Journal of Medical Microbiology (2016), **65**, 1363–1369 **DOI** 10.1099/jmm.0.000386

Review

Prevention of herpes zoster and its complications: from the clinic to the real-life experience with the vaccine

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The erpes zoster is an acute viral illness characterized by a vesicular rash of unilateral distribution, which can eventually cause severe complications, such as post-herpetic neuralgia, ophthalmic zoster, stroke or other neurological complications. In Europe, an incidence of between 2.0 and 4.6 cases per 1000 person-years is estimated, with an increase after 50 years of age. Currently, the therapeutic options for are only partially effective in limiting the acute phase, while the management of complications is frequently complex and not satisfactory. The overall burden of the disease and the elevated costs associated with diagnosis and clinical and therapeutic management led to the development of a new preventive approach through a live attenuated virus vaccine. The vaccine now available decreases the incidence of the disease, post-herpetic neuralgia and the burden of illness. Moreover, the vaccine is safe and well tolerated and it seems to confer long-term protection. Based on the clinical results and evidence provided by the Health Technology Assessment, several countries introduced immunization although with different recommendations and methods of funding.

Introduction

The varicella-zoster virus (VZV) is an α herpes virus, with airborne transmission and/or transmission by direct contact with the skin lesions of a sick person; the reservoir of infection is exclusively human. The virus can cause two different diseases: chickenpox, the primary infection, which usually occurs in childhood, and herpes zoster (HZ), the result of reactivation of the virus, which remains latent in the sensory ganglia after the primary infection. During reactivation, the sensory nervous ganglia are the site of viral replication correlated to neuropathic damage of the fibres with intense inflammation and necrosis; the virus migrates along the corresponding sensory nerve until it reaches the skin surfaces or the mucous membranes, causing the characteristic acute vesicular dermatitis with typical unilateral distribution (Gabutti et al., 2010). The onset of the rash is often preceded by a prodromal phase, which generally anticipates eruption by 48 to 72 h, characterized by pain and paraesthesia in the affected dermatomes (Johnson & Whitton, 2004). During the acute phase, the rash is initially erythematous maculopapular and then evolves into vesicles, pustules and finally scabs; the lesions exfoliate for about 10 days, and the skin usually returns to its intact state after 2 to 4 weeks.

The rash is often associated with a dermatomal pain syndrome caused by acute neuritis, described as a deep, burning pain with tingling and/or itching, or a stabbing pain, varying in intensity and severity (Dworkin et al., 2008). The duration of pain associated with HZ increases with the increasing age of the subject (Katz et al., 2004). The most frequent localization of the rash is thoracic (50–60 %), followed by the ophthalmic area (ophthalmicus HZ) (10–20 %) (Opstelten & Zaal, 2005). The ophthalmic form of HZ affects the first branch of the trigeminal nerve and is particularly dangerous regarding the risk of blindness if not treated immediately. VZV natural infection induces a specific long-term immunity, both humoral and cell mediated (CMI), against the clinical form of the disease. However, the acquired immunity neither prevents the virus from becoming dormant, in particular in the somatosensory ganglia, nor the possible subsequent reactivation of HZ. There is no specific immunological parameter that can identify the subjects that will develop HZ. The lack of anti-VZV-specific antibodies does not necessarily imply susceptibility, as the corresponding CMI may persist (Gershon et al.,

Abbreviations: BOI, burden of illness; CI, confidence interval; CMI, cell-mediated immunity; HZ, herpes zoster; PHN, post-herpetic neuralgia; QoL, quality of life; SPS, Shingles Prevention Study; STPS, Short-Term Persistence Substudy; VZV, varicella-zoster virus; ZEST, Zostavax Efficacy and Safety Trial.

