have to resort to interventional treatments for acute pain. In relation to ocular herpes, it is recommended to complement systemic treatment with the application of topical acyclovir preparations to the affected eye [69,70]. Otic HZ has no specific topical treatment. For antiviral treatment of Bell's palsy associated with HZ, famciclovir has the best rate of recovery of facial function [73].

There is insufficient evidence and expert agreement to make recommendations for specific topical treatment of acute HZ [69]. It is advisable to keep the lesions clean and dry, avoiding as much as possible any topical treatment [69].

WHAT IS THE MANAGEMENT OF MEDIUM AND LONG-TERM COMPLICATIONS: POSTHERPETIC NEURALGIA?

PHN is the most common complication of HZ infection. It is defined as neuropathic pain that persists 30 to 90 days after the cutaneous flare. It is characterized by continuous or paroxysmal, evoked or spontaneous, burning, and lacerating pain. It is associated with dysesthesias, paresthesias, hyperalgesia, hyperesthesia and allodynia. Pain usually alters the patient's quality of life and can lead to functional limitation, social isolation and psychological disorders. The most frequent clinical form is intercostal, affecting one or two pairs of intercostal roots and ganglia on one side. The most frequent lesion of the cranial nerves is in the trigeminal nerve, giving rise to ophthalmic HZ, which is accompanied by pain in 93% of patients.

Between 5-20% of patients with HZ will present PHN [73]. Its appearance is related to age, being more frequent after 50 years of age, the extension of the skin lesion and the intensity of the prodromal pain [74]. Other related factors are ophthalmic involvement, immunosuppression, the presence of other diseases such as diabetes or delayed initiation of herpes treatment.

Its pathogenesis has not been completely clarified. Histologically, alterations have been found in both the central and peripheral nervous system, with inflammation and necrosis from the peripheral nerve to the neurons of posterior medullary cords. There also appears to be demyelination with loss of inhibitory stimulus for nociceptive afferents in the spinal cord. There is sensitization of peripheral nociceptors with reduction of the excitation threshold; appearance of spontaneous ectop-

ic discharges in peripheral and central axons, medullary hyperexcitability and loss of inhibitory control of pain. An alteration of sodium channels has also been considered in this disease and the expression of neuronal genes after infection.

The management of PHN is based on prevention through vaccination in the population at risk, early administration of antivirals upon HZ infection and symptomatic control by individualized multimodal medication regimens and invasive procedures.

The only preventive measure at present is vaccination. Different studies have shown that vaccination with attenuated and recombinant virus reduces the occurrence of HZ zoster in the following 3 years [9,75], it reduces also the incidence of PHN, as well as the hospital admissions related to the disease [32,76].

As mentioned in the previous section, the use of antivirals (acyclovir, brivudine, valacyclovir and famciclovir) is recommended in patients over 50 years of age early in the acute phase, although there is no convincing evidence that antiviral treatment reduces PHN [71]. Nor have corticosteroids shown clear evidence of benefit [13,77].

The most commonly used treatments for the control of PHN are tricyclic antidepressants, gabapentin, pregabalin and, locally, lidocaine and capsaicin patches. Other drugs such as antiepileptics (valproic acid, carbamazepine, lamotrigine) and serotonin reuptake inhibitors have been used in refractory cases. Opioid analgesics have shown efficacy in PHN. Invasive therapies include botulinum toxin injections, sympathetic blockade with local anesthetics, epidural/intrathecal steroid injections and spinal cord stimulation [78] but the tolerability and safety of these procedures must be considered [79]. Finally, cognitive and behavioral therapies can improve the quality of life of these patients.

WHAT IS THE POSITION OF THE DIFFERENT HEALTH ADMINISTRATIONS IN SPAIN REGARDING VACCINES AGAINST ZOSTER?

