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REVIEW

Herpes zoster in frail elderly patients: prevalence, impact, management, and preventive strategies

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Abstract

Population aging is a worldwide phenomenon with significant and manifold impacts on society. Advanced age correlates with the onset of frailty. In this vulnerable state, the immune response is weakened and a higher susceptibility to infectious diseases is observed. The present narrative review aims to cover the topic of herpes zoster (HZ) and its complications in frail populations. The lifetime risk of developing HZ is estimated at about 20–30%, and the risk increases with age. In older people, HZ can lead to the inability to recover the lifestyle, the interests, and the level of activity that existed before its development. Severity of the disease at presentation and depression are the major correlates of pain burden in patients with acute HZ and postherpetic neuralgia (PHN). The frail elderly need careful assessment prior to treatment initiation and could be affected to a greater extent by treatment-related adverse events. In light of the significant burden caused by HZ and its complications in the frail elderly, the adoption of a preventive strategy appears to be promising, particularly using vaccination in appropriate age- and risk-groups. Although very few vaccine studies consider explicitly the frail elderly as their study population, there is evidence that the live, attenuated vaccine induces significant immunological responses. An adjuvanted recombinant subunit vaccine has recently been approved in Canada, in the United States, in the European Union, and in Japan, and will likely provide additional opportunities for prevention.

Keywords Herpes zoster · Frailty · Elderly · Treatment · Prevention · Epidemiology

Introduction

Population aging is a worldwide phenomenon with significant and manifold impacts on society.

In 2017, 13% of the global population was represented by people over 60 years old. Current estimates indicate that, in 2050, in most of the world's regions, with the exception of the African continent, about a quarter of the population will be aged ≥ 60 years and the ≥ 80-year-old population will treble [1].

Advanced age correlates with the onset of frailty: a condition that still lacks a standard definition. Frailty is commonly defined as a clinically identifiable state of vulnerability associated with the age-related decline of the functions and reserves of various physiological systems. It is important to highlight at this point that co/multi-morbidity and disability, though related to frailty and sometimes overlapping with it, represent distinct concepts [2]. There are currently two general models that try to describe and explain the features of frailty: the phenotype model [3] and the cumulative deficit model [4].

In the phenotype model, frailty is defined according to clinically observable traits that, if present, are predictive of a poorer outcome; specifically, the frailty syndrome (phenotype) is established when ≥ 3 of these criteria are fulfilled: unintentional weight loss (> 4.5 Kg in the previous

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year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity [3].

In the cumulative deficit model, the clinical deficits associated with aging (which can be symptoms, signs, abnormal test results, or diseases) are counted for an individual. More commonly in clinical practice, a concise Clinical Frailty Scale is constructed (ranging for example from Very Fit to Severely Frail), that allows for the existence of frailty over a spectrum, which is more in line with common clinical experience [4–6].

According to a holistic view of the individual, frailty is "a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, and social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes" [7].

As previously mentioned, the prevalence of frailty increases with age and, according to a recent study, is about 10% in people aged > 65 years, reaching between 25 and 50% in persons aged > 85 years [8].

Among the several avenues of research in this area, one of particular interest is the potential role of age-induced modifications of the immune-endocrine axis in determining frailty. Studies have investigated the interlinked phenomena of sarcopenia, immune senescence, and chronic inflammation in aging ("inflammageing"), finding alterations in blood hormone concentrations [for example, lower levels of dehydroepiandrosterone sulphate (DHEAS) and a higher cortisol:DHEAS ratio] and in both the innate and adaptive branches of the immune system at cellular and molecular (cytokines) levels [9–11].

This state of immunosenescence causes a higher susceptibility to infectious diseases [12].

Therefore, it is not surprising to find that the association between infectious agents and frailty has been investigated in several studies. In particular, herpesviruses, with their ability to establish lifelong latent infections with possible reactivations [13], have been studied for possible associations with frailty. Such studies have yielded conflicting results, with associations sometimes found between cytomegalovirus (CMV) antibodies and frailty, whereas antibodies against varicella zoster virus (VZV), Epstein–Barr Virus (EBV), and herpes simplex virus 1 and 2 (HSV-1 and HSV-2) were not associated with risks of incident frailty [14–16]. Considering the relevance of cell-mediated immunity (CMI) in the immune response to these viruses, measurement of antibodies might not be the most appropriate marker for investigating such associations [17, 18].

