Evaluation of efficacy and effectiveness of live attenuated zoster vaccine

G. GABUTTI, N. VALENTE, N. SULCAJ, A. STEFANATI
Department of Medical Sciences, University of Ferrara, Italy

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Summary
Herpes zoster (HZ) is a viral disease characterized by a dermatological and neurologic involvement caused by the reactivation of the latent varicella zoster virus (VZV) acquired during primary infection (varicella). HZ incidence increases with age and is related to waning specific cell-mediated immunity (CMI). The most frequent complication of HZ is post-herpetic neuralgia (PHN) characterized by chronic pain lasting at least 30 days, with impact on patients’ quality of life. Available treatments are quite unsatisfactory in reducing pain and length of the disease. The evaluation of the epidemiology, the debilitating complications (PHN), the suboptimal available treatments and the costs related to the diagnosis and clinical/therapeutic management of HZ patients have been the rationale for the search of an adequate preventive measure against this disease. The target of this intervention is to reduce the frequency and severity of HZ and related complications by stimulating CMI. Prevention has recently become possible with the live attenuated vaccine Oka/Merck, with an antigen content at least 10-fold higher than the antigen content of pediatric varicella vaccines. Clinical studies show a good level of efficacy and effectiveness, particularly against the burden of illness and PHN in all age classes. Accordingly to the summary of the characteristics of the product the zoster vaccine is indicated for the prevention of HZ and PHN in individuals 50 years of age or older and is effective and safe in subjects with a positive history of HZ.

Introduction
Herpes zoster (HZ) is an acute infectious disease sustained by the reactivation of varicella zoster virus (VZV); this latter is an ubiquitous pathogen that, after primary infection (varicella), becomes latent in sensory ganglia [1]. VZV is an alpha-herpes virus characterized by a fast replication cycle, a rapid inter-cellular spreading and the ability to establish latency, mainly in dorsal root ganglia [2, 3]. The virus contains a double-stranded DNA genome, has an icosahedral capsid (with 162 capsomers), a tegument and an envelope [4]. Envelope glycoproteins allow the virus to adhere to human cells, mainly in the respiratory tract; then the virus, before becoming latent, infects peripheral blood mononuclear cells (PBMC) and epidermal cells, causing the typical rash [5, 6]. VZV reservoir is exclusively human; the virus is air-transmitted and is quite labile outside host cells [7]. It could be also transmitted by skin lesions of subjects affected by varicella or zoster. In about a quarter of infected individuals, mainly in adulthood, latent VZV reactivates causing HZ. About 10-30% of people infected by VZV will develop an episode of HZ during their lifetime; HZ incidence is particularly high in elderly and in immunocompromised subjects [8]. Reactivation is strictly related to a decrease in the cell-mediated immunity (CMI); this latter is inversely related to age. During reactivation, the virus replicates, causes neuronal damage and inflammation, and a vesicular rash with dermatomal distribution. The rash typically involves the dermatomal distribution of one single sensory nerve and, in immunocompetent subjects, lasts for 2-3 weeks with moderate to severe pain. A rate of HZ cases are associated with pain lasting some weeks to months, and even years. This medical case is called post-herpetic neuralgia (PHN), and is usually defined as a pain lasting more than 90 days after the healing of the skin rash. PHN has a high impact on patients’ quality of life [9, 10].

Immunological aspects
VZV primary infection elicits innate immune response, characterized by IFN-α, IFN-γ and IL-6 release, as well as humoral and cell-mediated immunity [11]. CMI plays an important role in limiting viral replication and avoiding severe disease [12]; humoral immune response is probably less relevant, as suggested by uncomplicated varicella cases in agammaglobulinemic patients [13, 14]. However, VZV primary infection elicits a long lasting antibody-mediated and cell-mediated immune response. There is an ample consensus on the crucial role played by CMI in preventing VZV reactivation. Immunosenescence or immunosuppression that imply a decrease of VZV-specific CMI are strictly related to the occurrence of HZ cases [15]. An international debate is ongoing on the role of exogenous and endogenous boosting of
VZV-specific CMI; it has been suggested that exposure to varicella, causing an increase of specific CMI, could decrease the risk of VZV reactivation [16, 17]. This hypothesis is supported by studies demonstrating a decreased risk of HZ in subjects with household or occupational exposure to varicella [18]. Other authors believe that endogenous booster plays a role in preventing HZ incidence, as an increase of HZ cases has not been demonstrated in subjects surely not exposed to exogenous boosting [19]. Anyway, a HZ case elicits an increase of specific CMI, and this is probably the reason why relapse of HZ is quite rare [20].