2010). About 20 % of subjects older than 50 years do not show a measurable VZV-specific CMI, despite the persistence of specific antibodies and a positive past event for varicella (Yawn & Gilden, 2013). The onset of HZ is a multifactorial process, even if it is closely related to a decrease in VZV-specific CMI, which in turn is age dependent; the decline of CMI increases with age and the presence of immunosuppressive conditions. Therefore, as the proportion of the elderly and fragile population is increasing, a rise in the incidence of HZ cases is expected in the near future. Besides age, comorbidities that reduce VZV-specific CMI, such as diabetes, major depression, stressful events, immunosuppressive treatments, HIV infection, lymphoma, leukaemia, bone marrow or other organ transplants and systemic lupus erythematosus, may also increase the risk of HZ (Irwin et al., 1998; Lukas et al., 2012; Okamoto et al., 2009).

Basis for the search for an appropriate preventive measure against HZ

The overall burden of HZ in terms of epidemiological impact, complications and sequelae in the short and long terms, the availability of sub-optimal therapies and the high costs associated with diagnosis and clinical–therapeutical management of patients represent the rationale and the grounds for the development of an appropriate preventive measure against this disease. A specific intervention to reduce the frequency and severity of HZ and its sequelae stimulating the cell-mediated response was deemed necessary (Lukas et al., 2012). Over the years, varicella vaccines (live attenuated virus) with high antigenic titres have been shown to elicit a significant increase in VZV-specific CMI in immunocompetent elderly subjects (Oxman, 1995; Levin et al., 2003). A high-antigenic titre shingles vaccine was developed and produced. The antigenic content is >19 400 plaque-forming units (p.f.u.), an amount at least 10 times higher than the antigenic content of the vaccine for chickenpox for paediatric use produced by the same company (Zostavax SPC, 2016). The worldwide estimates suggest that more than 1.7 million new cases of HZ occur annually, with about 4 cases per 1000 person-years (Yawn & Gilden, 2013). The individual risk of developing HZ ranges from 24 % to 30 %, equal to one individual in four people (Gross et al., 2003). However, for subjects aged >85 years, this risk increases to one individual in two people (Schmader, 2001). The incidence of HZ does not show a seasonal or epidemic trend and markedly increases in people older than 50 years, even if immunocompetent (Donahue, 1995; Yawn et al., 2007). In Europe, 95 % of adults aged ≥50 years, having previously experienced chickenpox, maintain VZV in a latent form and are therefore at risk for developing HZ (Johnson et al., 2007). The prevalence rate increases with age: 1/1000 in children <10 years, 2/1000 in adults <40 years, 1 to 4/1000 in adults between 40 and 50 years, 7 to 8/1000 after 50 years and 10/1000 in ≥80 years (Pinchinat et al., 2013).

In Italy, there are about 22 million people aged ≥50 years, and 157 100 new cases of HZ are estimated annually, with an incidence of 6.3/1000 person-years (Gialloreti et al., 2010). HZ typically occurs only once in a lifetime; relapses are relatively uncommon because an episode of HZ leads to the reactivation of VZV-specific CMI (Johnson, 2007).

Complications occur in 13 % to 40 % of cases; the most common is post-herpetic neuralgia (PHN), with an estimated incidence of between 10 and 20 % of HZ cases (up to 30 % in the elderly). PHN is characterized by pain along the cutaneous nerve endings, persistent for a few months after the onset of the rash, which can manifest as one or more painful or paroxysmal burning or stabbing attacks, with spontaneous occurrence associated with paraesthesia, dysaesthaesia and allodynia. The rates of incidence are affected by the different definitions of PHN pain and age of observed patients, ranging from 6.5 % to 38 % at 1 month to 2.6 % to 27 % at 3 months.

Other complications of HZ in elderly or immunocompromised patients are bacterial superinfection of lesions, cutaneous dissemination with 20 or more skin lesions in dermatomes other than the first, lung infection, myocarditis, esophagitis, pancreatitis, gastric ulceration, stroke secondary to the granulomatous arteritis of the internal carotid artery in ophthalmic HZ, and other neurological complications such as encephalitis, myelitis, lesions of the sympathetic trunk, Ramsay–Hunt syndrome, paresis and paralysis (Volpi, 2007). HZ and PHN negatively affect the quality of life (QoL) of people living with impaired physical abilities, and also working activity and relational and psychological abilities.