The drop in CMI that occurs with advancing age correlates with the incidence/onset of herpes zoster (HZ) and, especially in the over 50 s, with both incidence and severity of HZ [19, 20].

In light of the above considerations, the occurrence of HZ in frail elderly individuals will become more prevalent in the future with its attendant problems of care, long-term complications, and prevention [21, 22].

The World Health Organization (WHO) promotes active aging as a way to optimize opportunities for health, participation, and security, in order to improve the quality of life of the elderly [23].

Among currently available preventive measures, vaccination certainly plays an important role in promoting active and healthy aging [24].

In the present narrative review, we aim to cover the topic of HZ (and its complications) in frail populations in terms of epidemiology, impact, clinical management, and preventive measures.

Varicella zoster virus (VZV) is an alpha herpesvirus, with human hosts as its exclusive reservoir, transmitted through the airborne route and through direct contact with lesions. Primary VZV infection causes varicella (chickenpox) following which the virus remains in a latent state within cranial or spinal nervous ganglia for years/decades [25].

HZ is a disorder involving the sensory ganglion, nerves, and skin, that is caused by the reactivation of VZV [26, 27].

HZ appears in the form of an often severe and painful rash, which typically resolves within 1 month of presentation. However, about 20% of the affected individuals will continue to experience pain in the area of the rash, also after resolution, developing postherpetic neuralgia (PHN) [28].

PHN is a common and much feared complication of HZ, usually defined as pain that persists for over 90 days following the onset of the herpetic rash. PHN can last for months or years, and have a significant impact on the quality of life of affected individuals [29]. In a study performed in Italy on immune competent individuals 50 years and older diagnosed with HZ, 89.6% of patients reported HZ-associated pain at the first medical examination [30]. Following a systematic review, the risk of developing PHN is variable (5–30%) due to different study design, definition of PHN, and population age. According to some studies, about 30–50% of patients that develop PHN will experience pain for more than a year [31].

Pain intensity at the rash onset, age, rash severity, length of prodromal pain, and cranial localization are more frequently reported as predictors of PHN, although it is unclear whether one or all of these factors are equally relevant [28, 32–35]. PHN can become a severe and debilitating condition affecting all aspects of a patient's life and placing an economic and social burden on patients' caregivers [36, 37].

Epidemiology and impact

In the prevaccine era, in temperate-climate regions, fewer than 5% of adults were still susceptible to primary infection with VZV (varicella), that was usually acquired before adolescence. In tropical-climate regions, VZV is more commonly acquired among adolescents and adults [38].

The lifetime risk of developing HZ is estimated at about 20–30% [39] and increases with age, such that 50% of the 85 years old population is expected to develop an episode of HZ [38]. Despite the fact that age is the most important risk factor for the occurrence of HZ and that 90% of affected patients are immunocompetent [30], disease- or treatment-related immunodepression can increase the risk of developing HZ [39].

Incidence rates of HZ in Europe, Asia-Pacific, and North America vary between 3 and 5/1000 person-years. At 60 years of age, the incidence rates are between 6 and 8/1000 person-years and reach up to 8–12/1000 person-years at 80 years of age. Available data for Asia, Africa, and Latin America are limited; it is likely that HZ is not currently perceived as a health priority in these regions, but, in the future, the proportion of elderly people living in those areas will increase with a concomitant increase of HZ cases [31].

In Europe, 1.7 ± 0.1 million new cases are estimated to occur every year. Considering different age groups, the following incidence rates can be observed: 1/1000 in children under 10 years, 2/1000 in adults under 40 years, 1–4/1000 in adults between 40 and 50 years, up to 7–8/1000 after 50 years, and 10/1000 in the over 80 years [40].

A recent study performed in the Japanese population, which has the highest percentage of elderly individuals in the world, showed that the incidence rate in individuals over 60 years and in the over 80 years is comparable to the worldwide rate in the same age groups and that women are affected to a higher extent (60.2% of cases) [41].