**Clinical aspects**

The clinical course of HZ consists of 4 phases: prodromic, acute, sub-acute and chronic [21]. The prodromic phase usually (70-80% of cases) starts 1-5 days before the onset of rash [22]; its symptoms are aspecific and include pruritus, burning sensations, fever, malaise and headache [23]. The acute phase is characterized by dermatomal skin rash with vesicles; the duration of the rash is related to the age of the subject (it increases with aging) and to the dermatomes involved. Vesicles evolve in crusts in few days and then lesions heal. VZV can be transmitted during the vesicular phase; contagiousness halts during the crusting phase [24]. Acute pain during rash is related to the neuritropism of the virus [25]. Pain in the acute phase is described as pulsating, shooting, burning or piercing; it can be continuous or intermittent, as well as it can be associated with pruritus, tingling and/or numbness. Many patients show allodynia, with pain due to a stimulus which does not normally provoke pain (e.g. contact of dresses on the skin) [26]; this latter may have an impact on quality of life and may be prognostic of incoming PHN [27]. Sub-acute phase usually comes before chronic disease (30-90 days after rash) [27]. Chronic phase is characterized by PHN, with a pain lasting up to months and even years [26]. Most patients classify this pain as moderate-severe, with a pain score ≥ 4 on a scale ranging between 0 and 10; they are usually treated with analgesics [28]. HZ can be severe, particularly in immunocompromised subjects; disseminated HZ, HZ ophthalamicus, encephalitis, facial palsy, Bell’s palsy and Ramsay Hunt syndrome are the most common complications of HZ [29]. HZ ophthalamicus implies an involvement of the first branch of the trigeminal nerve; it occurs in the 1-10% of all HZ cases [30] and it may be related (at least in 1/3 of cases) to the Hutchinson’s sign (nasociliary skin lesion). This latter is prognostic of ocular inflammation and corneal sensory denervation [31]. A delayed contralateral hemiparesis following HZ ophthalamicus is quite rare, but it is related to a high risk of neurological sequelae and to a case fatality ratio equal to 20-25% [32, 33]. Recently, two researches, performed in UK, have demonstrated a higher risk of stroke, transient ischemic attack and myocardial infarction in subjects younger than 40 years and affected by HZ; this risk is higher in subjects with HZ ophthalamicus [34-36].

Early diagnosis and timely therapy are essential in order to reduce frequency and severity of complications and to improve the outcome of infection. However, the therapeutic approach to HZ and its complications (PHN in particular) is quite difficult. Therapy should start as soon as possible (within max 72 hours from disease onset), in order to avoid a loss of efficacy [37]. Most of the therapeutic options are related to undesirable effects and allow to achieve only sub-optimal results. Therefore, PHN is difficult to prevent and to treat [38-41].

**Epidemiology**

Industrialized countries report a quite similar age-related incidence; 20-35% of subjects living in these countries has a HZ case during its lifetime [29]. Complications occur in 13-40% of cases [42]; 8-27% of subjects with HZ suffer of PHN [43]. HZ incidence increases with age, being four-fold higher in subjects ≥ 70 years of age than in < 60 year-old subjects [44]. In the USA 0.5-1 million HZ cases are estimated each year, accounting for an incidence equal to 2-3/1,000/year in the general population [45]. Incidence is low in subjects younger than 40 years of age (0.9-1.9/1,000/year); it increases to 2.5, 3.8, 6.1, 8.5 and 9.4 per 1,000 per year in subjects belonging to the age classes 40-49, 50-59, 60-69, 70-79 and ≥ 80 years, respectively [46, 47]. The estimates in Europe suggest that 1.7 ± 0.1 million of new cases occur every year; incidence rates increase with aging also in this geographical area (2/1,000 and 10/1,000 in < 40 and ≥ 80 year-old subjects, respectively) [48]. The female/male ratio is equal to 1.4, and incidence in females seems to increase with aging [49]; this pattern of incidence could be related to the greater attitude of females to look for medical advice [50]. In Italy, 157,000 new cases (annual incidence: 6.3/1,000 person-years) are estimated to occur each year; most cases (76.2%) are reported by ≥ 50 year-old subjects [51]. Twenty point six (20.6%) and 9.2% of HZ cases have PHN at 3 and 6 months, respectively [52]. In the period 1999-2005, 35,328 hospitalizations due to HZ have been reported (mean: 4,503/year); 62% of these hospitalizations involved subjects older than 65 years [53]. HZ and PHN have a negative impact on quality of life and on social life of affected people, reducing physical ability, implying malaise, fatigue, anorexia, weight loss, insomnia [54]. Besides, symptoms (skin lesions and pain) together with functional and social impairment related to HZ could have, particularly in case of chronic disease, an impact on patients’ psychology [55, 56].