An Italian study (HEROES) carried out in collaboration with general practitioners was aimed at verifying the rate of HZ-associated pain and the duration and management of pain in subjects >50 years old with newly diagnosed HZ for up to 6 months. Of the 413 subjects enrolled in the study, 370 (86.2 %) reported HZ-associated pain. At 3 and 6 months, the pain persisted in 20.6 and 9.2 % of cases, respectively, despite the treatment with anti-viral drug taken by 91.5 % of patients. The study showed that the QoL of patients suffering from chronic pain was lower than that observed in healthy subjects of the same age, confirming the impact of PHN on adults and elderly subjects (Bricout et al., 2014).

At a national level, the total expenditure for HZ and PHN for the Italian Health Service was estimated in 2005 to have amounted to more than €41 million per year. Direct costs amounted to €28.2 million, with an average spending for outpatient management ranging from €166 to €560 for HZ and PHN, respectively. With regard to hospital admissions, the average length of stay varied between 8 and 10 days, giving a cost for HZ and PHN of about €2700 per year. The indirect costs, defined as productivity loss and absence from work, represent a third of the total cost of the

disease, amounting to €13 million per year (Gialloreti et al., 2010).

The clinical and therapeutic management of HZ is complex and often unsatisfactory. The available treatment options are only partially effective and include the use of anti-viral, anti-inflammatory and analgesic drugs. The guidelines recommend that anti-viral treatment is started within 72 h of the onset of the rash and continued for 7 to 10 days; however, it is known that a timely diagnosis is often difficult due to the delayed access of the patient to the doctor's advice (Fashner & Bell, 2011).

Acute pain management also includes the use of oral corticosteroids, nonsteroidal anti-inflammatory drugs, opioids, tricyclic antidepressants and anticonvulsants (gabapentin and pregabalin) regulating the abnormal electrical activity of the nervous system related to neuronal damage.

PHN is often refractory to pharmacologic treatment despite the combined use of tricyclic antidepressants and strong analgesics (such as opioids and topical agents containing lidocaine or capsaicin). Although 50 % of patients with PHN take more than one drug, less than half of them achieve a satisfactory result in terms of symptom relief. The combined use of multiple drugs is also limited by the risk of side effects (Johnson et al., 2010).

The vaccine

HZ vaccination is an effective solution to prevent the onset of the disease. Currently, the only vaccine that has been licensed is a live attenuated virus vaccine, which contains the same VZV Oka strain used for chickenpox vaccination but with a greater average power, equal to 19 400 p.f.u. The novel aspect of the vaccine is that it prevents the clinical manifestation in an already infected subject in which the virus is latent in the ganglia of the sensory roots of the spinal and cranial cords. The boosting of the VZV-specific CMI response by the HZ vaccine hinders both reactivation of latent VZV and its replication, reducing the incidence and severity of the disease and controlling the subsequent neurological damage. The vaccine is available in the form of powder and solvent for dissolving in a solution for injectable suspension, and is administered subcutaneously as a single dose of 0.65 ml in the deltoid region of the arm. It can be administered to VZV-naïve subjects or patients with a past event of HZ, and can be co-administered with separate injections at different injection sites with the inactivated flu vaccine, but not with the 23-valent pneumococcal one due to possible reduced immunogenicity.

The contraindications are represented by previous hypersensitivity to any component of the vaccine, even present in trace form (e.g. neomycin); primary and acquired immunodeficiency (for acute and chronic leukaemia, lymphoma and other conditions involving bone marrow or the lymphatic system); immunosuppression for HIV/AIDS; deficit of cellular immunity; immunosuppressive therapy; active untreated tuberculosis; and pregnancy. The vaccination is not contraindicated in individuals who are receiving topical or inhaled corticosteroids or low-dose corticosteroids or for subjects who have received the varicella vaccine. In fact, both in the USA and in Italy, there are very few adults >50 years susceptible to VZV or who received the vaccine for chickenpox; for this reason, it is not necessary to investigate the immunological status and previous immunizations before vaccination (Harpaz et al., 2008).