Recent Italian data show an overall population rate of 6.4 cases/1000 person-years and a rising incidence rate with advancing age [42], thus confirming the observations from the previous studies [43].

The HEROES study analyzed the onset and persistence of pain in 413 immunocompetent patients over 50 years of age with a new diagnosis of HZ. Pain was reported by patients (89.6%) and then measured with a Visual Analog Scale (VAS) score (mean score 5.8). Among patients who completed the 3-month visit, 20.6% showed pain, thus fulfilling all the criteria that define PHN (mean VAS score 3.7). The percentage of patients with PHN increases with age. Predictive factors for the development of PHN were found to be the presence of a high number of vesicles (≥ 50), male sex, and a VAS score ≥ 3 [30]. Such a level of pain intensity is considered to be related to interference in Activities of Daily Life (ADLs). A subsequent analysis of the whole sample, showed that 73% of patients with a new diagnosis of HZ had comorbidities and 69% were over 65 years of age. The most frequent comorbidities were cardiovascular diseases (75%), diabetes (24%), and respiratory diseases (17%). The presence of pain at 3-month visit was significantly higher in patients with underlying conditions. Allodynia, paresthesia, pruritus, and VAS ≥ 3 were also more common in these patients [44].

Possible risks for people with HZ are ischemic events such as Transient Ischemic Attacks (TIAs), stroke, and myocardial infarction; these conditions are related to the systemic inflammatory state triggered by the virus, which also affects vascular structures with the possibility of inducing endothelial damage and thrombosis [45].

The risk of stroke is higher in the first month after the episode of HZ [relative risk RR = 1.78 (95% CI 1.70–1.88)] and tends to diminish with time. It is higher in cases of herpes zoster ophthalmicus (HZO) [RR = 2.05 (95% CI 1.82–2.31)] in the first month after the episode), since ocular involvement is more frequently associated with inflammation of cerebral blood vessels [46].

In older people, HZ can lead to a permanent drop of the ability to be independent and to the inability to recover preHZ lifestyle, interests, and level of activity. When pain persists in the form of PHN, the negative effect on the life of patients affects not only the physical, but also the social and psychological domains with an impact on spouses and relatives [37]. The most frequently affected daily activity in patients with HZ or PHN is sleep, whereas psychological manifestations include stress, anxiety, and depressive symptoms. Consequences in the family environment and in the social sphere affect over 50% of individuals with HZ and 81% of individuals with PHN [47]. A study showed that 20% of people surveyed claimed to be isolated from their family and friends, while they were affected with HZ or PHN, with a resultant reduction in communication in 19 and 27% of cases, respectively [48].

Besides affecting the quality of life of patients, HZ also has a strong impact on health care systems.

Hospitalization rates for HZ, considering the overall population, vary between 2 and 25/100,000 person-years [31].

Hospitalization rates are higher in the older age groups; in USA, the rate varies from 10.2/100,000 in the 60–69 age group to 65.1/100,000 in the over 80 s [49].

Following a systematic review of the relevant literature, the costs per hospitalized HZ case in Europe, USA, and Asia were estimated at 774.66-31,026.22 €, 9,041.36-23,219.82 €, and 118.13-707.23 €, respectively; a hospitalized PHN case in Europe has an average cost of 4,026.05 €, whereas in USA, the cost is estimated to be between 1,538.17 € and 3,130.88 €. The observed variation between different world

areas is not due to epidemiological differences but to factors such as the socioeconomic development level and the type of health care system of the selected country [50].

Data from England from 2004 to 2013 report a yearly average rate of 8.8/100,000 hospital admissions and confirm a high prevalence (71.5%) in individuals ≥ 60 years old (incidence of 28.4/100,000). Overall, 82% of cases occur in immunocompetent people and hospitalizations are more common in women. The yearly average number of days of hospitalization and the related cost stand at 41,780 days and 13 million £, respectively [51].