**NEW PREVENTIVE OPTION: ZOSTER VACCINE**

The burden in terms of morbidity and of short- and long-term complications, the sub-optimal therapeutic options and the high costs related to HZ has allowed the search of a new preventive approach by vaccination. Since many years it has been demonstrated that live attenuated VZV vaccines can boost VZV-specific CMI. In particular, live attenuated varicella vaccines, with a high anti-
The efficacy of the new zoster vaccine has been evaluated in two phase III clinical trials involving more than 38,000 subjects ≥ 60 years of age (SPS: shingles prevention study) and 22,000 subjects 50-59 years of age (ZEST: Zoster efficacy and safety trial), respectively [63, 64]. The SPS has allowed to collect data useful to obtain vaccine licensure in USA and in Europe. The SPS has been a multicenter, double-blinded, placebo controlled, randomized clinical trial, performed in the USA, enrolling immunocompetent subjects ≥ 60 years of age with a positive anamnesis of varicella or residing for at least 30 years in a VZV-endemic area. The exclusion criteria were positive anamnesis of zoster, allergy to any vaccinal component, immunosuppression or any other condition that could interfere with the evaluation of results. Randomized subjects received one dose (0.5 ml) of the zoster vaccine (n = 19,270) or of placebo (n = 19,276). The mean age of both groups was equal to 69 years (46% and 6.5% of subjects were ≥ 70 and ≥ 80 year old, respectively). The follow up period lasted a mean of 3.1 years (range 1 day-4.9 years).

The primary end point of the study was the evaluation of safety and efficacy of the vaccine. In particular, vaccine efficacy was evaluated as the reduction of the burden of illness (BOI). This end point includes incidence, severity and duration of acute and chronic pain related to HZ during a follow-up period of at least 6 months. The secondary end point of the study was vaccine efficacy against the incidence of PHN (pain with a ≥ 3 score on a scale ranging from 0 to 10 and lasting at least 90 days after the onset of rash). Pain and discomfort have been evaluated and measured by a questionnaire filled in by patients after the onset of HZ (Brief Pain Zoster Inventory). A score ≥ 3 has been considered clinically significant, as it is related to a relevant decrease of normal daily activities [65, 66]. Another secondary end point was the efficacy against the incidence of HZ. More than 95% of enrolled subjects have completed the study; a total of 957 HZ cases occurred, 315 among immunized subjects and 642 in subjects receiving placebo. Concerning the primary end point, the efficacy against BOI was equal to 61.1% (95%CI: 51.1-69.1).

During the study, 107 cases of PHN have been registered, 27 in immunized subjects and 80 in the placebo group. The efficacy against PHN has been equal to 66.5% (95%CI: 47.5-79.2); the efficacy against PHN stratified by age has been 65.7% (95%CI: 20.4-86.7) and 66.8% (95%CI: 43.3-81.3) in the age groups 60-69 and ≥ 70 years, respectively. The level of efficacy against PHN increased according to the definition of the duration of the chronic pain (58.9% and 72.9% for PHN defined as pain persisting 30 days and 182 days after rash onset, respectively).

The study has also demonstrated an efficacy against HZ equal to 51.3% (95%CI: 44.2-57.6); the level of efficacy decreased in older subjects (63.9% and 18% in 60-69 and ≥ 80 year-old subjects).

The level of efficacy against HZ decreased in older subjects, while the efficacy against PHN and BOI was not related to the age group considered. HZ occurring in immunized subjects lasted for a shorter time than cases registered in the placebo group (21 vs. 24 days; p = 0.03) [63]. Another efficacy study, called ZEST (Zoster Efficacy and Safety Trial), was performed in North America and in Europe in the period October 2007-January 2010. It was a double-blinded, placebo controlled, randomized clinical trial that involved subjects 50-59 year-old subjects with a positive anamnesis of varicella or living for at least 30 years in a VZV-endemic area [64]. Exclusion criteria were quite similar to the ones adopted in the SPS trial; a total of 22,439 were enrolled to receive a dose of zoster vaccine (n = 11,211) or placebo (n = 11,228). The mean follow-up period was 1.3 years (range 0 days-2 years).