In the USA, the Food and Drug Administration initially approved the vaccine in 2006 for individuals $\geq$60 years of age and, in 2011, also for adults aged between 50 and 59 years based on a large study on safety and efficacy in this age group. In Europe, marketing authorization was obtained in May 2006 for individuals aged 60 years and older, and in July 2007 this was extended to those aged 50 years and older. The HZ vaccine is not therapeutic and is not indicated for the treatment of HZ or PHN.

Efficacy

Many records on the HZ vaccine come from clinical trials and pre- and post-marketing studies. To date, 28 clinical trials have shown data on immunogenicity, clinical efficacy and safety, for a total of about 96 700 randomized patients, of which about 57 770 were immunized with the vaccine.

The clinical efficacy of the vaccine was demonstrated in two phase III studies: the Shingles Prevention Study (SPS) in subjects aged >60 years and the Zostavax Efficacy and Safety Trial (ZEST) in subjects aged between 50 and 59 years. The vaccine significantly reduced the risk of developing the disease and PHN and reduced the chronic pain associated with HZ.

The SPS involved 38 546 subjects aged $\geq$60 years, who were randomly assigned to receive a single dose of HZ vaccine (8270) or placebo (19 276). The mean duration of follow-up was 3.1 years. The efficacy of the vaccine was 51 % regarding the incidence of HZ, 67 % for PHN and 61 % concerning the burden of illness (BOI) measured by an endpoint that included the incidence, severity, duration of pain and discomfort associated with the disease. The vaccine was more effective in reducing the incidence of PHN regardless of age (66.8 and 65.7 % in >70 years and 66–69 years, respectively), while it was less effective in preventing the development of HZ in older individuals (63.9 % in 60–69 years against 37.6 % in subjects >70 years) (Oxman et al., 2005).

The ZEST study, involving more than 22 000 subjects aged between 50 and 59 years, showed a 69.8 % reduction in HZ incidence compared with placebo. The efficacy results are similar to those observed in the SPS in subjects aged 60 to 69 years, and were higher in patients older than 70 years (Schmader et al., 2012a).

The advantage provided by the vaccine in preventing HZ incidence was greatest in the younger age group, from 50 years of age, probably related to a better immune response,

while the efficacy in the prevention of PHN and severity of the disease was maintained in different age groups.

The efficacy of the vaccine was monitored over time through two studies of persistence in the short and long term: the Short-Term Persistence Substudy (STPS) and Long-Term Persistence Substudy. The first of these started in 2004 as a secondary study of the SPS, involving a total of 14 270 subjects (7320 vaccine recipients and 6950 receiving placebo) with a mean age of 73.3 years and a median follow-up of 1.2 years. The estimated efficacy in the STPS was 39.6 % for HZ, 60.1 % for PHN and 50.1 % for BOI (Schmader et al., 2012b). The Long-Term Persistence Study assessed the length of protection against HZ, PHN and BOI in about a third of the subjects previously vaccinated in the SPS and the STPS (6687 individuals with a mean age of 74.5 years), extending the follow-up to 12 years after vaccination with a mean follow-up of 9.7 years. The estimated efficacy was 21 % for the incidence of HZ, 35 % against the incidence of PHN and 37 % for BOI (Morrison et al., 2015).