In March 2021, a document of recommendations, drawn up by consensus at the Interterritorial Council of the Ministry of Health in Spain, is published [2]. In this document, the following vaccination recommendations are established, which would be mandatory in all Autonomous Communities:

- Population over 18 years of age with the following risk factors: hematopoietic progenitor transplantation, solid organ transplantation, treatment with anti-JKA drugs, HIV infection, hematological malignancies and solid tumors undergoing chemotherapy.
- General population over 65 years of age.

Based on this document, several limitations can be pointed out: the age of recommendation, the demographic choice of the cohorts and, finally, something inherent to the system, the lack of homogeneity in the application of the recommendations by the communities.

Firstly, it is not sufficiently explained why the indication in the general population is established at 65 years of age and not at 50 years of age, which is when the dramatic inflection in the HZ growth curve occurs. In fact, the CDC recommends vaccination against HZ for all immunocompetent adults over 50 years of age, whether or not they have had a previous episode of HZ and whether or not they have received previous vaccination against varicella (chickenpox) [80].

On the other hand, the aforementioned document states that an attempt will be made to vaccinate one or two age cohorts each year, starting with those who turn 65 and/or 80 years of age in the year in which the procedure is performed. Since the document states that vaccination in immunocompetents will be implemented based on availability, it seems clear that both the age threshold and the surprisingly odd selection of cohorts is determined by economic and logistical reasons of human resources and infrastructure. It is possible, assuming that vaccination will be carried out with two doses, but on a single basis, that this choice would allow vaccination to be completed in 6-8 years.

As for the application by the communities, it could be assumed that all would apply the recommendations uniformly, but the reality is that at least the times are different and even with regard to vaccination in immunocompromised patients, Andalusia only carries it out in those undergoing hematopoi-

Table 4 Status of Herpes Zoster vaccination in the Autonomous Communities

Territory	PLAN	GR Status	State Population >65
Andalusia	2021	Group I	¿?
Aragon	2021	All	Expected 2023
Asturias	2021	All	Yes
Balearic Islands	2021	All	Planned 2023
Canary Islands	2021	All	¿?
Cantabria	2021	All	Planned 2023
Castilla Mancha	2021	All	Planned 2023
Castilla Leon	2021	All	Planned 2023
Catalonia	2021	All	Yes
Extremadura	2021	All	¿?
Galicia	2021	All	¿?
La Rioja	2021	All	¿?
Madrid	2021	All	Yes
Murcia	2021	All	Planned 2023
Navarra	2021	All	¿?
Basque Country	2021	All	¿?
Valencia	2021	All	Planned 2023
Ceuta	2021	All	Planned 2023
Melilla	2021	All	Planned 2023

etic progenitor transplantation. It is not easy to know the exact situation in which they find themselves, nor even to know the availability of doses. Madrid purchased 250,000 doses of vaccine starting to vaccinate immunocompromised patients last January and the general population over 65 years of age in May 2022. With the information that can be obtained at the end of November 2022, only three communities, Madrid, Catalonia and Asturias applied the vaccination to both immunocompromised and immunocompetent patients, the latter following the recommendation of 65 and 80 years of age, although 6 more communities and the cities of Ceuta and Melilla have announced that they will do so during 2023 (Table 4).

In this situation, some doubts arise that it would be advisable for the administration to clear up. The first concerns the selection of cohorts. Assuming that it is over 65 years of age, there is no justification for choosing 2 extreme cohorts that will leave out, for years, population groups aged 70-75 years in which the incidence is very high. On the other hand, and partly as a consequence of this situation, since it is a vaccine that can be purchased on prescription at the pharmacy, although it is not financed by the SNS and is expensive, since the necessary doses exceed 400€, it is clear that the application of this rule could result in a loss of equity, since the population with greater purchasing power, not only over 65 but even over 50 years of age, could have access to the vaccine, something difficult for the most disadvantaged groups. Finally, up to now the dissemination to the population and health personnel is scarce, so that it is possible that vaccination is not being carried out as planned, even in the general population groups chosen. Vaccinating in nursing homes or systematically taking advantage of consultations with the elderly population would increase the number of vaccinated subjects and would make it possible to take stock of the management of doses and increase the population cohorts to be vaccinated (Table 4).