A recent Italian study analyzed data about hospital admissions from the period 2001–2013. The general hospitalization rate was 12.1/100,000 inhabitants/year with a decreasing temporal trend, from 16.5/100,000 in 2001 to 8.9/100,000 in 2013. The number of hospitalization increased with age [52]. For more details, see Table 1. The total economic impact of HZ and PHN in immunocompetent individuals > 50 years of age in Italy amounted to 41.2 million euros, of which at least a third was attributable to indirect costs related to productivity loss [43].

Management

Severity of the disease at presentation and depression are the major correlates of pain burden in patients with acute HZ and PHN [33, 34, 53].

The duration of HZ pain varies considerably, ranging from no pain or pain that lasts for only a few days after rash onset to pain that lasts for years after rash healing [26].

It is important to note that the frail elderly need careful assessment prior to treatment initiation and that they could be affected to a greater extent than "normal" adults by treatment-related adverse events, both in terms of frequency and in the possible severity of outcomes. More specifically, in the event of renal impairment, which is a frequent occurrence in the frail elderly, dosage has to be adjusted depending on creatinine clearance and adequate hydration needs to be ensured (another common problem in the frail elderly whose thirst reflex is diminished). The risk of neurological adverse events (such as headache, dizziness, confusion, tremor, convulsions, etc.) is also increased and their consequences can be serious, leading, for example, to falls with a high risk of fractures potentially leading to a vicious cycle of worsening frailty [54].

Table 1 Data from Italian study on hospitalization for HZ (2001–2013) [52]

Hospital admission (total number)	93,808
PHN-associated hospitalizations	6580
Yearly average number of hospital admissions	6391
Type of population	
Gender (%)	
Male	45.1
Female	54.9
Hospitalization for age class (%)	
< 49	16.1
50–69	27.6
> 70	56.3
Patient with a comorbidity (%)	32.5

Acute phase management of HZ

Antiviral treatment

In HZ patients, antiviral drugs accelerate the resolution of skin lesions and acute pain, and reduce the duration of chronic pain. Table 2 summarizes the doses, side effects, and contraindications of the drugs currently available for the management of acute HZ in adults. Acyclovir was the first oral antiviral therapy to be investigated for treatment; it decreases virus shedding and new lesion formation, accelerates healing, and decreases acute pain if started within 48–72 h of rash onset and given for 7 days. Valacyclovir, famciclovir, and brivudin are superior to acyclovir for the treatment of HZ, and have the advantage of simpler dosing regimens. The latter is not licensed in North America and its use requires caution as it is contraindicated in patients treated with 5-fluoropyrimidines (5-FPs) and substances that are converted by the body to 5-FPs (such as, for example, cancer treatment regimens with 5-fluorouracil or substances converted to 5-fluorouracil). Famciclovir is comparable with valacyclovir, but the suggested doses vary widely in different countries [55].

Analgesic treatment

There is no published evidence base for the optimal treatment of acute pain in HZ, but combining antiviral therapy with additional effective relief of acute pain is indicated from a clinical viewpoint (Table 3).

Selected Complications other than PHN

The most frequent complications of HZ are listed in Table 4 [56]. The incidence and burden of complications other than PHN have not been widely studied, but ocular diseases and facial palsy seem to be the most frequent HZ-related complications in several studies worldwide, although with different frequencies [57, 58].

Table 2 Dosages of drugs currently available for management of acute HZ in adults with normal renal function [55]

Drug	Dosage	Adverse events, contraindications, and comments
Oral aciclovir	800 mg, five times daily for 7 days	Nausea/vomiting < 3%, diarrhea < 3%, and headache < 3%. Similar to placebo rates
Intravenous (IV) aciclovir	5 mg/kg, three times daily 10 mg/kg, three times daily in the immunocompromised and in cases of encephalitis	Rapid IV infusion is not recommended as renal dysfunction may occur Uncommon, usually reversible CNS disturbances (agitation, disorientation, tremors, etc.) may occur especially in elderly patients and/or patients with renal failure
Oral brivudin	125 mg, once daily for 7 days	Nausea/vomiting 1.2–2.6%, vomiting 0.5–1.0%, headache 1.0–1.5%. Similar to placebo rates Contraindicated in case of administration of 5-FU (or similar drugs) within the previous 4 weeks because of blockade of 5-FU (or similar drugs) metabolism resulting in dangerous and potentially fatal 5-FU toxicity Adjustments in case of renal or liver failure are not needed
Oral valaciclovir	1000 mg, three times daily for 7 days	Nausea 6–15%, vomiting 1–5%, headache 12–28%. Similar to placebo rates
Oral famciclovir	Dose varies between different countries 500 mg three times daily (USA and Canada) 250 mg three times daily (Europe and Australia) 750 mg once daily (UK, Spain, Ireland, South Korea) All the above refer to a 7 day course of treatment	Nausea 7–12%, vomiting 1–5%, headache 22–39%. Similar to placebo rates

