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Prevention of Herpes Zoster and its complications: from the clinic to the real life experience with the vaccine.

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Abstract:	The Herpes Zoster (HZ) is an acute viral illness characterized by a vesicular rash, with unilateral distribution, which can eventually cause severe complications, such as the post-herpetic neuralgia (PHN), the ophthalmic zoster, stroke or other neurological complications. In Europe, an incidence between 2.0 and 4.6 cases per 1,000 persons-year is estimated, with an increase after 50 years of age. Currently, the therapeutic options for HZ are only partially effective to limit 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 the live attenuated virus vaccine. The vaccine now available decreases the incidence of the disease, the PHN and the burden of illness. Moreover the vaccine is safe, well tolerated and it seems to confer a long-term protection. On the basis of the clinical results and evidences provided by Health Technology Assessment, several countries introduced immunization, although with different recommendations and methods of funding.

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HZ, Herpes Zoster; PHN, post-herpetic neuralgia; VZV, varicella-zoster virus; OHZ, Herpes Zoster ophthalmicus; CMI, cell-mediated immunity; QoL, quality of life; NSAIDs, nonsteroidal anti-inflammatory drugs; PFU, plaque-forming units; FDA, Food and Drug Administration; SPS, Shingles Prevention Study; ZEST, Zostavax Efficacy and Safety Trial; BOI, burden of illness; STPS, Short-Term Persistence Substudy; LTPS, Long-Term Persistence Substudy; HCSP, Haut Conseil de la Santé Publique; QALY, Quality-Adjusted Life Year; LEA, Livelli Essenziali di Assistenza (Basic Levels of Assistance).

ABSTRACT

The Herpes Zoster (HZ) is an acute viral illness characterized by a vesicular rash, with unilateral distribution, which can eventually cause severe complications, such as the post-herpetic neuralgia (PHN), the ophthalmic zoster, stroke or other neurological complications. In Europe, an incidence between 2.0 and 4.6 cases per 1,000 persons-year is estimated, with an increase after 50 years of age. Currently, the therapeutic options for HZ are only partially effective to limit 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 the live attenuated virus vaccine. The vaccine now available decreases the incidence of the disease, the PHN and the burden of illness. Moreover the vaccine is safe, well tolerated and it seems to confer a long-term protection. On the basis of the clinical results and evidences provided by 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 the reactivation of the virus, that remains latent in the sensory ganglia after the primary infection. During the 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 the eruption by 48-72 hours, 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 2-4 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 subjects (Katz et al., 2004). The most frequent localization of the rash is thoracic (50-60%), followed by the ophthalmic area (OHZ, Ophthalmicus Herpes Zoster) (10-20%) (Opstelten & Zaal, 2005). The ophthalmic form of HZ affects the first branch of the trigeminal nerve and is particularly dangerous for the risk of blindness if not treated immediately. The 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 does not prevent the virus from becoming dormant, in particular in the somatosensory ganglia, neither 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., 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 cell-mediated immunity, 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 case is expected in the near future. Besides age, co-morbidities that reduce VZV-specific CMI, such as diabetes, major depression, stressful events, immunosuppressive treatments, HIV infection, lymphoma, leukaemia, bone marrow or other organs transplants, and systemic lupus erythematosus, may also increase the risk of HZ (Irwin et al., 1998; Lukas et al., 2011).

BASIS FOR THE SEARCH FOR AN APPROPRIATE PREVENTIVE MEASURE AGAINST HERPES ZOSTER

The overall burden of HZ in terms of epidemiological impact, complications and sequelae in the short and long term, 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., 2011). 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 (PFU), an amount at least 10 times higher than the antigenic content of the vaccine for chickenpox for paediatric use produced by the same company (Summary of Product Characteristics, Annex I). The worldwide estimates suggest that more than 1.7 million new cases of HZ occur annually, with about 4 cases per 1,000 persons/year (Yawn & Gilden, 2013). The individual risk of developing HZ ranges between 24% and 30%, equal to 1 individual in 4 people (Gross et al., 2003). However, for subjects aged> 85 years, this risk increases to 1 individual in 2 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 the VZV in a latent form and are therefore at risk of developing HZ (Johnson et al., 2007). The prevalence rate increases with age: 1/1,000 in children <10 years, 2/1,000 in adults <40 years, 1-4/1,000 in adults between 40-50 years, 7-8/1,000 after 50 years and 10/1,000 in ≥ 80 years (Pinchinat et al., 2013).