FUNDING

None to declare

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

REFERENCES

1. Johnson RW, Alvarez-Pasquin MJ, Bijl M, Franco E, Gaillat J, Clara JG, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther Adv Vaccines. 2015;3(4):109-20. 10.1177/2051013615599151 PMC4591524
2. Ministerio de Sanidad, Herpes Zoster: Recomendaciones Vacunacion. 2021. Available at: https://www.sanidad.gob.es/en/profesionales/saludPublica/prevPromocion/vacunaciones/programasDeVacunacion/docs/HerpesZoster_RecomendacionesVacunacion.pdf
3. Instituto de Salud Carlos III. Informes Anuales de la Red Nacional de Vigilancia Epidemiológica (RENAVE). Resultados de la vigilancia epidemiológica de las enfermedades transmisibles. informe anual. años 2017-2018. 2018. Available at: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/INFORMES/INFORMES%20RENAVE/RENAVE_Informe_anual__2017-2018.pdf
4. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open. 2014;4(6):e004833. 10.1136/bmjopen-2014-004833 PMC4067812
5. Gershon AA, Breuer J, Cohen JI, Cohrs RJ, Gershon MD, Gilden D, et al. Varicella zoster virus infection. Nat Rev Dis Primers. 2015;1:15016. 10.1038/nrdp.2015.16 PMC5381807
6. Hope-Simpson RE. THE NATURE OF HERPES ZOSTER: A LONG-TERM STUDY AND A NEW HYPOTHESIS. Proc R Soc Med. 1965;58(1):9-20. PMC1898279
7. Centers for Disease Control. Evolution of varicella surveillance--selected states, 2000-2010. MMWR Morb Mortal Wkly Rep. 2012;61(32):609-12.
8. Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T. Live vaccine used to prevent the spread of varicella in children in hospital. Lancet. 1974;2(7892):1288-90. 10.1016/s0140-6736(74)90144-5
9. Harpaz R. Do varicella vaccination programs change the epidemiology of herpes zoster? A comprehensive review, with focus on the United States. Expert Rev Vaccines. 2019;18(8):793-811. 10.1080/14760584.2019.1646129
10. Laing KJ, Ouwendijk WJD, Koelle DM, Verjans G. Immunobiology of Varicella-Zoster Virus Infection. J Infect Dis. 2018;218(suppl_2):S68-s74. 10.1093/infdis/jiy403 PMC6151075
11. Kang JH, Ho JD, Chen YH, Lin HC. Increased risk of stroke after a herpes zoster attack: a population-based follow-up study. Stroke. 2009;40(11):3443-8. 10.1161/strokeaha.109.562017
12. Franco-Paredes C, Bellehemeur T, Merchant A, Sanghi P, DiazGranados C, Rimland D. Aseptic meningitis and optic neuritis preceding varicella-zoster progressive outer retinal necrosis in a patient with AIDS. Aids. 2002;16(7):1045-9. 10.1097/00002030-200205030-00011
13. Ku CC, Padilla JA, Grose C, Butcher EC, Arvin AM. Tropism of varicella-zoster virus for human tonsillar CD4(+) T lymphocytes that express activation, memory, and skin homing markers. J Virol. 2002;76(22):11425-33. 10.1128/jvi.76.22.11425-11433.2002 PMC136789
14. Levin MJ. Varicella-zoster virus and virus DNA in the blood and oropharynx of people with latent or active varicella-zoster virus infections. J Clin Virol. 2014;61(4):487-95. 10.1016/j.jcv.2014.09.012
15. Abendroth A, Kinchington PR, Slobedman B. Varicella zoster virus immune evasion strategies. Curr Top Microbiol Immunol. 2010;342:155-71. 10.1007/82_2010_41 PMC3936337
16. Kennedy PG, Grinfeld E, Gow JW. Latent varicella-zoster virus is located predominantly in neurons in human trigeminal ganglia. Proc Natl Acad Sci U S A. 1998;95(8):4658-62. 10.1073/pnas.95.8.4658 PMC22546
17. Weinberg A, Zhang JH, Oxman MN, Johnson GR, Hayward AR,