Table 3 Treatment plan for pain associated with herpes zoster

Prevention of varicella	Varicella vaccination	As child
		'Catch-up' as adult
Prevention of herpes zoster and PHN	Herpes zoster vaccination	Age ≥ 50
		Immunocompetent
Management of herpes zoster	Psychosocial support	
	Prompt antiviral drug treatment	Table 2
	Analgesia	Paracetamol, NSAID
	Early neuropathic pain treatment	e.g. TCA, opioid or α2δ ligand
Management of postherpetic neuralgia	Tricyclic antidepressant drugs (TCA)	Nortriptyline
		Amitriptyline
		Desipramine
	Reuptake inhibitor of serotonin and norepinephrine	Duloxetine
	Anticonvulsants (α2δ ligands)	Pregabalin
		Gabapentin
	Opioids	Tramadol
		Oxycodone
		Morphine
	Topical agents	Lidocaine
		Capsaicin
	Combinations	TCA + topical
		α2δ ligand + topical
		Opioid + topical
		Opioid + α2δ ligand
		Opioid + α2δ ligand + topical

Table 4 Complications of herpes zoster [56]

Cutaneous	Visceral	Neurological	Ocular
Cutaneous dissemination	Neural extension	Postherpetic neuralgia	Loss of corneal sensation
Bacterial superinfection	Bronchitis	Aseptic meningitis	Panophthalmitis
Scarring	Esophagitis	Meningo-encephalitis	Keratitis
Cellulitis	Gastritis	Transverse myelitis	Scleritis
Zoster gangrenosum	Colitis	Ascending myelitis	Uveitis
	Cystitis	Peripheral nerve palsies	Chorioretinitis
	Myostitis	Diaphragmatic paralysis	Iridocyclitis
	Pericarditis	Cranial nerve palsies	Optic neuropathy
	Pleuritis	Sensory loss	Ptosis
	Peritonitis	Deafness	Mydriasis
	Visceral dissemination	Vestibular dysfunction	Lid scarring
	Pneumonia	Granultomatous cerebral	Secondary glaucoma
	Hepatitis	Angiitis	Acute retinal necrosis
	Myocarditis	Postherpetic itch	Progressive outer retinal necrosis
	Pericarditis		
	Arthritis		

Treatment of postherpetic neuralgia (PHN)

PHN can be difficult to treat. It requires a thorough evaluation of the characteristics of the symptoms and sensory findings, as well as of the extent to which everyday living activities are affected. Since treatments also have side effects, careful counselling with frequent reviews and a willingness to adjust doses is essential. After an appropriate trial of the first-line therapy, it may be necessary to progress to alternative treatments on more than one occasion.

There is evidence that tricyclic antidepressants (TCAs), gabapentinoids, opioids, and topical capsaicin are effective in PHN [59]. Topical lidocaine gel (5%) or topical lidocaine patch (5%) also showed efficacy for PHN [59]. A guidance for the use of drugs for PHN is shown in Table 5 [60].

Prevention

In light of the significant burden caused by HZ and its complications (mainly PHN), the adoption of a preventive strategy appears to be particularly promising. In this respect, two main forms of prevention can be envisaged:

- Prevention of HZ itself, and thus of its complications, using vaccination in appropriate age groups (primary prevention), Table 6.
- Prevention of complications of HZ (mainly PHN) as soon as the disease has manifested itself by early and aggressive treatment (in essence a form of secondary prevention), although only supported by relatively weak evidence.