Safety

The safety of the HZ vaccine was investigated in clinical trials involving over 57 000 people. The SPS on 38 546 subjects and its sub-study on a subgroup of 3345 subjects receiving the vaccine and 3271 placebo recipients monitored adverse effects. The reported that adverse reactions, between days 0 and 42 after vaccination, with a greater frequency in those who received the vaccine, were mostly mild (31.7 % of cases) and at the injection site: erythema (29 %), tenderness (26 %), swelling (21 %), itching (6 %), sometimes ecchymosis or induration (0.2 %) and, less frequently, headache. Other adverse events have been spontaneously reported in post-marketing surveillance, including arthralgia, myalgia, rash, nausea, lymphadenopathy, pyrexia and hypersensitivity reactions. Similar results were shown by the ZEST study, with an incidence of adverse events related to the vaccine higher than in subjects receiving placebo, but mainly mild and related to the injection site. One serious adverse reaction (anaphylactic reaction) in a vaccinated subject was reported. In a placebo-controlled trial, the estimated risk of systemic adverse events within 42 days was 1.41 % for vaccine recipients compared to 1.12 % for placebo, with a relative risk not statistically significant of 1.26 [95 % confidence interval (CI), 0.91–1.73] (Murray et al., 2011).

In clinical trials, no vaccine virus transmission was reported; however, the post-marketing experience with varicella immunization suggests that there is a theoretical risk of transmitting the attenuated vaccine virus from a vaccine to a susceptible individual (very uncommon eventuality). This risk should be evaluated against that of naturally developing HZ and potentially transmitting the wild-type VZV to a susceptible individual.

Effectiveness

In addition to pre-authorization clinical trials, further studies have been conducted in order to assess the efficacy and safety of the vaccine in clinical practice in different populations. All of these studies are retrospective, and effectiveness was therefore evaluated ex-post in immunocompromised subjects or with comorbidity, once the study was completed and the characteristics of the immunized people verified.

Zhang et al. (2012) conducted a retrospective study to evaluate the vaccination efficacy and risk of infection with HZ in elderly patients with immune-mediated diseases. From 2006 to 2009, they enrolled 463 541 Medicare beneficiaries aged $\geq$60 years with a diagnosis of rheumatoid arthritis (292 169), psoriatic arthritis (11 030), psoriasis (89 565), ankylosing spondylitis (4026) or inflammatory bowel disease (66 751 – Crohn's disease or ulcerative colitis). During the study, 18 683 (4.0 %) patients received the HZ vaccine. Over the period of more than 42 days after vaccination, 138 HZ cases were observed (6.7 cases per 1000 person-years; 95 % CI, 5.7–7.9). Among the 633 patients exposed to biological agents, no cases of varicella or HZ occurred within 42 days from vaccination (95 % CI, 0–5.4 per 1000 treated with anti-TNF and 0–4.7 for 1000 receiving biological drugs). The hazard ratio of HZ associated with vaccination was 0.61 (95 % CI, 0.52–0.71) (49 % of effectiveness). The study showed that the administration of the vaccine concurrently with biological drug treatments was not associated with an increased short-term risk of varicella or HZ (Zhang et al., 2012). Another retrospective study was performed by Langan et al. (2013), involving 766 330 subjects aged $\geq$65 years, from 2006 to 2009; of 29 758 recipients of the vaccine, 4469 were immunocompromised at the time of vaccination. The effectiveness was equal to 48 % (95 % CI, 39–56) against HZ and 62 % (95 % CI, 23–63) for PHN with definition at 30 days, and 59 % (95 % CI, 21–79) for PHN with definition at 90 days; in immunocompromised individuals, however, the effectiveness amounted to 37 % (95 % CI, 42–94) (Langan et al., 2013). Tseng et al. (2014) conducted a further cohort study, between 2007 and 2012, recruiting members of the Kaiser Permanente Southern California aged $\geq$60 years receiving chemotherapy with myelosuppressive agents; vaccination was carried out before the start of chemotherapy (6 months before on average) in 4710 subjects (16 766 unvaccinated) (Tseng et al., 2014). The incidence in the vaccinated subjects was 12.87/1000 compared to 22.05/1000 cases in the unvaccinated, with an efficacy against HZ of 42 % and no hospitalization in the immunized cohort. The study therefore also demonstrated the efficacy in HZ prevention in persons subsequently undergoing chemotherapy, providing further motivation for offering the HZ vaccine to subjects while they are immunocompetent.