Caulfield MJ, et al. Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. J Infect Dis. 2009;200(7):1068-77. 10.1086/605611 PMC4014851

18. Schwarz TF, Volpe S, Catteau G, Chlibek R, David MP, Richardus JH, et al. Persistence of immune response to an adjuvanted varicella-zoster virus subunit vaccine for up to year nine in older adults. Hum Vaccin Immunother. 2018;14(6):1370-7. 10.1080/21645515.2018.1442162 PMC6037441
19. Hastie A, Catteau G, Enemuo A, Mrkvan T, Salaun B, Volpe S, et al. Immunogenicity of the Adjuvanted Recombinant Zoster Vaccine: Persistence and Anamnestic Response to Additional Doses Administered 10 Years After Primary Vaccination. J Infect Dis. 2021;224(12):2025-34. 10.1093/infdis/jiaa300 PMC8672743
20. Harbecke R, Cohen JI, Oxman MN. Herpes Zoster Vaccines. J Infect Dis. 2021;224(12 Suppl 2):S429-s42. 10.1093/infdis/jiab387 PMC8482024
21. Harbecke R, Oxman MN, Arnold BA, Ip C, Johnson GR, Levin MJ, et al. A real-time PCR assay to identify and discriminate among wild-type and vaccine strains of varicella-zoster virus and herpes simplex virus in clinical specimens, and comparison with the clinical diagnoses. J Med Virol 2009;81 1310.
22. Kino Y, Minamishima Y. Diagnosis of zoster and evaluation of varicella vaccine with a passive haemagglutination assay. Vaccine. 1993;11(11):1151-3. 10.1016/0264-410x(93)90078-c
23. Herpes zoster vaccine (Zostavax). Med Lett Drugs Ther. 2006;48(1243):73-4.
24. Holcomb K, Weinberg JM. A novel vaccine (Zostavax) to prevent herpes zoster and postherpetic neuralgia. J Drugs Dermatol. 2006;5(9):863-6.
25. Ebede TL, Zippin JH. Varicella virus and the herpes zoster vaccine. A review of Zostavax and the new AFIP recommendations. J Drugs Dermatol. 2008;7(12):1173-6.
26. Holcomb K, Weinberg JM. A novel vaccine (Zostavax) to prevent herpes zoster. G Ital Dermatol Venereol. 2008;143(2):119-23.
27. Herpes zoster vaccine (Zostavax) revisited. Med Lett Drugs Ther. 2010;52(1339):41.
28. Shingrix--an adjuvanted, recombinant herpes zoster vaccine. Med Lett Drugs Ther. 2017;59(1535):195-6.
29. Bharucha T, Ming D, Breuer J. A critical appraisal of 'Shingrix', a novel herpes zoster subunit vaccine (HZ/Su or GSK1437173A) for varicella zoster virus. Hum Vaccin Immunother. 2017;13(8):1789-97. 10.1080/21645515.2017.1317410 PMC5557227
30. Deshpande L. Recombinant Zoster Vaccine (Shingrix) for the Prevention of Shingles. Am Fam Physician. 2018;98(8):539-40.
31. Maltz F, Fidler B. Shingrix: A New Herpes Zoster Vaccine. P t. 2019;44(7):406-33. PMC6590925 this article.
32. Izurieta HS, Wu X, Forshee R, Lu Y, Sung HM, Agger PE, et al. Recombinant Zoster Vaccine (Shingrix): Real-World Effectiveness in the First 2 Years Post-Licensure. Clin Infect Dis. 2021;73(6):941-8. 10.1093/cid/ciab125
33. GSK. Data sheet Shingrix. 2017. Available at: https://cima.aemps.es/cima/pdfs/es/ft/1181272001/FT_1181272001.pdf
34. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. . N Engl J Med 2020;(383(24)):2320-32. 10.1056/NEJMoa2026920.
35. López-Fauqued M, Campora L, Delannois F, El Idrissi M, Oostvogels L, De Looze FJ, et al. Safety profile of the adjuvanted recombinant zoster vaccine: Pooled analysis of two large randomised phase 3 trials. Vaccine. 2019;37(18):2482-93. 10.1016/j.vaccine.2019.03.043
36. Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. PLoS Med. 2013;10(4):e1001420. 10.1371/journal.pmed.1001420 PMC3621740 monitoring boards for Abbott and Astellas. The authors declare no other conflicts of interest.
37. Comunidad de Madrid. Inclusión de la vacuna frente a herpes zoster (HZ) en el calendario sistemático de vacunación. Información para profesionales sanitarios. 2022. Available at: https://www.comunidad.madrid/servicios/salud/vacunas-informacion-profesionales.
38. Urioste R. La ética imperfecta de las vacunas. . Redacción Médica 2021 Available at: https://www.redaccionmedica.com/opinion/ramiro-urioste-5933/la-etica-imperfecta-de-las-vacunas-8009
39. Yang YW, Chen YH, Wang KH, Wang CY, Lin HW. Risk of herpes zoster among patients with chronic obstructive pulmonary disease: a population-based study. Cmaj. 2011;183(5):E275-80. 10.1503/cmaj.101137 PMC3060212
40. Muñoz-Quiles C, López-Lacort M, Díez-Domingo J. Risk and impact of herpes zoster among COPD patients: a population-based study, 2009-2014. BMC Infect Dis. 2018;18(1):203. 10.1186/s12879-018-3121-x PMC5934818
41. Lai SW, Liu CS, Kuo YH, Lin CL, Hwang BF, Liao KF. The incidence of herpes zoster in patients with diabetes mellitus: A meta-analysis of cohort studies. Medicine (Baltimore). 2021;100(16):e25292. 10.1097/md.0000000000025292 PMC8078473
42. Saadatian-Elahi M, Bauduceau B, Del-Signore C, Vanhems P. Diabetes as a risk factor for herpes zoster in adults: A synthetic literature review. Diabetes Res Clin Pract. 2020;159:107983. 10.1016/j.diabres.2019.107983
43. Kuo CC, Lee CT, Lee IM, Ho SC, Yang CY. Risk of herpes zoster in patients treated with long-term hemodialysis: a matched cohort study. Am J Kidney Dis. 2012;59(3):428-33. 10.1053/j.ajkd.2011.10.049
44. Chen VC, Wu SI, Huang KY, Yang YH, Kuo TY, Liang HY, et al. Herpes Zoster and Dementia: A Nationwide Population-Based Cohort Study. J Clin Psychiatry. 2018;79(1). 10.4088/JCP.16m11312
45. Liao CH, Chang CS, Muo CH, Kao CH. High prevalence of herpes zoster in patients with depression. J Clin Psychiatry. 2015;76(9):e1099-104. 10.4088/JCP.14m09311
46. Muñoz-Quiles C, López-Lacort M, Díez-Domingo J, Orrico-Sánchez A. Herpes zoster risk and burden of disease in immunocompromised populations: a population-based study using health system integrated databases, 2009-2014. BMC Infect Dis. 2020;20(1):905. 10.1186/s12879-020-05648-6 PMC7708196