The end point of the trial was to assess vaccine efficacy, safety and tolerability in immunized group compared to the placebo one. Efficacy against HZ was 69.8% (95%CI: 54.1-80.6); 30 and 99 HZ cases were registered in the immunized and in the placebo group, respectively (p < 0.001). The efficacy of zoster vaccine in the ZEST study in the age group 50-59 years resulted similar to the one observed in the SPS trial in the age group 60-69 years (63.9%), and higher than in subjects ≥ 70 years of age (37.6%). The results obtained in the ZEST study were in line with those obtained during the SPS trial [63, 64]; the higher efficacy against HZ observed in the ZEST study is probably related to a better immune response of younger subjects [64].

The duration of efficacy has been evaluated as well in 2 persistence substudies: short-term persistence substudy (STPS) and long-term persistence substudy (LTPS). The STPS started in October 2005; in this open-label study zoster vaccine was offered to subjects previously enrolled in the SPS placebo group. The follow-up in this substudy involved zoster vaccine recipients in the SPS as well. A total of 14,270 subjects were enrolled in the STPS substudy: 7,320 subjects were zoster vaccine recipients and 6,950 were placebo recipients in the SPS trial. These latter were offered one dose of zoster vaccine; the mean age was equal to 73.3 years and the follow-up lasted for a mean of 1.2 years (range 1 day-2.2 years). Efficacy in the STPS has been evaluated against the 3 end points already used in the SPS trial: BOI, PHN and HZ incidence. In the STPS the efficacy has been assessed on data basically collected 4-7 years after the
immunization performed in the SPS; 84 and 95 HZ cases occurred in the group of immunized subjects and in the placebo group, respectively. The estimated efficacy in the STPS has been the following: 50.1% against BOI (95%CI: 14.1-71); 60.1% against PHN (95%CI: -9.8-86.7); 39.6% against HZ (95%CI: 18.2%-55.5).

Taking into account the combined results of SPS and STPS, vaccine zoster showed an efficacy equal to 58.6% (95%CI: 48.6-66.6), 64.9% (95%CI: 47.4-77.0) and 48.7% (95%CI: 42.0-54.7) against BOI, PHN and HZ, respectively. STPS vaccine efficacy for each end point was lower than in the SPS, anyway, a persistence of vaccine efficacy was demonstrated through year 5 after immunization [67].

The long-term persistence substudy (LTPS) evaluated 6,867 subjects that had been immunized during the SPS and the STPS [67, 68]; for this reason a control group was not available. The mean age at enrollment was equal to 74.5 years; the mean follow-up was 3.9 years (range 1 week-4.75 years). In the LTPS efficacy has been evaluated 7-10 years after immunization. The HZ incidence during the LTPS was 10.3/1,000 person-years and the efficacy was: 37% against BOI (95%CI: 27-46), 35% against PHN (95%CI: 27-48), and 37% against HZ (95%CI: 11-30).

**Zoster vaccine: evaluation of effectiveness**

Clinical trials (SPS, ZEST, STPS, LTPS) have demonstrated the efficacy and the safety of the new zoster vaccine. It is important to demonstrate that similar results are obtained in the “real life”; for this reason post-marketing effectiveness studies are relevant and have been performed.

In the period January 2007-December 2009, Tseng et al. have enrolled 2 groups of subjects included in the Kaiser Permanente Southern California health plan; the first one accounted for 75,761 subjects who received zoster vaccine, the second one accounted for 227,283 unimmunized subjects. The mean duration of the follow up was equal to 1.56 and 1.72 years for vaccinated and unvaccinated cohorts, respectively; during this period, 5,434 HZ cases occurred with an incidence equal to 13,000 person-years (95%CI: 12.6-13.3) and 6,4/1,000 person-years (95%CI: 5.9-6.8) in unimmunized and immunized subjects, respectively.