The effectiveness of the vaccine against HZ clinical manifestations in vaccinated persons was recently investigated, with particular attention paid to the prodromal phase. Marin et al. (2015) carried out a case–control study in subjects aged $\geq$60 years. Vaccination was associated with a 54 % reduction of HZ incidence (95 % CI, 32–69 %), a decrease of 58 % in prodromal symptoms (95 % CI, 31–75 %) and a

70 % reduction in prodromal medically assisted symptoms (95 % CI, 33–87 %). The vaccine was also effective against PHN, with definition at 30 days from the onset of the rash and a 61 % reduction (95 % CI, 22–80%) (Marin et al., 2015). In conclusion, these effectiveness studies are consistent with pre-marketing clinical studies, confirming a good safety and tolerability profile, as well as the efficacy against HZ and PHN in subjects ≥60 years. The vaccine can be administered to VZV-naïve individuals or those with a history of HZ, and in patients with immune-mediated diseases or mild immunosuppression; administration should occur at least 14 days before the start of immunosuppressive therapy or 1 month after the end of it. In any case, the contraindications reported on the data sheet should be borne in mind, and all patients must be evaluated for possible immunodeficiency prior to vaccine administration (Zostavax SPC, 2016).

Use of the vaccine globally and in Italy

Based on the scientific evidence and available assessments that confirm the impact of HZ vaccination and support its use worldwide, several countries have introduced vaccination, albeit with different recommendations and funding arrangements (with or without public support).

In the USA and Canada, since 2006 and 2010, respectively, immunization has been recommended for individuals older than 60 years. Despite the advantages of vaccination, the coverage rates were very low: only 1.9 % in 2007 and 6.7 % in 2008, with higher rates in the older population (4.7 % in those aged 60–64 years, 7.4 % among 65–74-year-olds, 7.6 % in those aged 75–84 years and 8.2 % in patients ≥85 years). In 2011, only 10 % of immunocompetent individuals older than 60 years were vaccinated in the USA, a coverage rate lower than that achieved in many other countries. The reasons were the lack of awareness by the individuals as well as the cost-effectiveness, the lack of or reduced healthcare funds, the lack of recommendation by physicians and some uncertainty on the duration of vaccine protection (Lu et al., 2011).

In Europe, the EUnetHTA (European network of 47 European organizations of Health Technology Assessment) recently conducted a study evaluating the methodology of the 'rapid relative effectiveness assessment' of the new HZ vaccine.

The report acknowledged the significance of HZ and PHN and the BOI in Europe, the limitations of current treatments and, in particular, the difficulty of PHN management. It also recognized the clinical efficacy of the HZ vaccine in the population >50 years of age, with a reduction in the frequency of new cases of HZ and its complications, also establishing a good safety profile and highlighting a period of protection up to at least 10 years. In Europe, several countries decided to recommend and/or fund vaccination: in people aged ≥50 years in Austria (since 2007), in Germany and Sweden (since 2010), in subjects ≥60 years in Greece (from 2011) and in older cohorts in the UK and in France (EUnetHTA, 2013).

The most interesting experience at the European level was in the UK. The immunization programme began in September 2013 on two cohorts: 70- and 79-year-old subjects. Official data suggested national average coverage rates, after 1 year, of 61.8 and 59.6 %, respectively. Given the positive response obtained, the UK health authorities decided to extend immunization (active call and reimbursement) to the cohort of 78-year-old subjects (Public Health England, 2013).

In France, the Haut Conseil de la Santé Publique adopted the recommendation for routine vaccination against HZ in older adults aged between 65 and 74 years in 2013; national reimbursement for all subjects aged between 65 and 74 years, with a catch-up for adults aged 75 to 79 years until the end of February 2017, was approved in 2015 (HCSP report, 2013).