47. Kennedy PGE, Gershon AA. Clinical Features of Varicella-Zoster Virus Infection. Viruses. 2018;10(11). 10.3390/v10110609 PMC6266119

48. Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. Clin Infect Dis. 2007;44 Suppl 1:S1-26. 10.1086/510206

49. Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. Herpes zoster recurrences more frequent than previously reported. Mayo Clin Proc. 2011;86(2):88-93. 10.4065/mcp.2010.0618 PMC3031432

50. Bastidas A, de la Serna J, El Idrissi M, Oostvogels L, Quittet P, López-Jiménez J, et al. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation: A Randomized Clinical Trial. Jama. 2019;322(2):123-33. 10.1001/jama.2019.9053 PMC6618796

51. Dagnew AF, Ilhan O, Lee WS, Woszczyk D, Kwak JY, Bowcock S, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. Lancet Infect Dis. 2019;19(9):988-1000. 10.1016/s1473-3099(19)30163-x

52. Vink P, Delgado Mingorance I, Maximiano Alonso C, Rubio-Viqueira B, Jung KH, Rodriguez Moreno JF, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumors, vaccinated before or during chemotherapy: A randomized trial. Cancer. 2019;125(8):1301-12. 10.1002/cncr.31909 PMC6766894

53. Vink P, Ramon Torrell JM, Sanchez Fructuoso A, Kim SJ, Kim SI, Zaltzman J, et al. Immunogenicity and Safety of the Adjuvanted Recombinant Zoster Vaccine in Chronically Immunosuppressed Adults Following Renal Transplant: A Phase 3, Randomized Clinical Trial. Clin Infect Dis. 2020;70(2):181-90. 10.1093/cid/ciz177 PMC6938982

54. Berkowitz EM, Moyle G, Stellbrink HJ, Schürmann D, Kegg S, Stoll M, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. J Infect Dis. 2015;211(8):1279-87. 10.1093/infdis/jiu606 PMC4371767

55. MSD. Data sheet Zostavax. 2006. Available at: https://cima.aemps.es/cima/pdfs/es/ft/06341011/FT_06341011.pdf

56. Mills R, Tyring SK, Levin MJ, Parrino J, Li X, Coll KE, et al. Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. Vaccine. 2010;28(25):4204-9. 10.1016/j.vaccine.2010.04.003

57. Godeaux O, Kovac M, Shu D, Grupping K, Campora L, Douha M, et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit candidate vaccine in adults ≥ 50 years of age with a prior history of herpes zoster: A phase III, non-randomized, open-label clinical trial. Hum Vaccin Immunother. 2017;13(5):1051-8. 10.1080/21645515.2016.1265715 PMC5443374

58. Willis ED, Woodward M, Brown E, Popmihajlov Z, Saddier P, Annunziato PW, et al. Herpes zoster vaccine live: A 10 year review of post-marketing safety experience. Vaccine. 2017;35(52):7231-9. 10.1016/j.vaccine.2017.11.013 PMC5739308

59. Privor-Dumm LA, Poland GA, Barratt J, Durrheim DN, Deloria Knoll M, Vasudevan P, et al. A global agenda for older adult immunization in the COVID-19 era: A roadmap for action. Vaccine. 2021;39(37):5240-50. 10.1016/j.vaccine.2020.06.082 PMC7332930

60. Bouza E, Ancochea-Bermúdez J, Campins M, Eirós-Bouza JM, Fargas J, García Rojas A, et al. The situation of vaccines for the prevention of infections in adults: An opinion paper on the situation in Spain. Rev Esp Quimioter. 2019;32(4):333-64. PMC6719651

61. Thomas-Crusells J, McElhaney JE, Aguado MT. Report of the ad-hoc consultation on aging and immunization for a future WHO research agenda on life-course immunization. Vaccine. 2012;30(42):6007-12. 10.1016/j.vaccine.2012.07.025

62. Lee JKH, Lam GKL, Shin T, Kim J, Krishnan A, Greenberg DP, et al. Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis. Expert Rev Vaccines. 2018;17(5):435-43. 10.1080/14760584.2018.1471989

63. McElhaney JE, Beran J, Devaster JM, Esen M, Launay O, Leroux-Roels G, et al. AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial. Lancet Infect Dis. 2013;13(6):485-96. 10.1016/s1473-3099(13)70046-x

64. Ting EEK, Sander B, Ungar WJ. Systematic review of the cost-effectiveness of influenza immunization programs. Vaccine. 2017;35(15):1828-43. 10.1016/j.vaccine.2017.02.044