In the following sections, we will focus on the former, given that the latter has been covered in the "Management"

Table 5 Number needed to treat and number needed to harm for effective treatments for postherpetic neuralgia [60]

Active treatment	Number of patient episodes	Number of studies	NNT (95% CI)	NNH (95% CI) minor harm	NNH (95% CI) major harm
Combined tricyclic antidepressants	248	4	2.64 (2.1–3.54)	5.67 (3.34–18.58)	16.9 (8.85–178)
Combined gabapentin	559	3	4.39 (3.34–6.07)	3.93 (2.64–7.66)	12.25 (7.69–30.2)
Combined pregabalin	411	3	4.93 (3.66–7.58)	4.27 (2.78–9.18)	–
Combined opioids	211	2	2.67 (2.07–3.77)	3.57 (2.16–10.23)	6.29 (4.16–12.8)
Tramadol	108	1	4.76 (2.61–26.97)	–	–
Topical lidocaine (5% patch)	64	1	2 (1.43–3.31)	–	–

Table 6 Summary of HZ vaccines (available and/or in development)

Vaccine	Type	Indications	Schedule(s)	Regulatory status	Notes
"Classic" OkaV	Live, attenuated	HZ and HZ-associated PHN prevention in subjects > 50 y.o	1 dose	Licensed	**Contraindicated in immunocompromised individuals** Must be kept frozen (< − 15 °C) prior to reconstitution
Refrigerator-stable OkaV	Live, attenuated	As for "Classic" OkaV	1 dose	Licensed	Can be stored between 2 and 8 °C prior to reconstitution
Heat-inactivated OkaV	Inactivated	N.A	1, 3, 4 doses (30 day interval between doses)	Not licensed	Preliminary trials in various groups of immunocompromised individuals yielded mixed results Immunogenicity (significant increase in VZV CMI)
Subunit vaccine	Recombinant subunit (gE), adjuvanted	HZ and HZ-associated PHN prevention in subjects > 50 y.o. (proposed indication)	2 doses (0–2 months)	Licensed in USA, Canada, European Union, and Japan	Based on recombinant VZV glycoprotein E as target epitope and a liposome-based adjuvant system ($AS01_B$)

section. It is sufficient to highlight here that the early and aggressive treatment option suffers from drawbacks, as alluded to earlier. From a pathophysiological stand point, in many cases, damage has already occurred before treatment initiation and from a "practical"/clinical stand point, the requirement for antiviral treatment to start within 72 h after HZ onset to be effective can prove difficult to fulfill in practice.

The live-attenuated Oka vaccine strain of VZV

The currently licensed vaccine is a live-attenuated Oka vaccine strain of VZV (OkaV); in this respect, it is identical to the varicella vaccine, but contains an approximately 14-fold higher concentration of OkaV virus than the varicella vaccine [61, 62].

The OkaV vaccine has been available both in USA and in the EU since 2006 and substantial knowledge on its efficacy, safety, and effectiveness has been accumulated. The main outstanding issue with the OkaV vaccine is related to the fact that it is a live-attenuated vaccine, which, in spite of it being the most attenuated of live viral vaccines [63], is currently contraindicated in immunocompromised individuals (immunodeficient or immunosuppressed), in line with other live-attenuated viral vaccines [61, 62]. This contraindication renders its use in immunocompromised individuals to be problematic. Since, as outlined in the introduction, the immune-endocrine axis is one of the body systems involved in the occurrence of frailty in the elderly, the above contraindication could represent a concern in HZ prevention in this special population, though it is by no means established that the immune system alterations associated with frailty confer an increased risk of adverse events upon OkaV vaccine administration [10]. On the other hand, many of the frail elderly also suffer from comorbidities that increase their likelihood of developing HZ and its attendant complications, and they would benefit from HZ prevention. The choice of vaccination in the elderly is, therefore, a delicate balancing act between safety and efficacy of vaccines and the risks of developing infectious diseases and their complications [64]. Most available studies of the use of OkaV vaccine in the elderly with comorbidities and/or varying degrees of immunocompromised conditions have not considered explicitly frailty criteria in the selection of the sample, although their findings could be applied with caution to the frail elderly who share many of the same conditions.