HZ incidence in unimmunized subjects resulted higher in older subjects (≥ 80 vs. 60-64 year old subjects, Hazard ratio (HR) 1.45, 95%CI: 1.3-1.63), lower in males (HR 0.75, 95%CI: 0.7-0.79), and in black people (HR 0.69, 95%CI: 0.62-0.76). HZ incidence was higher, even if not statistically significant, in unvaccinated patients in treatment with biologics or with anti-TNF during the 42 days following immunization. After controlling for demographic data, type of immune-mediated disease, the accesses to health care, the use of biologic or nonbiologic disease-modifying antirheumatic drugs (DMARDs) or oral glucocorticoids, the hazard ratio (HR) of HZ related to immunization resulted equal to 0.61 (95%CI: 0.52-0.71) and the vaccine effectiveness equal to 39%. This study has demonstrated that zoster vaccine is not related to an increased risk of varicella or HZ in patients under biologic treatment [70].

More recently, Langan et al. have studied a cohort of 766,330 subjects older than 65 years, enrolled in the period January 2006-December 2009, and involved in the Medicare programs A (covers inpatients care), B (covers physician services and facility costs) since at least 12 months and registered since at least 6 months in program D (drug benefit). As a whole, 29,758 subjects received zoster vaccine; 4,469 were immunosuppressed at the time of zoster immunization.

As a whole, 154 HZ cases occurred in vaccinated subjects, with an incidence rate of 7.8 cases/1,000 person-years (95%CI: 3.7-16.5). No varicella or HZ cases were registered in patients in treatment with biologics or with anti-TNF during the 42 days following immunization. After controlling for demographic data, type of immune-mediated disease, the accesses to health care, the use of biologic or nonbiologic disease-modifying antirheumatic drugs (DMARDs) or oral glucocorticoids, the hazard ratio (HR) of HZ related to immunization resulted equal to 0.61 (95%CI: 0.52-0.71) and the vaccine effectiveness equal to 39%. This study has demonstrated that zoster vaccine is not related to an increased risk of varicella or HZ in patients under biologic treatment [70].

Vaccine effectiveness against HZ in vaccinated subjects has been equal to 0.48 (95%CI: 0.39-0.56).

In immunocompromised subjects the vaccine effectiveness has been equal to 0.37 (95%CI: 0.06-0.58) (24 HZ cases in 1,981 immunosuppressed patients). The occurrence of PHN (30 days after HZ onset) has been equal to 16 PHN case in 71,457 immunized subjects and 1,665 PHN cases in 2,563,404 cases in unimmunized subjects; the effectiveness against PHN has been equal to 0.62 (95%CI: 0.37-0.77) and to 0.59 (95%CI: 0.21-0.79) at 30 and 90 days, respectively. Langan et al. have demonstrated a zoster vaccine effectiveness equal to 48%, 62% and 59% against HZ, PHN at 30 days and PHN at 90 days, respectively. The same study has confirmed the
zoster vaccine effectiveness in routine clinical use, even in immunosuppressed individuals [71].

A long-term effectiveness study has been planned in subjects ≥ 50 years of age included in the Kaiser Permanente Northen California health plan. The target is to immunize 15,000 subjects; a preliminary phase started in 2012, is already ongoing and two ad interim analysis are planned at the end of 2016 and 2020; the study will end in 2024 [68, 72].

**Zoster vaccine: evaluation of safety**

The studies SPS and ZEST has allowed to evaluated safety and tolerability of the new zoster vaccine. In detail, the SPS trial demonstrated an excellent tolerability and safety profile [63]. In this trial each enrolling site closely monitored adverse events in a subset of subjects (safety substudy). As a whole, the incidence of hospitalizations and deaths has been quite similar during the follow-up of both groups of subjects involved in the study. During the 42 days following immunization, a rash (usually mild) at the site of injection has been registered more frequently in immunized subjects than in those receiving placebo. Seven and 24 HZ cases has been registered in immunized and placebo-receiving subjects during the first 42 days after immunization. The Oka/Merck vaccinal strain has not been detected in any sample. Five severe adverse events (SAEs) have been reported; only 2 have been observed in the immunized group. The safety substudy pointed out a greater frequency of adverse events (AEs) involving the site of injection in the vaccine group than in the placebo; in immunized subjects the most frequent AEs have been erythema (35.8%), pain or tenderness (34.5%), swelling (26.2%), and pruritus (7.1%).

SAEs occurring during the first 42 days after immunization have been significantly higher in the vaccine group than in the placebo one (1.9% vs. 1.3%, p = 0.03). No significant differences in SAEs distribution accordingly to site or type of event has been demonstrated. No hospitalization was related to immunization [63].