In Italy, a panel of experts concluded that HZ and PHN are important clinical and public health problems, and in 2014, 'Lifetime immunization schedule' included the recommendation for the use of the HZ vaccine in subjects older than 50 years old and at risk, with the exception of seriously immunocompromised subjects, and vaccination without charge in at least a cohort of the elderly population (60 or 65 years), in order to progressively cover further groups of the population against a severely debilitating disease with high social impact (Bonanni et al., 2014). In an Italian cost-efficacy study, the vaccine proved highly cost-effective, with costs per quality-adjusted life year of €11 943 for persons aged 60 to 79 years, €9779 for subjects aged 65 to 79 years and €8729 for those aged between 70 and 79 years (Coretti et al., 2014). At the regional level, the modification of Section V of the Constitution, through Constitutional Law number 3 of October 2001, changed the structure of the institutional relationships among national, regional and local authorities, by introducing a devolution framework of competences and responsibilities in the health field. This change attributed to the regions the responsibility, almost exclusively, of the organization and the management of the health service, while the government has the responsibility to determine which health services are 'essential' (Basic Levels of Assistance, Livelli Essenziali di Assistenza) and should be offered to all citizens by all regions.

Sicily and Liguria decided to use the HZ vaccine in 2015: in Sicily, the vaccine is recommended in subjects older than 50 years and at risk, with the exception of severely immunosuppressed persons, and is also freely administered in at least a cohort of the elderly population (65 or 75 years) (Sicily Region, 2015). The Liguria region, instead, opted for the universal, free and active offer of the HZ vaccination in patients aged 65 years from the year 2015, with the aim of obtaining as the minimum target, during the same year, a coverage rate of 25 to 35 % in the elderly (Liguria Region, 2014).

In Veneto, the immunization is offered to patients at risk, immune to varicella and between 50 and 59 years, who have to undergo a bone marrow or solid organ transplant (more than 1 month before the graft), or patients with chronic inflammatory diseases taking low doses of immunosuppressive drugs (Veneto Region, 2014). In Friuli Venezia Giulia, the vaccine is provided free of charge for individuals older than 50 years belonging to risk groups and on prescription or, in co-payment, to subjects not belonging to risk groups (Friuli Venezia Giulia Region, 2014). The co-payment for subjects older than 50 years is also expected in the Molise region (Molise Region, 2015). In Calabria, since 2015, the vaccine has been offered to the cohort of 65-year-olds or to subjects aged 70 years who were not vaccinated at 65 years of age (Calabria Region, 2015). Outside these categories, the vaccine is administered upon payment of a fee, according to the regional price list. Lastly, in the autonomous province of Trento, from 1 July 2016, the HZ vaccine has been offered free of charge to subjects older than 65 years and to adults at risk (Autonomous Province of Trento, 2016.

In conclusion, HZ is a very common disease with a negative impact on QoL. The epidemiological evaluation, the frequent and debilitating complications (PHN), the available sub-optimal treatments and the costs associated with diagnosis and clinical/therapeutic management are the basis for seeking a proper preventive measure against this disease, in order to reduce both the frequency and severity. Prevention is currently possible by means of the live attenuated virus vaccine that stimulates CMI; clinical studies have shown good levels of efficacy, safety and tolerability. Based on both clinical findings and economic evidence, several countries around the world (USA, Canada, Austria, the UK, Germany/Saxony, Sweden, Greece, France and Italy) have introduced vaccination, albeit with different recommendations and financing methods.

However, in the first few years, some barriers related to the difficulty of vaccine distribution, the lack of physician recommendations or the cost of the vaccine have been encountered. It is therefore important to discuss how to offer the vaccine to the target population, including a common strategy to gradually ensure a fair offering, compatible with available resources, since the vaccination is cost-effective in terms of both prevention and healthcare economics.

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