In a very recent study, however, the immunogenicity of OkaV vaccine and immunologic markers of VZV-specific T-cell-mediated immunity (as an interferon-gamma ELISPOT assay) associated with a response to OkaV vaccine and cellular markers of immune senescence were evaluated specifically in the frail elderly. The study was performed in a cohort of 190 frail nursing home residents with a mean age of 89 years (range 80–102 years) and at least one comorbidity, and in a cohort of 50 community-dwelling seniors, used as a comparison group, with a mean age of 67 years (range 60–75 years) and a maximum of one comorbidity. Frailty was assessed with a validated 70-item (variables)

frailty index score based on the cumulative deficit model, and calculated as the ratio between the number of deficits and the total number of items. The two groups were given OkaV vaccine and had blood samples taken at the same visit the vaccine was administered and 6 weeks later. Results showed that, as foreseen, the frail elderly exhibited higher levels of immunosenescence at baseline, but interestingly, they were still able to respond to OkaV vaccine by mounting potentially protective responses. Clearly, as acknowledged by the authors, a limitation of the study is the limited time frame and the lack of direct information on protective clinical efficacy [65].

Another outstanding issue with the OkaV vaccine is related to the duration of protection, which has been shown to wane over time and which has not been established beyond 5 year postvaccination [62].

Other vaccines derived from the Oka vaccine strain of VZV

Heat-inactivated Zoster vaccine

To have a vaccine that could be safely administered to immune compromised individuals, attempts have been made to develop a heat-inactivated OkaV zoster vaccine. Some trials have been performed in different groups of immune compromised individuals, with mixed results but, at the time of writing, the heat-inactivated vaccine has not been licensed [66–68].

Adjuvanted VZV subunit vaccine

The sequencing of the VZV genome and the identification of the role of specific genes encoding specific viral components and of their function has made it possible to select candidates suitable for inclusion in a vaccine. The development of an adjuvanted VZV subunit vaccine, named Adjuvanted Recombinant Zoster Vaccine (RZV), therefore, represents a new approach to the problem of varicella and HZ prevention [63].

The RZV is based, on one hand, on the recombinant VZV glycoprotein E as the target epitope and, on the other hand, on a liposome-based adjuvant system ($AS01_B$). Studies have shown that a two-dose schedule can induce robust VZV-specific T-cell responses that last for at least 6 years after vaccination [63].

Two international phase III randomized, double-blind, placebo-controlled clinical trials were conducted concurrently at the same study sites and using the same methods to assess the efficacy and safety of RZV in preventing HZ in two different populations. The ZOE-50 study (NCT01165177) included adults ≥ 50 years of age [69] and ZOE-70 (NCT01165229) included adults ≥ 70 years of age [70]. In the ZOE-50 study, the incidence of HZ was 0.3/1,000 person-years (PY) in the RZV group and 9.1/1,000 PY in the placebo group with an estimated overall vaccine efficacy (VE) in preventing HZ of 97.2% [69]. In a pooled analysis of over 70 years old from both ZOE 50 and ZOE-70, the HZ incidence in the RZV group was 0.9/1,000 PY and 9.2/1,000 in the placebo group and the estimated overall VE against HZ was 91.3% [70].

If adult HZ vaccination was to be globally adopted, it could lead to a dramatic reduction in the incidence of PHN. Combining this with the long-term effect (40 + years) of childhood varicella vaccination, future generations might be largely immune to PHN.

According to available information, the protection is maintained for up to 4 year postvaccination and the duration of protection beyond 4 years is under investigation [71].

The vaccine has first been approved in Canada and in the United States, and more recently in Japan and in the European Union [72].

Conclusions

The concept of frailty has become an important tool in geriatric practice but, as is often the case with the elderly population, specific clinical studies are very few or unavailable. In the case of HZ prevention, to our knowledge, only two published studies were performed in a population of nursing home residents. It is very often the case that treatment (and prevention) decisions have to be extrapolated from data collected in other population groups, which requires caution given the propensity of the frail elderly to experience more frequent and more severe adverse effects to treatment, with outcomes that can lead to worsening degrees of frailty and higher mortality. Though not easy to perform, further research would be needed in this special and numerically growing population.

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Compliance with Ethical Standards

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Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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