The ZEST study confirmed the safety profile of zoster vaccine. The rate of at least one AEs was higher in immunized subjects than in those receiving placebo (73% vs. 42%), most of AEs were at the injection site. Few (0.7%) AEs have been reported as grade 3. Systemic AEs were reported in 35% of immunized subjects; 6.7% of these have been related to the vaccine. During the ZEST study the AEs incidence in immunized subjects has resulted higher than the one observed in the SPS study (63.9% vs. 48.3%); this fact could be possibly explained with a higher local reactogenicity in younger subjects [73]. The rate of subjects with SAEs during the first 42 days following immunization has been similar in immunized and in placebo group (0.6% vs. 0.5%). An anaphylactic reaction has been reported 15 minutes after vaccine administration with no sequelae. The molecular analysis of biological samples (n = 47) belonging to subjects with HZ-like rashes (n = 34) and varicella-like rashes (n = 124) identified wild-type virus in 11 cases; no Oka/Merck strain has been detected [64].

The safety profile of zoster vaccine has also been assessed in a study involving almost 12,000 subjects ≥ 60 years of age (5,983 immunized and 5,997 receiving placebo). During the first 42 days of follow up, a SAE was reported by 1.4% and 1.12% of immunized and placebo-receiving subjects, respectively (relative risk RR 1.26; 95%CI: 0.91-1.73; not statistically significant). During the follow up at 182 days, 5.7% (n = 340) and 5% (n = 300) subjects, immunized and placebo-receiving respectively, reported a SAE; the RR in this analysis was equal to 1.13 (95%CI: 0.98-1.32; not statistically significant). In conclusion, this study has demonstrated that the incidence of SAEs in the period 1-42 days and at 6 months was not statistically different comparing immunized and placebo-receiving subjects [74].

Zoster vaccine resulted well tolerated in a clinical trial involving subjects > 60 years of age on chronic/maintenance corticosteroids (5-20 mg of prednisone or equivalent daily/dose) for at least 2 week before enrollment and for > 6 weeks after immunization [62]. Two studies [75, 76] have shown that zoster vaccine is safe in subjects with a recent history of documented HZ in accordance to recommendations by CDC Advisory Committee on immunization practices already established in 2008 [77].

The good safety and tolerability profile of zoster vaccine has been confirmed in all effectiveness studies performed after licensure and commercial availability of the product. Generally, the most frequent AEs reported have been injection site reactions (redness, swelling and pain) (≥ 1/10) and headache (from ≥ 1/100 to < 1/10). No cases of secondary transmission of vaccinal strain have been reported; no age-related specific safety issues have been demonstrated.

Recently, a HZ case caused by VZV vaccine strain has been documented in an immunocompetent recipient of zoster vaccine [78]. The efficacy, effectiveness and safety profile of zoster vaccine has recently been confirmed in an European Health Technology pilot assessment [79].

**Conclusions**

The evaluation of the epidemiology, the frequent and debilitating complications (PHN), the sub-optimal available treatments and the costs related to the diagnosis and clinical/therapeutic management of HZ patients have been the rationale for the search of an adequate preventive measure against this important disease. The target of this specific intervention is to reduce the frequency and severity of HZ and related complications by stimulating CMI. High-antigen content vaccines elicit an effective CMI response, also in elderly subjects. Prevention has recently become possible with the live attenuated vaccine Oka/Merck, with an antigen content at least 10-fold higher than the antigen content of pediatric varicella vaccines. Clinical studies show a good level of efficacy and effectiveness, particularly against the burden of illness and PHN in all age classes. Protection seems to be long lasting and vaccine
safety matches registration requirements. Accordingly to the summary of the characteristics of the product the zoster vaccine is indicated for the prevention of HZ and HZ-related PHN of individuals 50 years of age or older and is effective and safe in subjects with a positive history of HZ. The evaluation of all the above mentioned points has already allowed some countries to recommend the use of zoster vaccine (e.g. USA, Canada, Austria, UK, Germany/Saxony, Sweden, Greece, France).

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- Correspondence: Giovanni Gabutti, Dept. of Medical Sciences, University of Ferrara, via Fossato di Mortara 64b, 44121 Ferrara, Italy - Tel. +39 0532 455568 - Fax +39 0532 205066 - E-mail: giovanni.gabutti@unife.it