In Italy, there about 22 million people aged ≥50 years and 157,100 new cases of HZ are estimated annually, with an incidence of 6.3 / 1,000 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 13-40% of cases; the most common is post-herpetic neuralgia (PHN), with an incidence estimated 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, dysesthesia, and allodynia. The rates of incidence are affected by the different definitions of PHN pain and age of observed patients, ranging from 6.5 - 38% at 1 month to 2.6 - 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 the PHN negatively affect the quality of life (QoL) of people living with impaired physical abilities, working activity, 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, the duration and the 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 at 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 quality of life 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 between € 166 and € 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 € 2,700 / 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/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 to be started within 72 hours after the onset of the rash and continued for 7-10 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 (NSAIDs), 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 treatments 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 PFU. 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 cord. 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 the 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, pregnancy. The vaccination is not contraindicated in individuals who are receiving topical or inhaled corticosteroids or low-dose corticosteroids or for subjects who received the varicella vaccine. In fact, both in the US 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 the vaccination (Harpaz et al, 2008).

In the United States, the Food and Drug Administration (FDA) initially approved the vaccine in 2006 for individuals ≥60 years of age and, in 2011, also for adults aged between 50 and 59 years on the basis of 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 over, and in July 2007 this was extended to those aged 50 years and over. 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 showed 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 50-59 years. The vaccine significantly reduced the risk of developing the disease and PHN and reduced the chronic pain associated with HZ.

The SPS study involved 38,546 subjects aged ≥60 years, who were randomly assigned to receive a single dose of HZ vaccine (8,270) 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 50-59 years, showed a 69.8% reduction of HZ incidence compared to placebo. The efficacy results are similar to those observed in the SPS study in subjects aged 60-69 years and were higher in patients over 70 years of age (Schmader et al., 2012a).

The advantage provided by the vaccine in preventing the 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 (LTPS). The first one started in 2004 as a secondary study of the SPS, involving a total of 14,270 subjects (7,320 vaccine recipients and 6,950 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 study was 39.6% for HZ, 60.1% for PHN and 50.1% for BOI (Schmader et al., 2012b). The long-term persistence study (LTPS) 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 studies (6,687 individuals with a mean age of 74.5years), 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., 2014).

SAFETY

The safety of the HZ vaccine was investigated in clinical trials involving over 57,000 people. The SPS study on 38,546 subjects and its sub-study on a subgroup of 3,345 subjects receiving the vaccine and 3,271 placebo

recipients monitored adverse effects. The reported adverse reactions, between day 0 and day 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%), 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 (SAEs) 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% CI: 0.91-1.73) (Morrison et al., 2014).

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 vaccinee to a susceptible individual (very uncommon eventuality). This risk should be evaluated against the one 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 these studies are retrospective and effectiveness therefore was evaluated ex-post in immunocompromised subjects or with co-morbidity, once the study was completed and the characteristics of the immunized people verified.

Zhang et al. conducted a retrospective study to evaluate the vaccination efficacy and the risk of infection with HZ in elderly patients with immune-mediated diseases. From 2006 to 2009, they enrolled 463,541 Medicare beneficiaries aged ≥60 years with a diagnosis of rheumatoid arthritis (292,169), psoriatic arthritis (11,030), psoriasis (89,565), ankylosing spondylitis (4,026), or inflammatory bowel disease (66,751 – Crohn's disease or ulcerative colitis). During the study, 18,683 (4.0%) patients received the HZ vaccine. During the period of more than 42 days after vaccination, 138 HZ cases were observed (6.7 cases per 1,000 person/year; 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 to 5.4 per 1,000 treated with anti-TNF and 0 to 4.7 for 1,000 receiving biological drugs). The hazard ratio of HZ associated with vaccination was 0.61 (95% CI: 0.52 to 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., involving 766,330 subjects aged ≥ 65 years, from 2006 to 2009; out of 29,758 recipients of the vaccine, 4,469 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 to 90 days; in immunocompromised individuals, however, the effectiveness amounted to 37% (95% CI: 42-94) (Langan et al., 2013). Tseng et al. conducted a further cohort study, between 2007 and 2012, recruiting members of Kaiser Permanente Southern California (KPSC) aged ≥60 years receiving chemotherapy with myelosuppressive agents; vaccination was carried out before the start of chemotherapy (six months before on average) in 4,710 subjects (16,766 unvaccinated) (Tseng et al., 2014). The incidence in the vaccinated subjects was 12.87/1,000 compared to 22.05/1,000 cases in the unvaccinated ones, with an efficacy against HZ of 42% and no hospitalization in the immunized cohort. The study therefore demonstrated the efficacy in HZ prevention also in persons that will subsequently undergo 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 to the prodromal phase. Marin et al. carried out a case-control study in subjects aged ≥ 60 years. Vaccination was associated with a 54% reduction of HZ incidence (95% CI: 32%-69%), a decrease of 58% of prodromal symptoms (95% CI: 31% -75%), and a 70% reduction of the 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, with a 61% reduction (95% CI: 22%-80%) (Marin et al., 2015). In conclusion, the 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, in patients with immune-mediated diseases or mild immunosuppression; the administration should occur at least 14 days before the start of immunosuppressive therapy or one 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 (Summary of Product Characteristics, Annex I).