65. Chen C, Beutels P, Wood J, Menzies R, MacIntyre CR, McIntyre P, et al. Retrospective cost-effectiveness of the 23-valent pneumococcal polysaccharide vaccination program in Australia. Vaccine. 2018;36(42):6307-13. 10.1016/j.vaccine.2018.08.084

66. Jiang Y, Yang X, Taniguchi K, Petigara T, Abe M. A cost-effectiveness analysis of revaccination and catch-up strategies with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in older adults in Japan. J Med Econ. 2018;21(7):687-97. 10.1080/13696998.2018.1465272

67. Thorrington D, van Rossum L, Knol M, de Melker H, Rümke H, Hak E, et al. Impact and cost-effectiveness of different vaccination strategies to reduce the burden of pneumococcal disease among elderly in the Netherlands. PLoS One. 2018;13(2):e0192640. 10.1371/journal.pone.0192640 PMC5806887

68. Willem L, Blommaert A, Hanquet G, Thiry N, Bilcke J, Theeten H, et al. Economic evaluation of pneumococcal vaccines for adults aged over 50 years in Belgium. Hum Vaccin Immunother. 2018;14(5):1218-29. 10.1080/21645515.2018.1428507 PMC5989887

69. Werner RN, Nikkels AF, MarinovićB, Schäfer M, Czarnecka-Operacz M, Agius AM, et al. European consensus-based (S2k) Guideline on the Management of Herpes Zoster - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV), Part 2: Treatment. J Eur Acad Dermatol Venereol. 2017;31(1):20-9. 10.1111/jdv.13957

70. Saguil A, Kane S, Mercado M, Lauters R. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management. Am Fam Physician. 2017;96(10):656-63.

71. Chen N, Li Q, Yang J, Zhou M, Zhou D, He L. Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2014(2):Cd006866. 10.1002/14651858.CD006866.pub3

72. Tyring SK, Beutner KR, Tucker BA, Anderson WC, Crooks RJ. Antiviral therapy for herpes zoster: randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. Arch Fam Med. 2000;9(9):863-9. 10.1001/archfami.9.9.863

73. Cao J, Zhang X, Wang Z. Effectiveness comparisons of antiviral treatments for Bell palsy: a systematic review and network meta-analysis. J Neurol. 2022;269(3):1353-67. 10.1007/s00415-021-10487-9

74. Zhou H, Wang Z, Jin H, Chen X, Lei L. A systematic review and meta-analysis of independent risk factors for postherpetic neuralgia. Ann Palliat Med. 2021;10(12):12181-9. 10.21037/apm-21-3028

75. Gagliardi AM, Andriolo BN, Torloni MR, Soares BG, de Oliveira Gomes J, Andriolo RB, et al. Vaccines for preventing herpes zoster in older adults. Cochrane Database Syst Rev. 2019;2019(11). 10.1002/14651858.CD008858.pub4 PMC6836378 none known Bernardo GO Soares: none known Juliana O Gomes: none known Regis B Andriolo: none known Eduardo C Cruz: none known

76. Lee C, Jiang N, Tang H, Ye C, Yuan Y, Curran D. Potential public health impact of the adjuvanted recombinant zoster vaccine among people aged 50 years and older in Beijing. Hum Vaccin Immunother. 2021;17(10):3735-46. 10.1080/21645515.2021.1932216 PMC8437530

77. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2013(3):Cd005582. 10.1002/14651858.CD005582.pub4

78. Patil A, Goldust M, Wollina U. Herpes zoster: A Review of Clinical Manifestations and Management. Viruses. 2022;14(2). 10.3390/v14020192 PMC8876683

79. Mallick-Searle T, Snodgrass B, Brant JM. Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. J Multidiscip Healthc. 2016;9:447-54. 10.2147/jmdh.S106340 PMC5036669

80. Dooling KL, Guo A, Patel M, Lee GM, Moore K, Belongia EA, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. MMWR Morb Mortal Wkly Rep. 2018;67(3):103-8. 10.15585/mmwr.mm6703a5 PMC5812314