USE OF THE VACCINE IN THE WORLD 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 the vaccination, albeit with different recommendations and funding arrangements (with or without public support).

In the United States and Canada, since 2006 and in 2010 respectively, immunization is recommended above 60 years of age. 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 above 60 years were vaccinated in the United States, 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 health care 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 European level was in the UK. The immunization program began in September 2013 on two cohorts: seventy-year-old and seventy-nine-year-old subjects. Official data suggested national average coverage rates, after one 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 seventy-eight-year-old subjects (Public Health England, 2013).

In France, the Haut Conseil de la Santé Publique (HCSP) 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 65-74 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 at risk above 50 years old, with the exception of seriously immunocompromised subjects, but also 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 (QALY) ranging from € 11,943 for persons aged 60-79 years; € 9,779 for subjects aged 65-79 years and € 8,729 for those aged between 70 and 79 years (Coretti et al., 2014). At 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 between 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, LEA) 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 at risk above 50 years of age, with the exception of severely immunosuppressed persons, and also freely administered in at least a cohort of elderly population (65 years or 75 years) (Sicily Region, 2015). 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 25-35% in the elderly (Liguria Region, 2014).

In Veneto, the immunization is offered to patients at risk, immune to varicella between 50-59 years, who have to undergo a bone marrow or solid organ transplant (more than one 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 over 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 over 50 year-old subjects is also expected in Molise Region (Region Molise, 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 (Region Calabria, 2015). Outside of these categories, the vaccine is administered upon payment of the fee, according to the regional price list. Lastly, in the Autonomous Province of Trento, from the first of July 2016, the HZ vaccine has been offered free of charge to over 65 year-old subjects and to adults at risk (Autonomous Province of Trento, 2016).

CONCLUSIONS

HZ is a very common disease, with a negative impact on the quality of life. 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 the frequency and the severity. Nowadays, prevention is possible by means of the live attenuated virus vaccine that stimulates cell-mediated immunity; clinical studies showed good levels of efficacy, safety and tolerability. Based on the clinical findings and also economic evidence, several countries around the world (United States, Canada, Austria, the United Kingdom, Germany/Saxony, Sweden, Greece, France, Italy) have introduced the vaccination, albeit with different recommendations and financing methods.

However, in the first years of experience, some barriers related to the difficulty of vaccine distribution, the lack of physician recommendations or the cost of the vaccine were 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 economy.

Abbreviations

HZ, Herpes Zoster; PHN, post-herpetic neuralgia; VZV, varicella-zoster virus; OHZ, Herpes Zoster ophthalmicus; CMI, cell-mediated immunity; QoL, quality of life; NSAIDs, nonsteroidal anti-inflammatory drugs; PFU, plaque-forming units; FDA, Food and Drug Administration; SPS, Shingles Prevention Study; ZEST, Zostavax Efficacy and Safety Trial; BOI, burden of illness; STPS, Short-Term Persistence Substudy;

LTPS, Long-Term Persistence Substudy; HCSP, Haut Conseil de la Santé Publique; QALY, Quality-Adjusted Life Year; LEA, Livelli Essenziali di Assistenza (Basic Levels of Assistance).

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